

ASTHMA CONTROL

Development and Preliminary Validation of the Asthma Intensity Manifestations Score (AIMS) Derived from Asthma Control Test, FEV₁, Fractional Exhaled Nitric Oxide, and Step Therapy Assessments

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Objective. Inherent asthma severity is difficult to assess clinically. The purpose of this study was to develop an Asthma Intensity Manifestations Score (AIMS) as a surrogate for asthma severity. **Methods.** Three hundred and four patients treated with inhaled corticosteroids completed the Asthma Control Test (ACT), underwent spirometry, and fractional exhaled nitric oxide (FENO) testing, and reported their current medications. These parameters (defined as ACT < 16, forced expiratory volume in 1 second [FEV₁] < 80% predicted, FENO > 50 ppb, and Expert Panel Report [EPR3] step care level > 3) were related to prior year outcomes to develop the AIMS and to follow-up year outcomes to validate it. **Results.** FENO was independently related to prior year short-acting beta agonist (SABA) ≥ 7 (odds ratio [OR] 2.9); ACT (OR 4.9), FEV₁ (OR 3.3), and step care (OR 3.9) were independently related to prior year systemic corticosteroid (SCS) ≥ 2. Thus, all the four items were chosen for the AIMS (0–4 points). AIMSs were linearly related to follow-up year SABA ≥ 7, any SCS, SCS ≥ 2, and emergency hospital care (all *p* < .01). Compared to patients with AIMSs < 2, patients with AIMSs ≥ 2 were at more than a fourfold greater risk of requiring ≥ 2 SCS in the following year and were at a 2–2.8-fold greater risk of experiencing other adverse outcomes during that time period. **Conclusions.** The AIMS is linearly related to future year adverse asthma outcomes. Further studies will be necessary to confirm its utility as a surrogate for asthma severity in clinical practice and clinical research.

Keywords asthma control, asthma exacerbations, asthma impairment, asthma risk, asthma severity, exhaled nitric oxide, spirometry

INTRODUCTION

Asthma severity and asthma control are separate constructs (1), but differentiating and applying them clinically has sometimes created confusion. The recent Expert Panel Report (EPR3) (1) defined asthma *severity* as the inherent intensity of the disease process and asthma *control* as the degree to which the clinical manifestations of the disease process are being mitigated. As defined in the EPR3, control can be empirically determined based on symptoms, rescue therapy use, functional limitation, pulmonary function, and risk of exacerbations. Although control is now emphasized as the goal of therapy, understanding inherent asthma severity is important for clinical work to determine the intensity of surveillance required and for clinical research to characterize study populations so as to facilitate comparisons between studies of different therapeutic modalities.

The EPR3 (1) suggested two ways to determine asthma severity clinically. The first is to measure symptoms, functional impairment, rescue therapy use, pulmonary function, and exacerbation frequency in patients not on controllers. However, this is not possible in many patients who are already on controllers when first evaluated. The second approach is to base severity on the lowest medication regimen required to achieve control. Although possi-

ble clinically, this is rarely rigorously done in clinical practice or clinical research.

We have previously shown that fractional exhaled nitric oxide (FENO) is related to both prior year (2) and future year (3) asthma manifestations (rescue therapy dispensings and exacerbations) independent of a disease control tool and pulmonary function. These findings are consistent with prior factor analysis studies (4–6) that have shown that airway inflammation, pulmonary function, and symptoms are separate domains of asthma manifestation intensity. We reasoned that the airway inflammation (as assessed by FENO), pulmonary function, and clinical control produced by a given level of step therapy could reflect disease activity in a meaningful way and act as a surrogate for inherent severity as described above in both clinical care (surveillance intensity) and clinical research (population characterization). We used data collected in a previous study (2, 3) to develop the Asthma Intensity Manifestations Score (AIMS) based on exacerbations and rescue medication dispensings in the 12 months prior to the date that the AIMS components were measured or determined. We then evaluated the AIMS on the prediction of future rescue therapy dispensings and exacerbations in those patients.

