Development and validation of a drug adherence index for COPD

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What is already known about this subject

- Despite adherence to inhaled chronic obstructive pulmonary disease (COPD) maintenance medication being associated with fewer exacerbations, reduced mortality, and reduced health care utilization, adherence rates are known to be low (ranging from ~60% to as low as 20% in real-world studies) and to decrease over time.
- A drug adherence index (DAI) is a predictive modeling tool that identifies patients who are most likely to change adherence status in the coming year and who may benefit from support or maintain adherence to their prescribed medication.

What this study adds

- This study developed a DAI using enrollment, medical, and/or pharmacy variables to predict future changes in adherence and nonadherence to long-acting bronchodilator medications among patients with COPD.
- The DAI demonstrated acceptable prediction for future nonadherence in adherent patients and future adherence in nonadherent patients. The DAI predicted future nonadherence better than future adherence.
- The DAI described here provides a disease-specific tool that could prove to be useful for identifying which patients would likely benefit from interventions aimed at improving and/or maintaining COPD inhaler adherence.

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ABSTRACT

BACKGROUND: Inhaled medications are the mainstay of treatment for chronic obstructive pulmonary disease (COPD). Despite their importance, adherence to these medications is low. Low adherence is linked to increased exacerbation rates, mortality rates, health care utilization, and, ultimately, increased costs. A drug adherence index (DAI) is a predictive modeling tool that identifies patients most likely to change adherence status so that they can be targeted for support programs. Optum has previously developed DAI tools for diabetes, hypertension, and high cholesterol. In this study, a COPD-specific DAI was developed. This DAI tool could be used to better target medication adherence support in patients with COPD, aiming to increase adherence.

OBJECTIVES: To develop a COPD-specific DAI using (a) enrollment, medical, and pharmacy variables and (b) only enrollment and pharmacy variables for potential application to pharmacy benefit managers and pharmacy plans.

METHODS: This was a retrospective observational study using health care claims among Medicare Advantage with Part D beneficiaries with COPD in the United States. Potential predictors of adherence were measured during a 1-year baseline period. The adherence outcome was measured during a subsequent 1-year at-risk period. Adherence to long-acting bronchodilators was defined as a proportion of days covered (PDC) $\geq 80\%$. Nonadherence was defined as a PDC of $< 80\%$. Patients were stratified according to their

adherence status at baseline, and logistic regression models were developed separately for each set of patients. Separate models were also developed using enrollment, medical, and pharmacy variables (primary objective) or using enrollment and pharmacy variables only (secondary objective).

RESULTS: A total of 61,507 patients met all inclusion and exclusion criteria. For the primary objective, at baseline, 31,142 patients were adherent and 30,365 patients were non-adherent. The final DAI model used to predict future nonadherence included 30 covariates, with 7 predictors from medical claims. The validated model c-statistic was 0.752. The final DAI model used to predict future adherence included 29 covariates; only 4 predictors were from medical claims. The validated

model c-statistic was 0.691. Findings were similar for the secondary objective using only enrollment and pharmacy variables.

CONCLUSIONS: This DAI was developed and validated specifically to predict future adherence status to long-acting bronchodilator medications among patients with COPD. The DAI models performed better for predicting nonadherence than predicting adherence. Both organizations with medical and pharmacy data and organizations with only pharmacy data could utilize the DAI tool to target patients for adherence programs, as results were similar with and without the use of medical variables.

Chronic obstructive pulmonary disease (COPD) is a progressive, treatable disease of the airways associated with substantial morbidity and mortality.¹ The worldwide prevalence and burden of COPD is projected to increase due to an aging population and continued exposure to COPD risk factors.¹ In the United States in 2015, the age-adjusted prevalence of COPD was reported to be 5.9%, and it was the third-leading cause of death.^{2,3} The direct medical costs of COPD in the United States are projected to reach \$49 billion by 2020.⁴

Exacerbations of COPD are a major contributor to the total COPD burden on the health care system.^{1,5} Acute exacerbations are linked with increased morbidity and mortality and reduced quality of life, contributing to hospitalizations and the health care burden in this population.^{6,7} Hospitalizations, largely due to acute exacerbations, are responsible for 85% of direct COPD medical costs.⁸ COPD management strategies that can reduce exacerbations should therefore reduce the direct medical costs of COPD.

Inhaled medications are the mainstay of treatment for COPD,¹ and bronchodilator adherence is a National Committee for Quality Assurance quality measure for the management of COPD exacerbations.⁹ However, real-world studies have reported medication adherence rates in COPD ranging from around 60% to as low as 20%.¹⁰⁻¹⁴ Acceptable adherence is generally defined as a proportion of days covered (PDC) of $\geq 80\%$.¹⁵ Moreover, adherence to COPD maintenance medication has been shown to decrease over time.¹⁶ Furthermore, the progressive nature of COPD leads to changes in medication and/or regimens,¹ potentially negatively affecting adherence.^{12,15} Good adherence to inhaled COPD maintenance medication is associated with reduced exacerbation rates, lower mortality rates, and reduced health care utilization.^{17,18} Indeed, a systematic review identified a link between poor adherence and increased costs of COPD.¹⁹ A strategic program to provide medication adherence support for patients who are likely to become

nonadherent could help raise population-level adherence, improve quality ratings, and reduce associated costs.

