

# Step-Up Care Improves Impairment in Uncontrolled Asthma: An Administrative Data Study

Robert S. Zeiger, MD, PhD; Michael Schatz, MD, MS; Qiaowu Li, MS; Feng Zhang, MS; Anna S. Purdum, PharmD, MS; and Wansu Chen, MS

**P**oor asthma control impairs health-related quality of life, increases resource utilization and cost, and persists as a major public health issue affecting more than 23 million individuals in the United States.<sup>1</sup> In 2007, direct and indirect costs for asthma totaled \$19.7 billion, with the cost of prescription drugs accounting for most of the direct medical expenses.<sup>1</sup>

The National Asthma Education and Prevention Program<sup>2</sup> and the Global Initiative for Asthma<sup>3</sup> (<http://www.ginasthma.com>) developed guidelines to improve asthma control and to reduce burden. These guidelines emphasize 2 major domains of asthma control: impairment and risk. Impairment refers to rescue medication use, symptoms, nocturnal awakenings, school and work absences, exercise problems, and pulmonary function. Risk addresses frequency and severity of exacerbations, loss of lung function, and adverse effects of medication. In addition, the guidelines established 6 step levels of treatment to implement based on a patient's asthma severity determined before treatment or level of control determined after therapy is instituted. Additional evidence is needed to determine whether appropriate step-up care in patients with uncontrolled asthma improves asthma control in large managed care organizations.

This study used administrative data to identify patients with uncontrolled asthma and their step level of care to determine whether step-up care is associated with improvements in subsequent asthma control. We hypothesized that step-up care instituted after a defined uncontrolled asthma event is associated with improvements in asthma control.

## METHODS

### Study Design

This institutional review board–approved retrospective cohort study was conducted using administrative pharmacy and utilization databases of health plan members of the Kaiser Permanente Southern California Region. The study design is shown in **Figure 1**.

**Determination of the Cohort With Asthma.** Patients were identified as having asthma if they met at least 1 of the following criteria<sup>4</sup> in both 2005

and 2006: (1) any discharge diagnosis of asthma in the health plan and contracting hospital databases (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* code 493.xx);(2) emergency department or

**Objective:** To determine whether step-up care recommended by national asthma guidelines improves asthma control in a large managed care organization.

**Study Design:** Cohort analysis.

**Methods:** A cohort with uncontrolled asthma, defined as impairment or risk in a 1-year consecutive period, was identified using electronic medical records among continuously enrolled patients with asthma aged 12 to 56 years. Guideline-based step level of care was determined 3 months before and 3 months after the index event of uncontrolled asthma according to an algorithm of asthma medication dispensing using electronic pharmacy data. Impairment based on short-acting  $\beta$ -agonist canisters dispensed and risk based on asthma emergency or hospital care were compared during the following year in patients with vs without step-up care, adjusting for demographics, prior utilizations, asthma risk, and comorbidities.

**Results:** Uncontrolled asthma was identified in 7694 eligible patients (mean [SD] age, 35.7 [14.4] years; 54.0% female). Step-up care during the 3-month period after the uncontrolled asthma event was seen in 2160 of 7177 patients (30.1%) with classifiable step care. Step-up care was associated with significant reductions in impairment, with adjusted relative risks of 0.78 (95% confidence interval [CI], 0.73-0.85) during the first 6 months and 0.84 (95% CI, 0.78-0.90) during the full 12-month follow-up period. Emergency or hospital care was unaffected by step-up care. Subgroups with uncontrolled asthma defined by impairment only and risk only showed outcomes generally similar to those of the entire cohort.

**Conclusion:** Guideline-based step-up care in uncontrolled asthma was determined by administrative data and was shown to be associated with significant and clinically meaningful improvements in asthma impairment but not risk.

(*Am J Manag Care* 2010;16(12):897-906)

For author information and disclosures, see end of text.

### In this issue

Take-Away Points / p898

[www.ajmc.com](http://www.ajmc.com)

Full text and PDF

Web exclusive

eAppendices A-E

### Take-Away Points

Determination of national asthma guideline–based step-up care in uncontrolled asthma by administrative data may be useful for improving quality of care in managed care organizations.

- Step-up care after determination of uncontrolled asthma is documented in a minority of patients.
- Greater improvement in the impairment domain (short-acting  $\beta$ -agonist canisters dispensed) of asthma control is seen in patients with uncontrolled asthma receiving step-up asthma care compared with those not receiving step-up asthma care.
- Real-time determination of uncontrolled asthma by administrative data is recommended to identify patients in whom step-up asthma care is needed to improve asthma control.

outpatient asthma-related diagnosis; or (3) at least 2 asthma-related drug dispensings (excluding oral corticosteroids) in the pharmacy database, including  $\beta$ -agonists (excluding oral terbutaline sulfate) and all asthma controller drugs.

**Determination of the Cohort With Uncontrolled Asthma.** Uncontrolled asthma was defined as impairment or risk in a 1-year consecutive period within the first 18 months (January 1, 2005, to June 30, 2006) of the entire 36-month study period (Figure 1).

Impairment was defined as at least 7 short-acting  $\beta$ -agonist (SABA) canisters dispensed in 1 year. In a clinical setting, asthma impairment is defined based on rescue therapy, symptoms, functional limitations, and pulmonary function<sup>2</sup>; however, only rescue therapy use can be obtained in administrative data. We validated the number of SABA canisters dispensed in 1 year as a long-term measure of asthma control because it correlates with patient-reported measures of asthma impairment.<sup>5</sup> The SABA cut point of at least 7 canisters dispensed per year defined impairment because at least 70% more asthma control problems<sup>6</sup> occurred in patients receiving at least 7 vs 6 or fewer canisters dispensed per year.<sup>5</sup>

Risk was captured by at least 2 unique exacerbations within a year. These included asthma-related emergency department visits or hospitalizations (emergency or hospital care was defined as a primary diagnosis of asthma [ICD-9-CM code 493.xx] or as a secondary diagnosis of asthma when the primary diagnosis was related to a respiratory disease) or oral corticosteroid courses with a provider visit for asthma within 2 days of dispensing.