METHODS

Patients

The 304 patients in this study have been previously described (3). Briefly, they were atopic patients with

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persistent asthma who were aged 12–56 years and on regular inhaled corticosteroid treatment with or without add-on therapy. They were enrolled in a study visit where they completed a questionnaire and had study procedures performed (see below). The study was approved by the Kaiser Permanente Southern California (KPSC) Institutional Review Board (Study Number 5211). Written informed consent was obtained from each participant.

Potential AIMS Components

The potential AIMS components and their cutoff values used in this study are summarized in Table 1. The cutoff for FENO (50 ppb) was based on recent American Thoracic Society (ATS) recommendations (7). Cutoff values for the Asthma Control Test (ACT), forced expiratory volume in 1 second (FEV₁), and step therapy were based on definitions of more severe or uncontrolled asthma presented in the EPR3 guidelines (1). Spirometry captured FEV₁, FEV₁% predicted, and FEV₁/Forced vital capacity (FVC) using the KOKO electronic pneumotach spirometer (Ferraris Respiratory, Louisville, CO, USA) by ATS standards and over-reading for quality assurance (8). FENO measurements were performed prior to or at least 20 minutes after spirometry using the NIOX MINO handheld device following manufacturer's recommendations for calibration and assessment (Aerocrine AB, Solna, Sweden). Step level of care was determined based on self-reported medication intake over the prior month and classified according to the EPR3 step care algorithms for patients aged 12 years and older (1).

Definition of Outcomes

Information on KPSC pharmacy dispensings and healthcare utilization for the year before and the year following the study visit was captured in patients' electronic medical records and was extracted from the KPSC research data warehouse. Short-acting beta agonist (SABA) dispensings were evaluated as a dichotomous variable (≥ 7 SABA canisters dispensed: yes/no), since we have previously validated that ≥ 7 SABA canisters dispensed in a year is a surrogate for asthma impairment based on administrative data (9). A systemic corticosteroid (SCS) dispensing was defined as an oral or parenteral corticosteroid dispensed or administered within 2 days of either (1) an outpatient visit coded as an asthma exacerbation or uncontrolled asthma or (2) an asthma-related emergency department

(ED) visit or hospitalization with a primary diagnosis of asthma (493.xx) or a secondary diagnosis of asthma when the primary diagnosis was related to a respiratory disease. For the development of the AIMS, we chose the two outcomes (SABA ≥ 7 and SCS ≥ 2) that are closest to the EPR3 domains of impairment and risk, respectively (1), in the year *prior* to the measurement of the AIMS components. For the purpose of validation, the same outcomes in the year *following* the measurement of the AIMS components were used as well as any SCS, any asthma-related ED visit or hospitalization, and either SABA ≥ 7 or SCS ≥ 2 .

Data Analysis

Development of the AIMS. Independent relationships between potential AIMS components and the two prior year outcomes were evaluated by means of logistic regression analysis. Only the components that successfully predicted at least one of the prior year outcomes were selected to construct the AIMS. AIMS was defined as the total points of the chosen components, with one point for each component (Table 1).

Validation of the AIMS. For validation, outcomes in the year *following* the determination of the AIMS elements were used. Relationships of AIMS to the following outcomes were evaluated by means of Mantel-Haenszel Chi-Square for linear trend: (1) proportion of patients with SABA ≥ 7 ; (2) proportion of patients with any SCS; (3) proportion of patients with ≥ 2 SCS; (4) proportion of patients with an asthma ED visit or hospitalization; and (5) uncontrolled asthma defined by either SABA ≥ 7 or ≥ 2 SCS. In addition, Spearman correlation coefficients between AIMS and number of SABA canisters dispensed and number of SCS dispensings were calculated. Predictive properties (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], relative risk, and area under the receiver operating characteristic [ROC] curve) of an AIMS cutoff based on the distribution of AIMSs and relationships to outcomes were also determined for each outcome. Because some studies may involve patients who are not on controllers and because of the principle of parsimony, we also explored the relationship of a three-component (ACT, FENO, and FEV₁) AIMS with the follow-up year outcomes.

For all analyses, a two-sided $p < .05$ was considered as significant. Analyses were performed using SAS software (version 9.1 for Windows, SAS Institute, Cary, NC, USA).