Optum previously developed a drug adherence index (DAI) for medications used to treat diabetes, hypertension, and high cholesterol.²⁰ A DAI is a predictive modeling tool that identifies patients who are most likely to change adherence status in the coming year. The model therefore allows for specific targeting of patients suitable for medication adherence support. The aim of this study was to develop a DAI using enrollment, medical, and/or pharmacy variables to predict future changes in adherence and nonadherence to long-acting bronchodilator medications among patients with COPD.

The overall objective of this study was to develop COPD-specific DAI models. The primary objective was to generate DAI models using enrollment, medical, and pharmacy variables, while the secondary objective was to generate DAI models using enrollment and pharmacy variables only. This secondary set of models was developed for potential application to pharmacy benefit managers and pharmacy plans that only have access to pharmacy claims.

Methods

STUDY DESIGN

This was a retrospective observational study of Medicare Advantage Prescription Drug plan (MAPD) beneficiaries diagnosed with COPD from the Optum Research Database. This study used medical data, pharmacy data, and enrollment information covering the period from January 1, 2011–August 31, 2016. The patient identification period spanned from January 1, 2011–August 31, 2014. The study design included a 1-year baseline period followed by a 1-year at-risk period; the definition of each is summarized in Figure 1. Additionally, the study design was modeled on Pharmacy Quality Alliance (PQA) measures.

MAPD patients were stratified by adherence or nonadherence to long-acting bronchodilators during the 1-year baseline period according to a PDC of $\geq 80\%$ or $< 80\%$, respectively. Adherence to long-acting bronchodilators was determined based on pharmacy claims.

This study used deidentified retrospective claims data, and as such, did not require institutional review board review and approval or informed consent procedures.

DATA SOURCE

The Optum Research Database is a large, geographically diverse U.S. administrative claims database that includes enrollment information and medical and pharmacy claims data. As of 2016, the Optum Research Database included

FIGURE 1 Study Schematic for the Development and Validation of the Drug Adherence Index

COPD = chronic obstructive pulmonary disease; ED = emergency department.

6.4 million Medicare Advantage beneficiaries and represented approximately 17% of those enrolled in Medicare Advantage plans in the United States. Medical claims and coding conform to insurance industry standards and include *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *Tenth Revision* (ICD-10-CM) diagnosis and procedure codes,^{21,22} Current Procedural Terminology codes,²³ or Healthcare Common Procedure Coding System codes.²⁴

INCLUSION/EXCLUSION CRITERIA

Patients who had either a COPD diagnosis or a pharmacy claim for

COPD medications were eligible for inclusion in the study. Initial selection criteria during the identification period (January 1, 2011–August 31, 2014) aligned with PQA measures and included 1 inpatient hospitalization or 2 outpatient (i.e., office or other outpatient visit) and/or emergency department (ED) visits within 1 year with an ICD-9-CM COPD diagnosis in any position or at least 1 pharmacy claim for roflumilast, tiotropium, aclidinium, umeclidinium, or umeclidinium/vilanterol combination or at least 2 prescriptions for ipratropium or ipratropium/albuterol combination within 1 year.

The start of the baseline period (i.e., start date) was defined as the day after the initial selection criteria were met. The index date was assigned as the start date + 364 days. This ensured that patients would meet the COPD inclusion criteria during the entire baseline period. The subsequent at-risk period consisted of the 1 year following the index date. Patients were also required to have continuous eligibility during the baseline and at-risk periods; at least 1 pharmacy claim for an inhaled COPD medication during the baseline period; at least 2 pharmacy claims for a long-acting inhaled bronchodilator on 2 unique dates of service during the at-risk period; and be 40 years or older on the start date.

Patients were excluded from the study if they had at least 1 claim during the baseline period with an ICD-9-CM diagnosis code for cancer in any position, except cancer types that are typically considered to have little effect on lung function (e.g., non-melanoma skin cancer, breast cancer, and prostate cancer)²⁵; at least 2 prescription claims on different dates of service during the baseline period for medications indicated for the treatment of cancer; or at least 1 fill for a nebulized bronchodilator during the at-risk period per the PQA Technical Specifications.²⁶

PREDICTORS AND OUTCOMES

To support development of the DAI, potential predictors of adherence were measured during the baseline period, and adherence outcomes were measured during the at-risk period. For the primary objective analysis, a total of 5,350 candidate predictors of adherence, based on both medical and pharmacy claims, were considered ([Supplementary Table 1](#), available in online article), including patient characteristics (e.g., age, gender); clinical characteristics (e.g., exacerbation