The “index date” of uncontrolled asthma for impairment was the date of the seventh SABA canister dispensing, and the index date for risk was the date of the second exacerbation event during a consecutive 1-year interval within the first 18 months of the study. For patients with both impairment and risk events within the 1-year interval, the date of the last event was used as the index date to determine asthma step care (Figure 1).

Eligible study patients were health plan members aged 12 to 56 years who met the study definition of having uncontrolled

asthma and from 2005 to 2007 were continuously enrolled and had health plan drug benefit. The eligible cohort is shown in Figure 2.

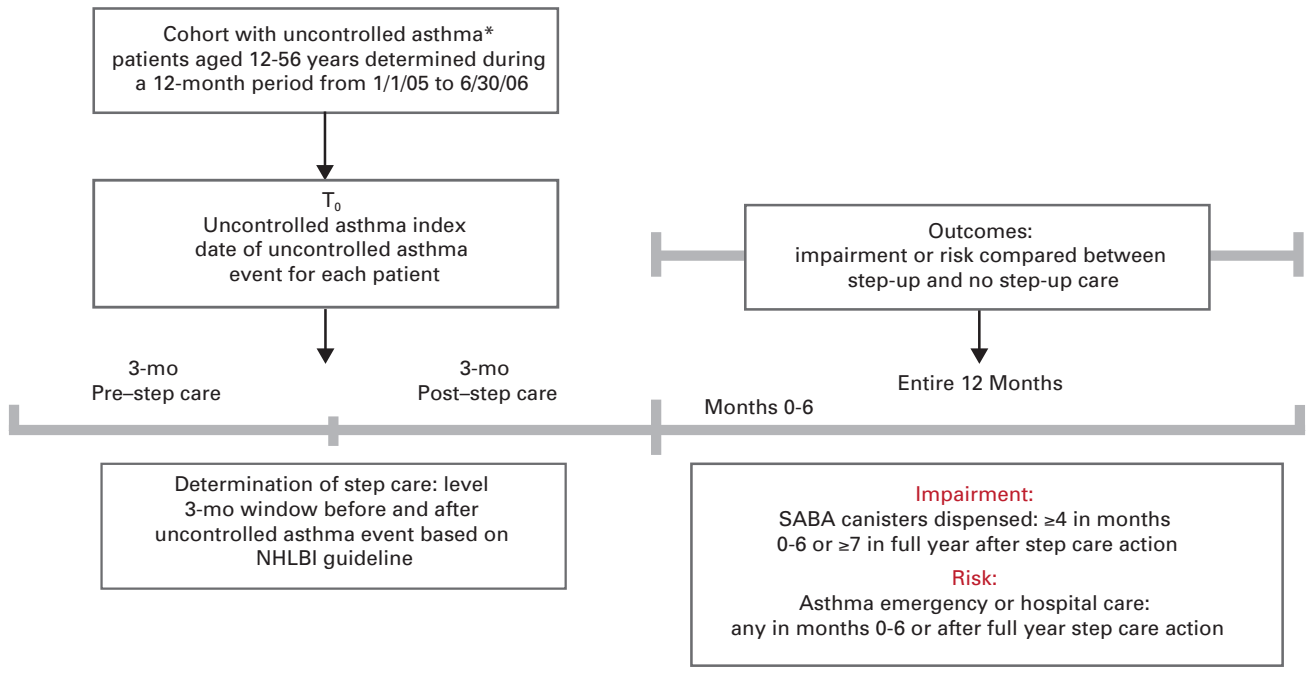
**Step Care.** Asthma drug dispensing was determined using the health plan pharmacy information management system,<sup>4</sup> in which the prescription directions for use, specific drug class and name, and quantities dispensed are available. Daily dosage of inhaled corticosteroid was calculated as the following:  $([\text{No. of Canisters}] \times [\text{No. of Puffs per Canister}] \times [\text{Strength in Micrograms per Puff}]) / \text{No. of Days' Supply}$ .

Inhaled corticosteroids were categorized as low dose, medium dose, or high dose based on the calculated daily dosage and on their individual potency using the estimated comparative daily dosages recommended by National Heart, Lung, and Blood Institute guidelines<sup>2</sup> for persons 12 years or older. Fluticasone propionate plus salmeterol (Advair) was the only combination inhaled corticosteroid and long-acting  $\beta$ -agonist therapy dispensed during step care determination. Strengths of Advair Diskus 100/50, 250/50, and 500/50 were categorized as low-dose, medium-dose, and high-dose inhaled corticosteroid, respectively.

Step level of care was determined using drug dispensing 3 months before and 3 months after the uncontrolled asthma index date based on guidelines for patients 12 years or older as follows<sup>2</sup>: (step 1) no drugs or only SABA dispensed; (step 2) monotherapy low-dose inhaled corticosteroid, leukotriene modifier, mast cell stabilizer, or theophylline; (step 3) (a) combination low-dose inhaled corticosteroid with long-acting  $\beta$ -agonist, leukotriene modifier, mast cell stabilizer, or theophylline or (b) monotherapy medium-dose inhaled corticosteroid; (step 4) (a) combination medium-dose inhaled corticosteroid with long-acting  $\beta$ -agonist, leukotriene modifier, mast cell stabilizer, or theophylline or (b) monotherapy high-dose inhaled corticosteroid; (step 5) high-dose inhaled corticosteroid plus long-acting  $\beta$ -agonist with or without omalizumab; and (step 6) high-dose inhaled corticosteroid plus long-acting  $\beta$ -agonist plus oral corticosteroid with or without omalizumab. Electronic medical records of patients in step 6 were reviewed to determine that the oral corticosteroid dispensed was for maintenance therapy and not for acute use only. Patients were then divided into categories of step-up care or no step-up care based on whether the post–step care was at least 1 step level higher than the pre–step care level. Patients were considered unclassifiable and were excluded from the final analyses when pharmacy data did not allow step classification because of incomplete or missing information.

## Step-Up Care Improves Impairment in Uncontrolled Asthma

■ **Figure 1. Study Design Schemata**



NHLBI indicates National Heart, Lung, and Blood Institute;  $T_0$ , index date of uncontrolled asthma.