TABLE 1.—Points for potential components of the Asthma Intensity Manifestations Score (AIMS) ($n = 304$).

Parameter	Definition	Points = 0		Definition	Points = 1	
		N	Percentage (%)		N	Percentage (%)
ACT	≥ 16	247	81.3	< 16	57	18.8
FEV ₁	$\geq 80\%$ predicted	213	70.1	$< 80\%$ predicted	91	29.9
FENO	≤ 50 ppb	234	77.0	> 50 ppb	70	23.0
EPR3 step care	1–3	93	63.5	4–5	111	36.5

Note: ACT, Asthma Control Test; FEV₁, forced expiratory volume in 1 second; FENO, fractional exhaled nitric oxide; EPR3, Expert Panel Report.

RESULTS

Patient Characteristics

Patients were 35.9 ± 14.9 years old and 60.6% were female. Proportions of patients above and below the cut-offs of the potential AIMS components are shown in Table 1. Step care >3 was most common (36.5%) and ACT <16 was least common (18.8%). Of all the patients, 22.2% received ≥ 7 SABA in the prior year and 7.1% received ≥ 2 SCS for an asthma exacerbation in the prior year. Incidences of follow-up year outcomes are summarized in Table 2. Any uncontrolled marker (SABA ≥ 7 or ≥ 2 SCS) occurred in 22% of patients, while ≥ 2 SCS were seen in only 4.6% of patients.

Development of the AIMS

Only FENO >50 ppb was related to prior year SABA ≥ 7 (Table 3). All four potential AIMS components were significantly related to prior year SCS ≥ 2 in bivariate analyses, but only ACT <16 , FEV₁ $<80\%$ predicted, and step care >3 (but not FENO) were related to prior year SCS ≥ 2 after adjusting for the other components (Table 3). Thus, because both impairment (represented in this study by SABA ≥ 7) and risk (represented in this study by SCS ≥ 2) are considered integral domains of asthma severity and control (1), all four items (ACT, FEV₁, FENO, and step therapy) were chosen for the AIMS tool, with total points

ranging from 0 (least disease intensity) to 4 (most disease intensity).

Validation of the AIMS

Significant linear relationships were demonstrated between AIMS point totals and all follow-up year outcomes (Table 4). Significant ($p < .0001$) correlations were observed between AIMSs and number of SABA dispensed ($\rho = 0.26$) and number of SCS ($\rho = 0.24$). Based on the distribution of total scores, predictive properties of an AIMS ≥ 2 were evaluated. An AIMS ≥ 2 provided a reasonable balance of sensitivities (44.6–64.3%) and specificities (73.3–77.3%) for the various outcomes (Table 5). The highest discrimination (area under the ROC curve = 0.69) was provided for SCS ≥ 2 in the follow-up year (Table 5). PPVs ranged from 10.5% to 37.7%, depending on the prevalence of the outcomes, and negative predictive values were all 83–98% (Table 5). Compared to patients with AIMSs <2 , patients with AIMSs ≥ 2 were at more than a fourfold greater risk of receiving SCS ≥ 2 in the following year and were at a 2–2.8-fold greater risk of experiencing other adverse asthma outcomes during that time period (Table 5).

The three-component tool was linearly related to all outcomes, most strongly to the SABA outcomes (Table 6). Compared to the four-component tool, a score of ≥ 2 on the three-item tool identified a more severe group of patients, with a higher PPV, specificity, and relative risk for adverse outcomes (Table 7). The NPVs of the three-component tool remained high (81–97%) (Table 7). The discrimination (area under the ROC curve) was somewhat higher for the four-item tool (Table 5) than the three-item tool (Table 7) for four of five outcomes.