TABLE 1 MAPD Patient Demographics

Demographics	Primary Objective (N = 61,507)				Secondary Objective (N = 61,507)			
	Baseline Nonadherent (n = 30,365)		Baseline Adherent (n = 31,142)		Baseline Nonadherent (n = 30,746)		Baseline Adherent (n = 30,761)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, years	70.71	8.74	71.17	8.42	70.74	8.75	71.14	8.41
	n	%	n	%	n	%	n	%
Age group, years								
40-44	142	0.47	116	0.37	144	0.47	114	0.37
45-54	1,435	4.73	1,159	3.72	1,447	4.71	1,147	3.73
55-64	3,919	12.91	3,685	11.83	3,960	12.88	3,644	11.85
65-74	14,655	48.26	15,394	49.43	14,798	48.13	15,251	49.58
75-79	5,103	16.81	5,286	16.97	5,167	16.81	5,222	16.98
80+	5,111	16.83	5,502	17.67	5,230	17.01	5,383	17.50
Gender								
Female	17,709	58.32	17,689	56.80	17,944	58.36	17,454	56.74
Male	12,656	41.68	13,453	43.20	12,802	41.64	13,307	43.26
U.S. division								
New England	2,744	9.04	3,189	10.24	2,818	9.17	3,115	10.13
Mid-Atlantic	3,400	11.20	3,733	11.99	3,436	11.18	3,697	12.02
East North Central	5,818	19.16	6,442	20.69	5,898	19.18	6,362	20.68
West North Central	3,235	10.65	3,498	11.23	3,273	10.65	3,460	11.25
South Atlantic	9,745	32.09	9,082	29.16	9,843	32.01	8,984	29.21
East South Central	1,951	6.43	1,657	5.32	1,968	6.40	1,640	5.33
West South Central	711	2.34	570	1.83	716	2.33	565	1.84
Mountain	1,582	5.21	1,649	5.30	1,597	5.19	1,634	5.31
Pacific	1,179	3.88	1,322	4.25	1,197	3.89	1,304	4.24

MAPD = Medicare Advantage Prescription Drug plan; SD = standard deviation.

history); Agency for Healthcare Research and Quality (AHRQ) classification²⁷; Diabetes Complications Severity Index (DCSI)²⁸; COPD medication utilization (e.g., baseline controller medication fill); American Hospital Formulary Service (AHFS) drug class²⁹; and other predictors from historical models (e.g., health care utilization, comorbid conditions). The predictor variables used also included those previously published as part of the COPD Treatment Ratio validation.²⁵ For the secondary objective analysis, 4,954 candidate predictors of adherence were considered, including demographic characteristics and measures based on pharmacy claims (medical-based measures were excluded). The outcome, adherence or nonadherence to long-acting bronchodilators during the at-risk period, was calculated using PDC, defined according to the PQA-defined PDC metric as

adopted by the Centers for Medicare & Medicaid Services. PDC was calculated by dividing the total days that all drugs in the category were available by the total days in the measurement period. Adherence was classified as a PDC of $\geq 80\%$. Nonadherence was classified as a PDC of $< 80\%$. PDC was calculated during the baseline period and during the at-risk period.

ANALYSIS

Logistic regression models were developed separately for 2 mutually exclusive patient groups defined by baseline adherence (nonadherent and adherent; [Supplementary Table 2](#), available in online article). Logistic regression models were created to predict future adherence among patients who were nonadherent during the baseline period

TABLE 2 Summary of Outcome Measures for MAPD DAI Models

Objective	Sample, n	Data Sources	Baseline	Outcome	Predictors, n	Model C-statistic	Validated C-statistic
Primary	31,142	Medical+pharmacy	Adherent	Nonadherence	30	0.753	0.752
	30,365	Medical+pharmacy	Nonadherent	Adherence	29	0.693	0.691
Secondary	30,761	Pharmacy only	Adherent	Nonadherence	16	0.746	0.745
	30,746	Pharmacy only	Nonadherent	Adherence	24	0.690	0.688

DAI=drug adherence index; MAPD=Medicare Advantage Prescription Drug plan.

and to predict future nonadherence among patients who were adherent during the baseline period. Models were developed using both medical and pharmacy predictors and separately using only pharmacy predictors.

For each DAI model, predictor variables were evaluated and excluded if they did not possess sufficient variability for model stability. Standard selection procedures (e.g., forward, backward, and stepwise) were applied to the set of predictor variables to arrive at a final set of variables for each model. The c-statistic was used to determine the predictive ability of each model. For each final model, internal validity was estimated with 100 bootstrap samples. Model fit statistics, univariate and multivariable odds ratios with 95% confidence intervals, and P values were reported for each of the final models in addition to the Wald chi-square statistic, which is reported to measure the impact of each predictor on the predictive model.