\*Cohort with uncontrolled asthma was determined by seventh dispensing of a short-acting  $\beta$ -agonist (SABA) canister or a second asthma exacerbation (asthma emergency or hospital care or oral corticosteroid course associated with a healthcare visit in a 12-month period).

Immunotherapy could not be captured accurately by our electronic databases during the time of the study. Only 4 patients were taking omalizumab during the study and therefore were of inadequate sample size to allow separate analysis.

### Data Analysis

**Patient Demographics.** Patient characteristics were captured by administrative data (Table 1). Census block group levels of family household income and educational attainment estimates in 2006 were supplied by Nielsen Claritas (<http://www.claritas.com>) and were obtained for more than 95% of members through geocoding, a technique that links members' addresses to census geographic areas.<sup>4</sup> Databases did not capture smoking history or race/ethnicity during the study period.

**Outcomes (Comparisons Between Step-Up Care vs No Step-Up Care).** Impairment was defined as at least 7 SABA canisters dispensed in the full year<sup>5</sup> or as at least 4 SABA canisters dispensed in months 0 through 6 after the 3-month post-step care period. Risk was defined as a severe asthma exacerbation requiring asthma emergency or hospital care during the first 6 months and entire year after the 3-month post-step care period. Asthma emergency or hospital care was selected as the risk outcome because it is more specific for asthma risk and

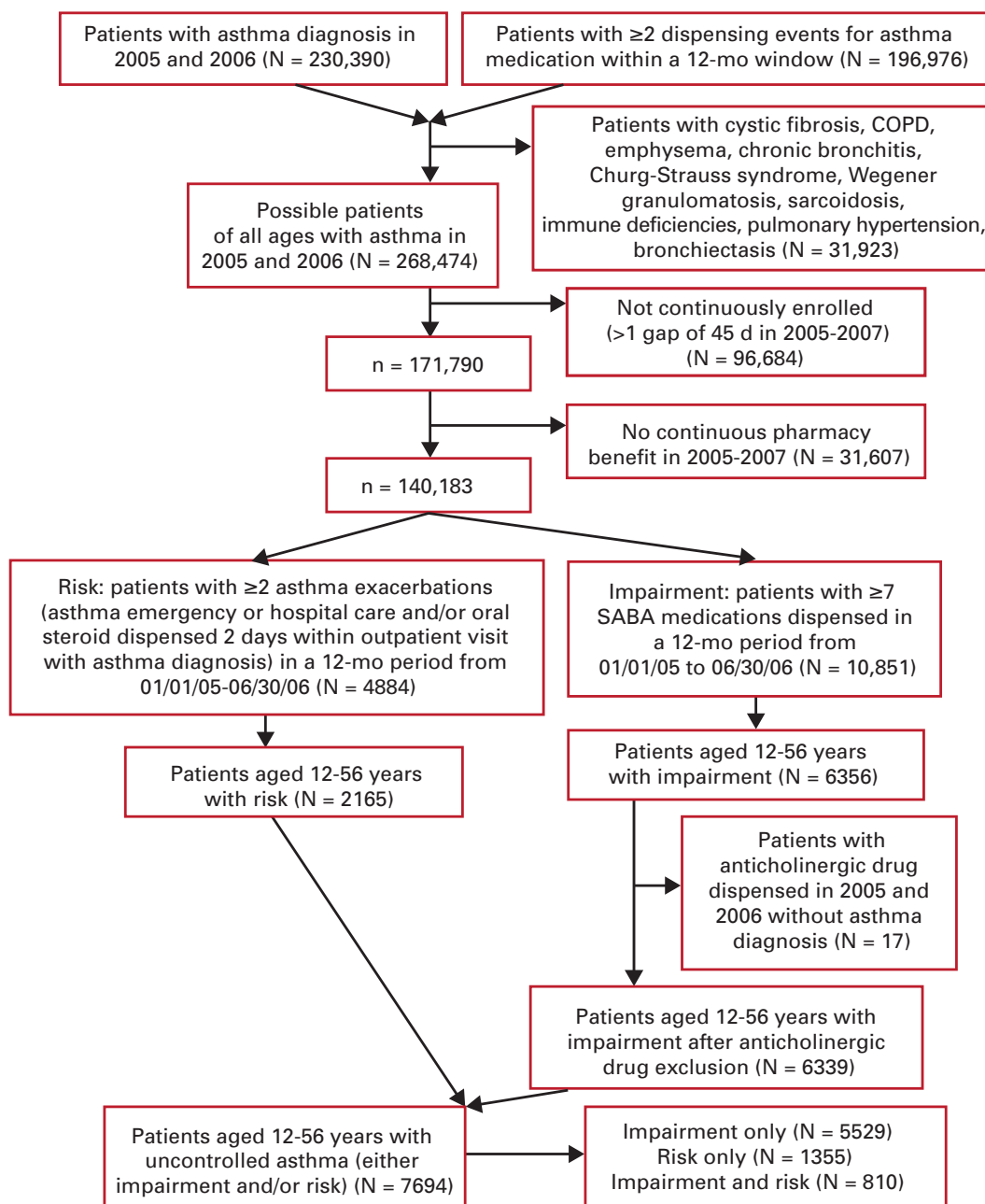
represents more severe exacerbations than oral corticosteroid dispensing; furthermore, the latter is affected by its frequent prophylactic dispensing during routine visits to be used for future worsening asthma.

### Statistical Analysis

Descriptive analyses for individual resource use items entered as a dichotomous variable (eg,  $\geq 7$  SABA canisters dispensed [yes or no]) or as a count variable (eg, the number of SABA canisters dispensed) were conducted to illustrate their association with step care. Counts and proportions were obtained for categorical variables, and the mean (SD) and median (range) were used for continuous variables. Bivariate associations were assessed as appropriate by  $t$  test, analysis of variance,  $\chi^2$  test, or nonparametric methods (eg, Wilcoxon rank sum test and Kruskal-Wallis analysis of variance). Significance was set at 2-tailed  $P < .05$ .