DISCUSSION

Asthma severity is defined as the inherent intensity of the disease process (1). This characteristic of asthma would be important to understand for each patient, as it influences the likelihood of achieving control and the probable intensity of therapy needed to do so. However, defining asthma severity clinically has been problematic. The most well-established system recommended by national guidelines was to evaluate symptoms, rescue therapy use, functional impairment, pulmonary function, and history of exacerbations in patients naïve to controller therapy (1). However, an increasing number of patients with persistent asthma are already on controller therapy when first evaluated, precluding this approach to defining severity. An approach recommended in Global Initiative for Asthma guidelines (10) for patients already on therapy was to define severity based on the above parameters adjusted for medication intensity. This approach was validated in two studies (11, 12), but has not been widely adopted. Most recently, defining severity based on the least amount of medication required to achieve control has been recommended (1), but rigorous determination of this end point is rarely accomplished.

TABLE 2.—Number and percentage of outcomes in the follow-up year ($n = 304$).

Outcome	N	%
SABA ≥ 7	62	20.4
Any SCS	65	21.4
≥ 2 SCS	14	4.6
Asthma ED visit or hospitalization	19	6.3
SABA ≥ 7 or ≥ 2 SCS	67	22.0

Note: SABA, short-acting beta agonist canisters; SCS, systemic corticosteroid dispensings; ED, emergency department.

TABLE 3.—Crude and adjusted relationships of potential components of the Asthma Intensity Manifestations Score (AIMS) to prior year short-acting beta agonist (SABA) dispensing ≥ 7 and systemic corticosteroid (SCS) dispensing ≥ 2 for an exacerbation.

Parameter	OR (95% CI)			
	SABA ≥ 7		SCS ≥ 2	
	Crude	Adjusted ^a	Crude	Adjusted ^a
ACT <16	1.2 (0.6–2.3)	1.0 (0.5–2.1)	6.3 (2.6–15.5)	4.6 (1.8–12.1)
FEV ₁ $<80\%$ predicted	1.5 (0.9–2.7)	1.3 (0.7–2.3)	4.7 (1.9–11.5)	3.0 (1.1–8.2)
FENO >50 ppb	3.0 (1.7–5.5)	3.0 (1.7–5.6)	2.5 (1.0–6.1)	2.0 (0.7–5.8)
EPR3 step therapy ≥ 4	1.2 (0.9–2.7)	1.3 (0.7–2.4)	5.2 (2.0–13.9)	4.0 (1.4–11.2)

Notes:

$p < .05$ are shown in bold. ACT, Asthma Control Test; FEV₁, forced expiratory volume in 1 second; FENO, fractional exhaled nitric oxide; EPR3, Expert Panel Report; CI, confidence interval; OR, odds ratio.

^aFor all other parameters listed.

TABLE 4.—Occurrence of outcomes in the follow-up year by four-component (ACT, FENO, FEV₁, and step care level) Asthma Intensity Manifestations Score (AIMS).

Outcome	Percentage of outcome by AIMS					P-value ^b
	0 ^a (n = 94)	1 ^a (n = 124)	2 ^a (n = 61)	3 ^a (n = 17)	4 ^a (n = 8)	
SABA ≥ 7 canisters	9.6	17.7	26.2	58.8	62.5	<.0001
Any SCS	9.6	21.8	31.2	33.3	50.0	<.0001
≥2 SCS	1.1	3.2	6.6	17.7	25.0	.0001
Any asthma ED visit or hospitalization	4.3	4.0	8.2	11.8	37.5	.003
SABA ≥ 7 or ≥ 2 SCS	10.6	20.2	27.9	58.8	62.5	<.0001

Notes: SABA, short-acting beta agonist canisters; SCS, systemic corticosteroid dispensings; ED, emergency department; ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second.

^aAIMS point total.

^bMantel-Haenszel Chi-Square for linear trend.

TABLE 5.—Predictive properties of four-component (ACT, FENO, FEV₁, and step care level) Asthma Intensity Manifestations Score (AIMS) ≥ 2 for the various asthma outcomes during the follow-up year.