When generating the DAI model for the secondary objective, the same methodology used for the primary objective was employed to estimate the logistic regression models but excluded candidate covariates derived from medical claims; specifically, variables pertaining to baseline exacerbations, type of COPD diagnosis, comorbidities, and procedures were excluded.

Results

STUDY POPULATION

[Supplementary Figure 1](#) (available in online article) shows the flow of patients included in this study. A total of 245,326 patients met the initial baseline period criteria and 86,214 patients remained after applying the at-risk requirements. The final study population was restricted to patients enrolled in an MAPD (n=61,507 patients).

The average age of patients was approximately 71 years and more than 55% of patients were female (Table 1).

OUTCOME MEASURES

The results for each model are summarized in Table 2. A total of 31,142 and 30,365 MAPD patients were classified as adherent and nonadherent, respectively, to long-acting inhaled bronchodilator treatment at baseline. The final predictive model for nonadherence among the MAPD patients who were adherent at baseline included 30 covariates from medical and pharmacy claims (Table 3). The 7 predictors from medical claims were as follows:

- COPD severity score³⁰
- ≥1 medical claim with a diabetes diagnosis
- ≥1 medical claim with a mild liver disease diagnosis
- Provider specialty: cardiology
- First fill of medication occurs at least 91 days before index date (STAR eligible: COPD)
- ≥1 medical claim with a substance-related disorder diagnosis (AHRQ 48)
- ≥1 medical claim with a disease of the urinary system diagnosis (AHRQ 87)

The model c-statistic and the validated c-statistic were 0.753 and 0.752, respectively, suggesting that the model was not overfit to the data and had good predictive performance (Table 2). The final predictive model for adherence among the MAPD patients who were nonadherent at baseline included 29 covariates (Table 3). The medical-based predictors included in the final model were the following:

- COPD severity score³⁰
- ≥1 claim for an ambulatory site of service
- ≥1 medical claim with an asthma diagnosis
- The number of COPD-related outpatient visits

The model c-statistic and the validated model c-statistic were 0.693 and 0.691, respectively (Table 2).

Using only pharmacy variables to predict future nonadherence to long-acting bronchodilators among the 30,761 MAPD patients who were adherent at baseline resulted in a model with 16 predictors (Table 4) and a validated c-statistic of 0.745 (Table 2). Among the 30,746 MAPD patients who were nonadherent at baseline, the DAI

TABLE 3 Logistic Regression Model Predicting Future Adherence Status Using Medical and Pharmacy Variables

Independent Variables (Captured During Baseline)	Estimate	Odds Ratio	Lower 95% CI	Upper 95% CI	Chi-Square	P Value
Outcome: Future nonadherence^a among adherent patients at baseline						
Intercept	5.702	–	–	–	486.179	<0.001
Count of pharmacy claims for central nervous system agents (AHFS 28:00)	0.008	1.008	1.006	1.010	55.155	<0.001
Count of pharmacy claims for anticholinergic agents (AHFS 12:08)	0.053	1.055	1.044	1.066	92.982	<0.001
Count of pharmacy claims for adrenals (AHFS 68:04)	0.023	1.023	1.012	1.034	17.902	<0.001
MPR ≥ 80% for pharmacy claims for anticholinergic agents (AHFS 12:08)	–0.298	0.742	0.687	0.802	57.804	<0.001
MPR ≥ 80% for pharmacy claims for anti-inflammatory agents (AHFS 48:10)	–0.275	0.760	0.703	0.821	48.380	<0.001
≥ 1 pharmacy claim for antilipemic agents, miscellaneous (AHFS 24:06.92)	–0.343	0.710	0.588	0.857	12.733	<0.001
≥ 1 pharmacy claim for eye, ear, nose, and throat anti-infectives, miscellaneous (AHFS 52:04.92)	–0.395	0.674	0.535	0.849	11.254	<0.001
Count of pharmacy claims for corticosteroids (AHFS 48:10.08)	0.052	1.054	1.041	1.066	76.229	<0.001
Count of controller medication classes	0.204	1.226	1.176	1.279	89.752	<0.001
COPD severity score ^b	–0.010	0.990	0.986	0.995	16.712	<0.001
Number of units of controller medication	–0.127	0.881	0.872	0.890	612.827	<0.001
≥ 1 medical claim with a diabetes diagnosis ^b	0.130	1.139	1.066	1.217	14.791	<0.001
Number of units of ICS	0.067	1.069	1.048	1.090	44.569	<0.001
≥ 1 medical claim with a mild liver disease diagnosis ^b	0.109	1.115	1.050	1.184	12.493	<0.001
Number of units of methylxanthine	0.108	1.114	1.092	1.137	112.662	<0.001
PDC for COPD medications, per 0.10 change	–0.524	0.592	0.564	0.621	449.758	<0.001
Count of unique service dates with a claim for a COPD medication, pharmacy claims only	–0.042	0.959	0.947	0.970	46.187	<0.001
Number of units of phosphodiesterase inhibitor	0.088	1.092	1.045	1.140	15.460	<0.001
Provider specialty: Cardiology ^b	0.122	1.130	1.064	1.200	15.857	<0.001
Pharmacy costs: First quartile vs. third and fourth quartiles	0.250	1.285	1.152	1.433	20.188	<0.001
Pharmacy costs: Second quartile vs. third and fourth quartiles	0.222	1.248	1.159	1.344	34.624	<0.001
Count of unique pharmacy claim fill dates for all medications	–0.005	0.995	0.993	0.997	26.976	<0.001
Number of SAMA units	–0.065	0.937	0.910	0.966	18.072	<0.001
Number of SAMA/SABA units	–0.033	0.968	0.958	0.978	39.507	<0.001
≥ 2 severe exacerbations	–0.416	0.659	0.521	0.835	11.991	<0.001
STAR eligible: COPD ^b	–0.595	0.552	0.472	0.645	55.391	<0.001
≥ 1 medical claim with a substance-related disorder diagnosis (AHRQ 48) ^b	0.314	1.369	1.161	1.615	13.967	<0.001
≥ 1 medical claim with a disease of the urinary system diagnosis (AHRQ 87) ^b	0.105	1.110	1.045	1.180	11.550	<0.001
Geographic division: South Atlantic	0.120	1.128	1.060	1.199	14.686	<0.001
Count of unique medications	0.014	1.014	1.007	1.020	16.347	<0.001