Univariate and multivariate Poisson regression analyses with a robust error variance (SAS/GENMOD) were constructed to calculate the unadjusted and adjusted relative risk (RR) and the 95% confidence interval [CI] for the outcome variables, as this type of regression model provides better estimates in health investigations involving common binary outcomes (prevalence rate  $>10\%$ ) than logistic regression.<sup>7,8</sup> All

■ **Figure 2.** Consort Diagram



Consort diagram for determination by administrative data of uncontrolled asthma in patients aged 12 to 56 years enrolled in the Kaiser Permanente Southern California region who met the study eligibility criteria in 2005 and 2006. Patients with the following diagnoses in 2005 and 2006 were excluded: any diagnosis for cystic fibrosis, chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, Churg-Strauss syndrome, Wegener granulomatosis, sarcoidosis, immune deficiencies, pulmonary hypertension, or bronchiectasis, as well as the use of inhalational anticholinergic drugs (ipratropium bromide or tiotropium bromide) without an asthma diagnosis. The consort diagram does not allow determination of the rate of uncontrolled asthma in the group aged 12 to 56 years, as age for uncontrolled asthma can only be determined at the time of the uncontrolled event. The 140,183 patients noted in the figure are patients of all ages with asthma. Of these patients, we could identify 70,426 patients aged 12 to 56 years (using January 1, 2005, to determine age for a population analysis) who met the study eligibility criteria for asthma before determination of their asthma control status. Therefore, as an estimate, the incidence of uncontrolled asthma among the patients aged 12 to 56 years with asthma is 10.9% (7694 of 70,443). SABA indicates short-acting  $\beta$ -agonist.

## Step-Up Care Improves Impairment in Uncontrolled Asthma

**Table 1.** Characteristics of the Total Cohort With Uncontrolled Asthma and Its Subgroups in the Year Before the Index Event of Uncontrolled Asthma or at the Index Date

Characteristic	Total Cohort (N = 7694)	Impairment Only (n = 5529)	Risk Only (n = 1355)	Risk and Impairment (n = 810)	PValue <sup>a</sup>
Age, mean (SD), y	<b>35.7</b> (14.4)	35.4 (14.3)	37.2 (14.4)	35.3 (14.7)	<.001
Female sex, No. (%)	<b>4153</b> (54.0)	2711 (49.0)	950 (70.1)	492 (60.7)	<.001
Geocoded median household income, mean (SD), \$	(N = 7532) <b>58,579</b> (25,021)	(n = 5405) 59,279 (25,084)	(n = 1331) 57,526 (25,361)	(n = 796) 55,585 (23,731)	<.001
Geocoded educational attainment of high school graduation or less, mean (SD), %	(N = 7528) <b>24.7</b> (18.1)	(n = 5402) 23.8 (17.8)	(n = 1330) 27.2 (19.2)	(n = 796) 26.6 (17.9)	<.001
Medicare, No. (%)	<b>134</b> (1.7)	104 (1.9)	13 (1.0)	17 (2.1)	<.05
Medicaid, No. (%)	<b>227</b> (3.0)	144 (2.6)	46 (3.4)	37 (4.6)	<.01
Private pay, No. (%)	<b>572</b> (7.4)	453 (8.2)	78 (5.8)	41 (5.1)	<.001
Health plan member, mean (SD), y	(N = 7680) <b>13.6</b> (8.4)	(n = 5520) 13.9 (8.4)	(n = 1353) 12.9 (8.5)	(n = 807) 12.8 (7.9)	<.001
Any nonasthma emergency de- partment visit, No. (%)	<b>2319</b> (30.1)	1309 (23.7)	595 (43.9)	415 (51.2)	<.001
Outpatient visits, mean (SD)	<b>10.3</b> (12.4)	8.8 (11.6)	14.1 (13.4)	14.2 (13.7)	<.001
Step care level before the index date of uncontrolled asthma, No. (%)					<.001
1	<b>4296</b> (55.8)	3309 (59.8)	671 (49.5)	316 (39.0)	
2	<b>700</b> (9.1)	500 (9.0)	106 (7.8)	94 (11.6)	
3	<b>1330</b> (17.3)	918 (16.6)	257 (19.0)	155 (19.1)	
4	<b>807</b> (10.5)	531 (9.6)	151 (11.1)	125 (15.4)	
5	<b>242</b> (3.1)	145 (2.6)	41 (3.0)	56 (6.9)	
6	<b>122</b> (1.6)	51 (0.9)	26 (1.9)	45 (5.6)	
Unclassified	<b>197</b> (2.6)	75 (1.4)	103 (7.6)	19 (2.3)	
Any asthma emergency or hospi- tal care, No. (%)	<b>1045</b> (13.6)	287 (5.2)	426 (31.4)	332 (41.0)	<.001
Any oral corticosteroid course plus asthma visit, No. (%)	<b>2967</b> (38.6)	939 (17.0)	1277 (94.2)	751 (92.7)	<.001
Asthma risk stratification, No. (%)					<.001
Low	<b>3794</b> (49.3)	3794 (68.6)	0	0	
Medium	<b>2614</b> (34.0)	1319 (23.9)	929 (68.6)	366 (45.2)	
High	<b>1286</b> (16.7)	416 (7.5)	426 (31.4)	444 (54.8)	
Any allergy or pulmonary visit, No. (%)	<b>1575</b> (20.5)	918 (16.6)	368 (27.2)	289 (35.7)	<.001
SABA canisters dispensed, mean (SD)	<b>9.4</b> (5.4)	10.6 (4.5)	2.7 (1.8)	12.4 (6.4)	<.001
≥15 SABA canisters dispensed, No. (%)	<b>960</b> (12.5)	748 (13.5)	0	212 (26.2)	...
SABA indicates short-acting β-agonist.					
<sup>a</sup> Comparisons between the 3 subgroups by analysis of variance.					