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TABLE 3 Logistic Regression Model Predicting Future Adherence Status Using Medical and Pharmacy Variables (*continued*)

Independent Variables (Captured During Baseline)	Estimate	Odds Ratio	Lower 95% CI	Upper 95% CI	Chi-Square	P Value
Outcome: Future adherence^c among nonadherent patients at baseline						
Intercept	-0.823	–	–	–	65.586	<0.001
≥1 pharmacy claim for smooth muscle relaxants (AHFS 86:00)	-0.271	0.763	0.674	0.863	18.504	<0.001
MPR ≥80% for pharmacy claims for eye, ear, nose, and throat (AHFS 52:00)	0.201	1.223	1.101	1.358	14.060	<0.001
MPR for pharmacy claims for autonomic drugs (AHFS 12:00), per 0.10 change	0.027	1.027	1.016	1.038	22.798	<0.001
MPR for pharmacy claims for skin and mucous membrane agents (AHFS 84:00), per 0.10 change	0.036	1.037	1.022	1.052	23.294	<0.001
Count of pharmacy claims for anticholinergic agents (AHFS 12:08)	-0.058	0.944	0.930	0.957	65.848	<0.001
Count of pharmacy claims for adrenals (AHFS 68:04)	-0.108	0.898	0.878	0.918	91.792	<0.001
MPR ≥80% for pharmacy claims for beta-adrenergic-blocking agents (AHFS 24:24)	0.113	1.120	1.050	1.193	12.069	<0.001
MPR for pharmacy claims for anticholinergic agents (AHFS 12:08), per 0.10 change	0.060	1.062	1.048	1.077	76.221	<0.001
Count of pharmacy claims for corticosteroids (AHFS 48:10.08)	-0.112	0.895	0.878	0.912	129.391	<0.001
MPR ≥80% for pharmacy claims for corticosteroids (AHFS 48:10.08)	0.354	1.425	1.275	1.593	38.900	<0.001
Count of unique AHFS level 4 categories	-0.027	0.974	0.967	0.980	57.434	<0.001
≥1 pharmacy claim for a controller medication and ≥4 pharmacy claims for rescue medication	-0.317	0.728	0.610	0.869	12.407	<0.001
≥1 pharmacy claim for a medication used to treat COPD	-1.193	0.303	0.269	0.342	377.342	<0.001
COPD severity score ^b	0.012	1.012	1.008	1.016	28.954	<0.001
Number of units of controller medication	0.102	1.107	1.093	1.122	227.146	<0.001
Number of units of ICS/LABA	0.072	1.074	1.056	1.094	62.611	<0.001
Number of units of methylxanthine	-0.082	0.921	0.897	0.945	38.549	<0.001
Count of pharmacy claims for oral corticosteroids	0.107	1.113	1.082	1.144	55.894	<0.001
PDC ≥0.60 for COPD medications	0.422	1.525	1.423	1.634	142.602	<0.001
PDC ≥0.60 for statin medications	0.241	1.272	1.163	1.393	27.355	<0.001
Ambulance services ^b	0.164	1.178	1.089	1.274	16.743	<0.001
≥4 rescue canisters	0.501	1.650	1.389	1.959	32.572	<0.001
≥1 pharmacy claim for any medication with a 90-day supply	0.158	1.171	1.100	1.247	24.589	<0.001
Pharmacy costs: First quartile vs. fourth quartile	-0.530	0.589	0.529	0.655	94.193	<0.001
Pharmacy costs: Second quartile vs. fourth quartile	-0.396	0.673	0.610	0.741	64.028	<0.001
Pharmacy costs: Third quartile vs. fourth quartile	-0.222	0.801	0.728	0.881	20.826	<0.001
STAR eligible: Statins	-0.164	0.849	0.776	0.930	12.546	<0.001
≥1 medical claim with an asthma diagnosis (AHRQ 68) ^b	-0.124	0.883	0.828	0.942	14.317	<0.001
Count of COPD-related outpatient visits ^b	0.021	1.021	1.011	1.031	15.930	<0.001

^aModel c-statistic = 0.753; validated c-statistic = 0.752.^bVariable from medical claims.^cModel c-statistic = 0.693; validated c-statistic = 0.691.