**Table 2.** Frequencies of Step-Up Care and No Step-Up Care During the 3-Month Period Immediately After the Index Event of Uncontrolled Asthma in the Total Cohort With Uncontrolled Asthma and Its Subgroups<sup>a</sup>

Variable	No. (%)			
	Total Cohort (N = 7177)	Impairment Only (n = 5437)	Risk Only (n = 983)	Risk and Impairment (n = 757)
Step-up care	2160 (30.1)	1464 (26.9)	461 (46.9)	235 (31.0)
No step-up care	5017 (69.9)	3973 (73.1)	522 (53.1)	522 (69.0)

<sup>a</sup>Patients in whom step care could not be classified were excluded. *P* < .001 for comparison between subgroups.

point estimates and 95% CIs were generated using SAS software (version 9.1 for Windows; SAS Institute, Cary, North Carolina).

The following covariates were available for selection for the multivariate models: (1) baseline variables, including age at the time of the uncontrolled asthma index event, sex, and geocoded educational and income attainment; (2) prior-year variables, including number of SABA canisters dispensed, asthma exacerbations (any asthma emergency or hospital care or any asthma oral corticosteroid dispensing determined<sup>9,11</sup>), total nonasthma emergency department visits and outpatient visits,<sup>4</sup> allergy or pulmonary specialist visits,<sup>10,11</sup> and comorbidities (gastroesophageal reflux disease, sinusitis, and nasal polyposis); and (3) the pre-index date step level of care. Covariates were selected according to Akaike information criterion by means of stepAIC function in R statistical software version 2.9.0 (<http://www.r-project.org>).

## RESULTS

### Cohort With Uncontrolled Asthma

A total of 7694 patients aged 12 to 56 years with uncontrolled asthma were eligible for the study based on asthma impairment or risk definitions (Figure 2). Of these patients with uncontrolled asthma, 5529 (71.9%) were identified as having asthma impairment only, 1355 (17.6%) as having asthma risk only, and 810 (10.5%) as having both asthma impairment and risk.

**Demographics.** The mean patient age was 35.7 years of age, 54.0% were female, and patients were health plan members on average for more than a decade (Table 1). About three-quarters had more than a high school education, and the cohort was middle class by mean income. Compared with the impairment-only subgroup, the risk-only and risk and impairment subgroups had significantly more women, less education and income, and more subsidized insurance.

**Asthma Burden.** Among the cohort, half of the patients met criteria for medium-to-high risk stratification asthma cat-

egories,<sup>9</sup> and slightly less were in step 2 or higher care. During the year before the uncontrolled asthma index date, frequencies were 13.6% for asthma emergency or hospital care, 38.6% for oral corticosteroid courses, and 12.5% for 15 or more SABA canisters dispensed<sup>9</sup> (Table 1). Compared with the impairment-only subgroup, the risk-only and risk and impairment subgroups had statistically more asthma burden.

**Comorbidities.** Respiratory and allergy comorbidities were common, with frequencies of 20.5% for allergic rhinitis, 15.4% for sinusitis, and 8.2% for gastroesophageal reflux disease (eAppendix A available at [www.ajmc.com](http://www.ajmc.com)). Most respiratory comorbidities occurred significantly less frequently in the impairment-only subgroup than in the risk-only and risk and impairment subgroups.

### Step Care Changes

Of 7694 patients with uncontrolled asthma, 7177 (93.3%) were classified as receiving step 1 to step 6 care based on pharmacy databases (Table 2). In the total classifiable cohort, 2160 (30.1%) received step-up care during the 3-month period after the uncontrolled asthma index event. Patients with uncontrolled asthma by impairment only received step-up care significantly less frequently (26.9%) than those with uncontrolled asthma by risk only (46.9%). Step-up care most frequently was from step level 1 than from the other levels among the cohort with uncontrolled asthma and its subgroups (eAppendix B).

### Characteristics of the Cohort Relative to Step Care Changes

Compared with patients without step-up care, those with step-up care were similar demographically but had significantly higher asthma risk stratification, greater asthma and nonasthma healthcare utilization, more sinusitis, and fewer SABA canisters dispensed in the year before the uncontrolled asthma index event (Table 3). Among the subgroups with uncontrolled asthma, small but significant differences in some prior-year characteristics occurred between patients with step-up care vs no step-up care (eAppendix C).



## Step-Up Care Improves Impairment in Uncontrolled Asthma

**Table 3.** Characteristics of the Total Cohort With Uncontrolled Asthma With vs Without Step-Up Care in the Year Before the Index Event of Uncontrolled Asthma or at the Index Date<sup>a</sup>

Characteristic	Step-Up Care (n = 2160)	No Step-Up Care (n = 5017)
Age, mean (SD), y	35.4 (14.3)	35.6 (14.4)
Female sex, No. (%)	1161 (53.8)	2638 (52.6)
Geocoded median household income, mean (SD), \$	(n = 2114) 58,887 (24,654)	(n = 4906) 58,493 (25,043)
Geocoded educational attainment of high school graduation or less, mean (SD), %	(n = 2113) 24.4 (18.0)	(n = 4904) 24.7 (18.2)
Medicare, No. (%)	29 (1.3)	95 (1.9)
Medicaid, No. (%)	69 (3.2)	141 (2.8)
Private pay, No. (%)	145 (6.7)	390 (7.8)
Health plan member, mean (SD), y	(n = 2153) 13.4 (8.2)	(n = 5010) 13.6 (8.4)
Any nonasthma emergency department visit, No. (%)	675 (31.3) <sup>b</sup>	1431 (28.5)
Outpatient visits, mean (SD)	9.9 (11.1)	10.0 (12.7)
Any asthma emergency or hospital care, No. (%)	334 (15.5) <sup>c</sup>	588 (11.7)
Any oral corticosteroid course plus asthma visit, No. (%)	921 (42.6) <sup>c</sup>	1599 (31.9)
Asthma risk stratification, No. (%)		
Low	988 (45.7) <sup>c</sup>	2765 (55.1)
Medium	781 (36.2)	1485 (29.6)
High	391 (18.1)	767 (15.3)
Any allergy or pulmonary visit, No. (%)	441 (20.4)	986 (19.7)
SABA canisters dispensed, mean (SD)	8.9 (5.4) <sup>c</sup>	10.1 (5.1)
≥15 SABA canisters dispensed, No. (%)	227 (10.5) <sup>c</sup>	711 (14.2)
Step care level before the index date of uncontrolled asthma, No. (%)		
1	1752 (81.1) <sup>c</sup>	2385 (47.5)
2	198 (9.2)	478 (9.5)
3	144 (6.7)	1101 (21.9)
4	48 (2.2)	718 (14.3)
5	18 (0.8)	218 (4.3)
6	0	117 (2.3)
Gastroesophageal reflux disease, No. (%)	156 (7.2)	415 (8.3)
Sinusitis, No. (%)	348 (16.1) <sup>b</sup>	696 (13.9)
Nasal polyps, No. (%)	20 (0.9)	41 (0.8)

SABA indicates short-acting β-agonist.