AHFS = American Hospital Formulary Service; AHRQ = Agency for Healthcare Research and Quality; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; MPR = medication possession ratio; PDC = proportion of days covered; SAMA = short-acting muscarinic-antagonist; SABA = short-acting beta-agonist; STAR eligible = first fill of medication occurs at least 91 days before index date.

TABLE 4 Logistic Regression Model Predicting Future Adherence Status Using Pharmacy Variables

Independent Variables (Captured During Baseline)	Estimate	Odds Ratio	Lower 95% CI	Upper 95% CI	Chi-Square	P Value
Outcome: Future nonadherence^a among adherent patients at baseline						
Intercept	5.927	–	–	–	557.208	<0.001
Count of pharmacy claims for central nervous system agents (AHFS 28:00)	0.010	1.010	1.008	1.012	86.786	<0.001
MPR ≥80% for pharmacy claims for anticholinergic agents (AHFS 12:08)	–0.288	0.749	0.701	0.802	70.524	<0.001
MPR ≥80% for pharmacy claims for anti-inflammatory agents (AHFS 48:10)	–0.237	0.789	0.740	0.841	52.836	<0.001
MPR for pharmacy claims for adrenals (AHFS 68:04), per 0.10 change	–0.027	0.973	0.964	0.982	37.067	<0.001
≥1 pharmacy claim for antilipemic agents, miscellaneous (AHFS 24:06.92)	–0.387	0.679	0.563	0.819	16.341	<0.001
Count of pharmacy claims for antipsychotic agents (28:16.08)	–0.015	0.985	0.977	0.994	11.154	<0.001
Count of controller medication classes	0.213	1.237	1.187	1.289	100.650	<0.001
Number of units of controller medication	–0.113	0.893	0.885	0.900	700.825	<0.001
CTR, per 0.10 change	0.042	1.043	1.029	1.058	34.593	<0.001
Number of units of ICS	0.070	1.072	1.052	1.093	53.273	<0.001
Number of units of methylxanthine	0.090	1.094	1.074	1.115	87.073	<0.001
Count of pharmacy claims for oral corticosteroids	0.031	1.031	1.015	1.047	15.165	<0.001
PDC for COPD medications, per 0.10 change, pharmacy claims only	–0.566	0.568	0.541	0.595	545.793	<0.001
Count of unique pharmacy claim fill dates for all medications	–0.006	0.994	0.993	0.996	35.368	<0.001
STAR eligible: COPD	–0.847	0.429	0.369	0.498	121.237	<0.001
Count of unique medications	0.016	1.017	1.011	1.022	31.853	<0.001

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to predict future adherence using enrollment and pharmacy variables included 26 covariates (Table 4) and had a validated c-statistic of 0.688 (Table 2).

The c-statistic values for predicting nonadherence were generally lower than those for predicting adherence, suggesting the DAI predicted nonadherence better than adherence. A classification table has been included ([Supplementary Table 3](#)) where the cut point for classification (i.e., which patients to target) can be chosen based on the tradeoff between sensitivity and specificity. The receiver operating characteristics curves are also provided as [Supplementary Figure 2](#) (available in online article).

Discussion

This DAI was developed specifically to predict change in adherence status to long-acting bronchodilator medications among patients with COPD by any health plan with or without access to medical claims. Our findings demonstrate that this DAI can be a useful tool when predicting patient

adherence status in the year ahead. The DAI models performed better for predicting future nonadherence among patients who were adherent at baseline than predicting future adherence among patients who were nonadherent at baseline. A possible explanation for this is that both adherent and nonadherent patients tend toward nonadherence in the future.