<sup>a</sup>Patients in whom step care could not be classified were excluded.

<sup>b</sup> $P < .05$ .

<sup>c</sup> $P < .001$ .

### Impairment and Risk Outcomes

*Univariate Analyses.* For 7177 patients having uncontrolled asthma with classifiable step care, at least 4 SABA canisters were dispensed at a frequency of 35.9% in months 0 through 6, and at least 7 SABA canisters were dispensed at a frequency of 39.7% for the entire follow-up year after step care

([eAppendix D](#)). The incidence of any asthma emergency or hospital care was 4.2% in months 0 through 6 and 7.0% for the entire follow-up year after step care. The incidences of SABA canisters dispensed and subsequent emergency or hospital care were highest in the risk and impairment subgroup. Compared with no step-up care, step-up care was associated

**Table 4.** Poisson Regression Analyses of Impairment and Risk Outcomes Up to 1 Year After Step-Up Care Compared With No Step-Up Care in the Total Cohort With Uncontrolled Asthma and Its Subgroups<sup>a</sup>

Variable	Relative Risk (95% Confidence Interval)							
	Total Cohort (N = 7177)		Impairment Only (n = 5437)		Risk Only (n = 983)		Risk and Impairment (n = 757)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Impairment								
≥4 SABA canisters dispensed in months 0-6	<b>0.73</b> (0.68-0.79)	<b>0.78</b> (0.73-0.85)	<b>0.80</b> (0.74-0.86)	<b>0.81</b> (0.75-0.88)	<b>0.52</b> (0.31-0.89)	<b>0.56</b> (0.33-0.95)	0.96 (0.81-1.13)	0.95 (0.80-1.12)
≥7 SABA canisters dispensed in the full year	<b>0.78</b> (0.73-0.83)	<b>0.84</b> (0.78-0.90)	<b>0.85</b> (0.79-0.91)	<b>0.86</b> (0.80-0.93)	<b>0.55</b> (0.32-0.95)	0.65 (0.37-1.12)	1.04 (0.91-1.20)	1.03 (0.90-1.19)
<b>Risk</b>								
Any asthma emergency or hospital care in months 0-6	<b>1.29</b> (1.03-1.63)	1.20 (0.95-1.51)	1.24 (0.88-1.74)	1.19 (0.84-1.68)	0.66 (0.37-1.16)	0.75 (0.43-1.31)	<b>1.58</b> (1.10-2.27)	<b>1.43</b> (1.02-2.01)
Any asthma emergency or hospital care in the full year	1.19 (0.99-1.42)	1.11 (0.93-1.32)	1.17 (0.91-1.52)	1.17 (0.90-1.52)	0.72 (0.48-1.08)	0.85 (0.57-1.26)	1.30 (0.97-1.74)	1.18 (0.90-1.54)

<sup>a</sup>Variables used for adjustment include the following: (a) at the index date of uncontrolled asthma, age, sex, and geocoded educational attainment; (b) at 1 year before the index date of uncontrolled asthma, asthma emergency or hospital care in the year before the index event, oral corticosteroid course plus asthma visit, short-acting β-agonist (SABA) canisters dispensed, nonasthma emergency department visits, outpatient visits, allergy or pulmonary visits, gastroesophageal reflux disease, sinusitis, and nasal polyps; and (c) at 3 months before the index date of uncontrolled asthma, pre-index date step care. Patients in whom step care could not be classified were excluded. Boldface indicates statistical significance.

with reduced impairment (SABA canisters dispensed) for up to 1 year for the total cohort with uncontrolled asthma and its impairment-only and risk-only subgroups (eAppendix D). The rates for 2 or more emergency or hospital care events were statistically similar at 2.5% for step up therapy and 2.0% for no step-up therapy; there were no significant differences in step-up therapy vs no step-up therapy among subgroups of the cohort (data not shown).

**Poisson Regression Analyses.** Unadjusted and adjusted RRs and 95% CIs comparing step-up care vs no step-up care are given for impairment (SABA canisters dispensed) and risk (asthma emergency or hospital care) during the outcome period (Table 4). Adjustments generally reduced RR effect size mildly but not the direction of effect for impairment and risk outcomes.

**Impairment.** In the total cohort with uncontrolled asthma, step-up care (vs no step-up care) was associated with a significant reduction in impairment during the outcome periods of months 0 through 6 (adjusted RR, 0.78; 95% CI, 0.73-0.85) and the full year (adjusted RR, 0.84; 95% CI, 0.78-0.90) (Table 4). In adjusted analyses, impairment was significantly

reduced in the impairment-only subgroup at both periods and in the risk-only subgroup at months 0 through 6. No effect on impairment was observed in the risk and impairment subgroup.

**Risk.** In the total cohort with uncontrolled asthma and its impairment-only and risk-only subgroups, risk of any asthma emergency or hospital care was unaffected by step-up care in the adjusted model for the outcome periods of months 0 through 6 or the full year (Table 4). In the risk and impairment subgroup, there was a weak significant increase in asthma emergency or hospital care in months 0 through 6 but not in the full year.

## DISCUSSION

To our knowledge, this is the first study to use administrative databases to determine among patients with uncontrolled asthma the relationship of asthma step-up care to subsequent asthma control. In the total cohort with uncontrolled asthma, step-up care within 3 months of an uncontrolled asthma event was associated in the adjusted model with a significant and



## Step-Up Care Improves Impairment in Uncontrolled Asthma

meaningful 16% to 22% improvement in impairment as assessed by SABA dispensing within 6 months and lasting for at least 1 year (Table 4). The improvement in impairment was also seen in the impairment-only and risk-only subgroups, with a greater effect size at the 6-month follow-up in the latter.

Step-up care was unassociated with reduced asthma risk as measured by asthma emergency or hospital care in the entire cohort with uncontrolled asthma. There was an inconsistent increase in risk seen at 6 months but not at other times in the risk and impairment subgroup, which had the highest level of asthma risk stratification (Table 1). The frequency of 2 or more emergency or hospital care events in the outcome year was low, similar between those with step-up care vs no step-up care, but was of insufficient power to allow accurate analysis. These findings are consistent with the primary analyses (Table 4), which showed that step-up therapy did not affect asthma risk as assessed by at least 1 emergency or hospital care event in the outcome period of months 0 through 6. We consider the frequency of 1 asthma emergency or hospital care event in the first 6 months after step care determination to represent “risk” as defined in the National Asthma Education and Prevention Program guidelines,<sup>2</sup> as this would be prorated to 2 in 12 months, which is the frequency of exacerbations considered to represent uncontrolled asthma risk in the guidelines. In the clinical assessment of patients, medication adjustments would generally be recommended if a patient develops an asthma emergency or hospital care event within 6 months of a visit or a change in medical care. Possible reasons for a lack of effect on risk between groups include the challenge in administrative studies to adequately control for asthma severity<sup>9,12</sup> or the need for more intensive interventions than those measured by step-up care in administrative data. Observational investigations in severe or difficult-to-treat asthma document a high frequency of severe asthma exacerbations, despite up to 3 controller drugs and asthma specialist care.<sup>13</sup> The challenge in reducing exacerbations is seen in clinical trials in which up to 30% of children and adolescents with persistent asthma using inhaled corticosteroids experience acute asthma exacerbations.<sup>14</sup> In addition, step-up care was considerably less frequent in patients already receiving higher-level step care (eAppendix E), which might indicate that clinicians are reluctant to increase from already high step care levels.

These findings suggest that greater implementation of step-up care could have a greater effect on improving asthma control. In fact, a higher frequency of step-up care in the risk-only subgroup (46.9% of patients) compared with the impairment-only subgroup (26.9% of patients) was associated with a greater reduction in impairment compared with no step-up care (lower RRs) during months 0 through 6 (Table 2). Moreover, the risk-only subgroup was the only subgroup to show

a consistent, although nonsignificant, numerical reduction in emergency or hospital care (Table 4). The opportunity to institute step-up care was also greater in the risk-only subgroup compared with the impairment-only subgroup, as the date of determination of uncontrolled asthma risk was associated with a visit in real time, while the date of determination of asthma impairment was assessed by administrative data not necessarily associated with a visit.

Asthma management programs follow national guidelines; however, routine determination of uncontrolled asthma status is neither optimally determined nor assessed in real time for population management. Episodic asthma therapy facilitates step-up care directed at exacerbations (risk) but not impairment.<sup>15</sup> As already noted, the present study confirms that only a minority of patients are stepped up within 3 months of a defining uncontrolled asthma event based on impairment only, but almost half are stepped up owing to risk (Table 2). Providers do not routinely assess exact numbers of SABA canisters dispensed, although evidence shows that increased SABA use is associated with poorer quality of life and with greater healthcare resource utilization.<sup>5,16-19</sup>

The major limitation of our study is potential residual confounding by severity that is inherent in administrative studies, despite extensive adjustments. We were unable to adjust for race/ethnicity or smoking history because the databases did not have complete profiles. As in our other investigations, we used geocoded household education and income as proxies. Moreover, the algorithm used to classify step care in administrative data was based on recommendations in the Expert Panel report 3 guidelines,<sup>2</sup> but its accuracy has not been validated against patient report. The large sample size of the total cohort with uncontrolled asthma was adequate for the primary analyses; however, sample sizes of the subgroups may have been insufficient to accurately determine the effect size of step-up care in the subgroups.

Objective measures such as spirometry are rarely captured in electronic databases and were unavailable in the present study.<sup>20</sup> Nonetheless, the criterion used to define asthma in this study, “physician-diagnosed asthma,” recorded as ICD-9-CM coding for asthma and pharmacy dispensing of asthma drugs, represents a valid way to identify patients with asthma in epidemiologic studies in managed care organizations.<sup>21,22</sup> Adherence was not assessed during the outcome period so as not to confound its effect on step-up care. We did not adjust for multiple comparisons because epidemiologists and health services researchers have differences of opinion regarding the importance of adjusting for multiple comparisons in prespecified retrospective data analyses.<sup>23</sup>

In summary, within the limitations inherent in retrospective administrative studies, the present study developed ad-

ministrative data logistics to determine uncontrolled asthma based on National Heart, Lung, and Blood Institute guidelines<sup>2</sup> and levels of asthma step care and demonstrated that step-up care was associated with significant and clinically meaningful improvements in asthma impairment in a large managed care organization. These findings support national guidelines that recommend step-up in asthma care to improve asthma control and emphasize the need to enhance implementation of such recommendations in real time when uncontrolled asthma status is determined by administrative data. This proactive approach is particularly relevant because multiple and often differing patient factors influence clinicians to adjust asthma therapy.<sup>24,25</sup>

#### Acknowledgment

We recognize and thank Michael S. Broder, MD, and Eunice Chang, PhD, from Partnership for Health Analytic Research LLC (Beverly Hills, California) for their assistance in determining the step care algorithm by administrative data and for general guidance in conducting the study.

**Author Affiliations:** From the Department of Allergy (RSZ, MS), Kaiser Permanente Medical Center, San Diego, CA; Department of Research and Evaluation (QL, FZ, WC), Kaiser Permanente Southern California, Pasadena, CA; and Genentech, Inc (ASP), San Francisco, CA.

**Funding Source:** The study was supported by an investigational grant to the Department of Research and Evaluation, Kaiser Permanente Southern California, from Genentech, Inc. The protocol was developed by Kaiser Permanente Southern California research group. The sponsor approved the protocol, with suggestions. Kaiser Permanente Southern California performed data collection, extraction, and analysis and wrote the manuscript.