The final DAI models that used enrollment, medical, and pharmacy variables were mainly composed of pharmacy- and enrollment-based predictors. As such, pharmacy benefit managers and other organizations with only pharmacy claims data could use these tools to identify patients for adherence intervention programs. This COPD-specific DAI can be easily calculated and could be applied to a health care system for identifying which patients should be proactively targeted for intervention, with the aim of improving and/or maintaining bronchodilator adherence and subsequently improving COPD outcomes. The ability to identify specific patients at greatest risk for nonadherence and/or those who are most likely to become adherent with

TABLE 4 Logistic Regression Model Predicting Future Adherence Status Using Pharmacy Variables (continued)

Independent Variables (Captured During Baseline)	Estimate	Odds Ratio	Lower 95% CI	Upper 95% CI	Chi-Square	P Value
Outcome: Future adherence^b among nonadherent patients at baseline						
Intercept	-0.578	–	–	–	44.222	
≥1 pharmacy claim for smooth muscle relaxants (AHFS 86:00)	-0.255	0.775	0.685	0.876	16.575	<0.001
MPR ≥80% for pharmacy claims for eye, ear, nose, and throat (AHFS 52:00)	0.194	1.215	1.094	1.348	13.348	<0.001
MPR for pharmacy claims for autonomic drugs (AHFS 12:00), per 0.10 change	0.023	1.023	1.012	1.035	16.642	<0.001
MPR for pharmacy claims for skin and mucous membrane agents (AHFS 84:00), per 0.10 change	0.036	1.037	1.022	1.052	23.297	<0.001
≥1 pharmacy claim for adrenals (AHFS 68:04)	-0.248	0.781	0.710	0.858	26.318	<0.001
Count of pharmacy claims for anticholinergic agents (AHFS 12:08)	-0.058	0.943	0.930	0.957	64.492	<0.001
MPR ≥80% for pharmacy claims for beta-adrenergic-blocking agents (AHFS 24:24)	0.120	1.128	1.058	1.202	13.735	<0.001
MPR for pharmacy claims for anticholinergic agents (AHFS 12:08), per 0.10 change	0.061	1.063	1.049	1.078	79.899	<0.001
Count of pharmacy claims for corticosteroids (AHFS 48:10.08)	-0.049	0.952	0.939	0.966	47.390	<0.001
Count of unique AHFS level 3 categories	-0.022	0.978	0.972	0.985	38.455	<0.001
MPR ≥80% for pharmacy claims for corticosteroids (AHFS 48:10.08)	0.346	1.414	1.265	1.580	37.379	<0.001
≥1 pharmacy claim for a medication used to treat COPD	-1.204	0.300	0.269	0.335	458.729	<0.001
Number of units of controller medication	0.123	1.130	1.116	1.145	341.678	<0.001
Number of units of rescue medication	0.026	1.026	1.020	1.033	66.546	<0.001
Number of units of ICS	-0.082	0.921	0.900	0.942	49.953	<0.001
Number of units of methylxanthine	-0.105	0.900	0.877	0.924	63.002	<0.001
≥1 pharmacy claim for a systemic corticosteroid	0.217	1.242	1.130	1.365	20.352	<0.001
Count of unique service dates with claims for COPD medications, pharmacy claims only	-0.031	0.970	0.953	0.987	11.840	<0.001
PDC ≥0.60 for COPD medications, pharmacy claims only	0.480	1.616	1.502	1.739	165.331	<0.001
PDC ≥0.60 for statin medications, pharmacy claims only	0.241	1.273	1.164	1.392	27.866	<0.001
≥1 pharmacy claim for any medication with a 90-day supply	0.148	1.160	1.090	1.234	21.774	<0.001
Pharmacy costs: First quartile vs. fourth quartile	-0.461	0.630	0.566	0.701	71.625	<0.001
Pharmacy costs: Second quartile vs. fourth quartile	-0.319	0.727	0.659	0.801	41.725	<0.001
Pharmacy costs: Third quartile vs. fourth quartile	-0.166	0.847	0.771	0.931	11.945	<0.001
STAR eligible: Statins	-0.167	0.846	0.773	0.926	13.279	<0.001
Geographic division: Mid Atlantic	0.149	1.161	1.066	1.264	11.873	<0.001

^aModel c-statistic = 0.746; validated c-statistic = 0.745.^bModel c-statistic = 0.690; validated c-statistic = 0.688.

AHFS = American Hospital Formulary Service; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CTR = COPD treatment ratio; MPR = medication possession ratio; ICS = inhaled corticosteroid; PDC = proportion of days covered; STAR eligible = first fill of medication occurs at least 91 days before index date.

additional support allows for efficient use of outreach and patient engagement resources as opposed to targeting and engaging much larger nonspecific populations. The idea here would be to run the model on a regular basis, allowing

the identification of the variables that drive adherence. This predictive model therefore offers an opportunity to move on from the current dogma on this topic, namely that “the longer I take a drug, the less likely I am to adhere.”