**Author Disclosures:** Dr Zeiger reports serving as a paid consultant for Aerocrine, AstraZeneca, Genentech, GlaxoSmithKline, MedImmune, Merck, and Schering. Dr Zeiger also reports receiving grants from Aerocrine, Genentech, GlaxoSmithKline, and Merck. Dr Schatz reports serving as a paid research consultant for Amgen and Merck and receiving grants from Aerocrine, Genentech, GlaxoSmithKline, and Merck. Dr Purdum is employed by Genentech, Inc, the source of funding for this study. The other authors (QL, FZ, WC) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

**Authorship Information:** Concept and design (RSZ, MS, ASP); acquisition of data (RSZ); analysis and interpretation of data (RSZ, MS, QL, FZ, ASP, WC); drafting of the manuscript (RSZ, QL); critical revision of the manuscript for important intellectual content (RSZ, MS, FZ, WC); statistical analysis (RSZ, MS, QL, FZ, WC); obtaining funding (ASP); administrative, technical, or logistic support (MS); and supervision (RSZ).

**Address correspondence to:** Robert S. Zeiger, MD, PhD, Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Blvd, San Diego, CA 92111. E-mail: robert.s.zeiger@kp.org.

## REFERENCES

- 1. Epidemiology and Statistics Unit, Research and Program Services Division, American Lung Association.** Trends in asthma morbidity and mortality, February 2010. <http://www.lungusa.org/finding-cures/our-research/trend-reports/asthma-trend-report.pdf>. Accessed November 3, 2010.
- 2. National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute.** Expert Panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. Accessed November 3, 2010.

- 3. National Institutes of Health.** *Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2006. NIH publication 02-3659.
- 4. Zeiger RS, Hay JW, Contreras R, et al.** Asthma costs and utilization in a managed care organization. *J Allergy Clin Immunol.* 2008;121(4):885-892.e5.
- 5. Schatz M, Zeiger RS, Vollmer WM, et al.** Validation of a  $\beta$ -agonist long-term asthma control scale derived from computerized pharmacy data. *J Allergy Clin Immunol.* 2006;117(5):995-1000.
- 6. Vollmer WM, Markson LE, O'Connor E, Frazier EA, Berger M, Buist AS.** Association of asthma control with health care utilization: a prospective evaluation. *Am J Respir Crit Care Med.* 2002;165(2):195-199.
- 7. Zou G.** A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* 2004;159(7):702-706.
- 8. Barros AJ, Hirakata VN.** Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol.* 2003;3:e21.
- 9. Schatz M, Nakahiro R, Jones CH, Roth RM, Joshua A, Petitti D.** Asthma population management: development and validation of a practical 3-level risk stratification scheme. *Am J Manag Care.* 2004;10(1):25-32.
- 10. Schatz M, Cook EF, Nakahiro R, Petitti D.** Inhaled corticosteroids and allergy specialty care reduce emergency hospital use for asthma. *J Allergy Clin Immunol.* 2003;111(3):503-508.
- 11. Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M.** Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits [published correction appears in *J Allergy Clin Immunol.* 1991;90(2):278]. *J Allergy Clin Immunol.* 1991;87(6):1160-1168.
- 12. Covar RA, Szefer SJ, Zeiger RS, et al.** Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol.* 2008;122(4):741-747.e4.
- 13. Zeiger RS, Chipps BE, Haselkorn T, Rasouliyan L, Simons FE, Fish JE.** Comparison of asthma exacerbations in pediatric and adult patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol.* 2009;124(5):1106-1108.
- 14. Childhood Asthma Management Program Research Group.** Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med.* 2000;343(15):1054-1063.
- 15. Yawn BP, Wollan PC, Bertram SL, et al.** Asthma treatment in a population-based cohort: putting step-up and step-down treatment changes in context. *Mayo Clin Proc.* 2007;82(4):414-421.
- 16. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R.** Inhaled steroids and the risk of hospitalization for asthma. *JAMA.* 1997;277(11):887-891.
- 17. Schatz M, Nakahiro R, Crawford W, Mendoza G, Mosen D, Stibolt TB.** Asthma quality-of-care markers using administrative data. *Chest.* 2005;128(4):1968-1973.
- 18. Lieu TA, Quesenberry CP, Sorel ME, Mendoza GR, Leong AB.** Computer-based models to identify high-risk children with asthma. *Am J Respir Crit Care Med.* 1998;157(4, pt 1):1173-1180.
- 19. Senthilselvan A, Lawson JA, Rennie DC, Dosman JA.** Regular use of corticosteroids and low use of short-acting  $\beta$ 2-agonists can reduce asthma hospitalization. *Chest.* 2005;127(4):1242-1251.
- 20. Macy E, Schatz M, Gibbons C, Zeiger R.** The prevalence of reversible airflow obstruction and/or methacholine hyperreactivity in random adult asthma patients identified by administrative data. *J Asthma.* 2005;42(3):213-220.
- 21. Wang SW, Liu X, Wiener DJ, Sennett C, Bowers BW, Legorreta AP.** Comparison of prevalence, cost, and outcomes of a combination of salmeterol and fluticasone therapy to common asthma treatments. *Am J Manag Care.* 2001;7(9):913-922.
- 22. Orsini L, Limpa-Amara S, Crown WH, Stanford RH, Kamal K.** Asthma hospitalization risk and costs for patients treated with fluticasone propionate vs montelukast. *Ann Allergy Asthma Immunol.* 2004;92(5):523-529.
- 23. Rothman KJ.** No adjustments are needed for multiple comparisons. *Epidemiology.* 1990;1(1):43-46.
- 24. Diette GB, Patino CM, Merriman B, et al.** Patient factors that physicians use to assign asthma treatment. *Arch Intern Med.* 2007;167(13):1360-1366.
- 25. Okelo SO, Patino CM, Riekert KA, et al.** Patient factors used by pediatricians to assign asthma treatment. *Pediatrics.* 2008;122(1):e195-e201. ■