Previous studies have attempted to identify the reasons for poor adherence in COPD.¹⁰ Overall, nonadherence is a multifactorial issue with socioeconomic, therapy-related, condition-related, health system-related, and patient-related factors.³¹ The frequency of medication administration has been described as an important factor in patient adherence. For example, adherence in COPD was found to decrease with an increasing daily dosing frequency.¹⁵ When examined over the course of a 12-month study, PDC was shown to be 43.3%, 37.0%, 30.2%, and 23.0% for once-daily, twice-daily, 3-times-daily, and 4-times-daily dosing patient cohorts, respectively.¹⁸ Similarly, the use of multiple inhalers has been associated with higher discontinuation rates than the use of a single inhaler in COPD.³² Poor inhaler satisfaction has also been related to poor compliance.^{33,34} The ability to identify patients who are at risk of becoming nonadherent in the future could help us to recognize those who would benefit most from optimal regimen selection. The choice of inhaler and regimen selection is of course important, and the patient should be fully involved in this process. Unfortunately, we did not look specifically at the utility of this model as a function of dosing frequency, treatment duration, or how a change in medications may have influenced results. However, these functions would be of value and worth consideration in future studies assessing the DAI.

Patient education on COPD and inhaler treatments could improve adherence to treatments. A systematic review of 51 observational research studies in asthma found consistent links between stronger inhaler-necessity beliefs and adherence.³⁵ Another study using patient surveys identified age and regular assessment of inhaler technique as factors associated with inhaler adherence in COPD.³⁶ The Real-life Experience and Accuracy of inhaLer use (REAL) survey of 764 patients with COPD found self-reported adherence was significantly lower in patients aged ≤ 65 years compared with older patients.³³ In that study, almost a third of patients (29%) had not received guidance on whether their inhaler technique was correct in the previous 2 years; patients whose technique had been checked during that time period were significantly more adherent than unchecked patients ($P=0.020$).³⁶ Other factors commonly associated with adherence include health literacy, patients' confidence in their physician, and the presence of certain comorbidities.³⁷

Ultimately, this all underlines the point that a DAI is just a tool. It is important we remember that, even with the very best targeting model, patient outcomes are dependent on the strength of available interventions. Although there is presently little research looking at DAIs paired with interventions and their outcomes on care, the known importance of interventions in improving adherence³⁸ suggests that any

tool that can highlight those at risk has the potential to offer value.

LIMITATIONS

This study has some limitations to consider. All variables were defined based on the presence of codes on administrative claims (i.e., medical and pharmacy claims); the presence of a code does not guarantee that the patient has the diagnosis, underwent the procedure, or took the medication. Similarly, missing data and absence of a claim with a code of interest are not distinguishable in claims data.

The results of this analysis are primarily applicable to patients with COPD in stable managed care settings and therefore may not be generalizable to the wider U.S. COPD population. The PDC was calculated using pharmacy claims rather than an actual patient diary/log and may not accurately reflect true adherence. Both the length of time a patient has been diagnosed and how long they have been taking their medication may affect the PDC. It could also be affected by dosing frequency. As these were not part of the study design, their inclusion in future studies could help to improve the models. This analysis was completed for MAPD patients, and no information on plan type/patient-paid costs for medication were included.

Overall, the study looked at individual-level factors that influence adherence, but there may also be larger systemic-level factors at play. The age of this dataset (covering January 1, 2011–August 31, 2016) is another possible limitation. Given that the data presented here are now over 4 years old, its current relevance could be disputed, particularly after the advent of ICD-10.³⁹ However, the methodology and framework for development of a COPD-specific DAI have been detailed and could be replicated using only ICD-10 data. Additionally, the secondary objectives provide an alternative predictive model that is unaffected by the change in diagnosis coding.

Study strengths include that the DAI model relied on claims data, which are readily available to national quality-of-care organizations and payers. In addition, this study utilized a large administrative claims database and therefore included a large sample of COPD patients for DAI development. The very minor decreases in the validated c-statistics suggest that the DAI models are not overfit to the data.

Conclusions

This DAI was developed specifically to predict future adherence status with regard to long-acting bronchodilator medications among patients with COPD. The DAI demonstrated acceptable prediction for both future nonadherence

in adherent patients and future adherence in nonadherent patients. The DAI predicted nonadherence better than adherence. The DAI could be implemented in a health care system to identify which patients should be targeted for interventions aimed at improving and/or maintaining inhaler adherence and outcomes in COPD.

DISCLOSURES

This study was sponsored and funded by GlaxoSmithKline (HO-16-17938). The study sponsor participated in the conception and design of the study, analysis and interpretation of the data, and drafting and critical revision of the report and approved submission of the manuscript. All authors had access to the results of the analyses, reviewed and edited the manuscript, approved the final draft, and were involved in the decision to submit the manuscript for publication.

The data contained in the Optum database contain proprietary elements owned by Optum and, therefore, cannot be broadly disclosed or made publicly available at this time. The disclosure of these data to third parties assumes certain data security and privacy protocols are in place and that the third party has executed a license agreement that includes restrictive agreements governing the use of the data.

Bengtson, Buikema, and Bankcroft are employees at Optum, and Schilling is a former employee of Optum; their employment was not contingent on this work. Optum was funded by GlaxoSmithKline to conduct the study. Stanford was an employee of GlaxoSmithKline at the time of this study and holds stock in GlaxoSmithKline.

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