Property	Outcome				
	SABA ≥ 7 canisters	Any SCS	≥ 2 SCS	Asthma ED visit or hospitalization	SABA ≥ 7 or ≥ 2 SCS
Sensitivity	50.0	44.6	64.3	52.6	47.8
Specificity	77.3	76.2	73.5	73.3	77.2
PPV	36.1	33.7	10.5	11.6	37.7
NPV	85.8	83.5	97.7	95.9	83.9
Relative risk (95% CI)	2.5 (1.6–3.9)	2.0 (1.3–3.1)	4.6 (1.6–13.2)	2.8 (1.2–6.7)	2.3 (1.5–3.5)
Area under the ROC curve	0.64*	0.60*	0.69*	0.63*	0.63*

Notes: SABA, short-acting beta agonist canisters; SCS, systemic corticosteroid dispensing; CI, confidence interval; ROC, receiver operating characteristic; ED, emergency department; ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; PPV, positive predictive value; NPV, negative predictive value.

**p* < .05 for comparison with area under the receiver operating characteristic (ROC) curve = 0.5 (no predictability) by likelihood ratio chi-square.

TABLE 6.—Occurrence of outcomes in the follow-up year by three-component (ACT, FENO, and FEV₁) Asthma Intensity Manifestations Score (AIMS).

Outcome	Percentage of outcome by AIMS				P-value ^b
	0 ^a (n = 141)	1 ^a (n = 120)	2 ^a (n = 31)	3 ^a (n = 12)	
SABA ≥ 7 canisters	12.8	20.0	35.5	75.0	<.0001
Any SCS	16.3	22.5	32.3	41.7	.007
≥2 SCS	2.8	2.5	12.9	25.0	.0007
Any asthma ED visit or hospitalization	5.0	4.2	9.7	33.3	.006
SABA ≥ 7 or ≥ 2 SCS	14.9	21.7	35.5	75.0	<.0001

Notes: SABA, short-acting beta agonist canisters; SCS, systemic corticosteroid dispensing; ED, emergency department; ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second.

^aAIMS point total.

^bMantel-Haenszel Chi-Square for linear trend.

TABLE 7.—Predictive properties of three-component (ACT, FENO, and FEV₁) Asthma Intensity Manifestations Score (AIMS) ≥ 2 for the various asthma outcomes during the follow-up year.

Property	Outcome				
	SABA ≥ 7 canisters	Any SCS	≥ 2 SCS	Asthma ED visit or hospitalization	SABA ≥ 7 or ≥ 2 SCS
Sensitivity	32.3	23.1	50.0	36.8	30.0
Specificity	90.5	88.3	87.6	87.4	90.3
PPV	46.5	34.9	16.3	16.3	46.5
NPV	83.9	80.8	97.3	95.4	82.0
Relative risk (95% CI)	2.8 (1.9–4.4)	1.8 (1.1–2.9)	6.1 (2.2–16.4)	3.5 (1.5–8.5)	2.6 (1.7–3.9)
Area under the ROC curve	0.61*	0.56*	0.69*	0.62*	0.60*

Notes: SABA, short-acting beta agonist canisters; SCS, systemic corticosteroid dispensing; CI, confidence interval; ROC, receiver operating characteristic; ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ED, emergency department; PPV, positive predictive value; NPV, negative predictive value.

**p* < .05 for comparison with area under the receiver operating characteristic (ROC) curve = 0.5 (no predictability) by likelihood ratio chi-square.

With the limitations of prior approaches and the observations that symptoms, pulmonary function, and airway inflammation appear to be independent reflections of the asthma disease process (4–6), we sought to develop and preliminarily validate an asthma intensity score that would serve as a surrogate for inherent asthma severity. We reasoned that such a score should potentially take into account symptoms (and related features of rescue therapy use and functional impairment), pulmonary function, inflammation (measured in this study by FENO), and intensity of therapy. This study shows that a simple five-level score based on previously defined cutoffs of the ACT, FEV₁, FENO, and step therapy is linearly related to future markers of asthma impairment and risk. Specifically, compared to patients with scores of 0 or 1, patients with a score of 2 or above are more than four times more likely to experience two or more exacerbations in the subsequent 12 months and more than twice as likely to experience asthma-related hospitalizations or ED visits and excess beta agonist dispensings.

Ideally, clinical tools are developed in one population and validated in another. Alternatively, a single sample can be split into a development or training set and a validation or testing set. However, although we felt the information collected in this 2-year study could be very valuable in developing a disease intensity score, the sample size was not large enough to split, especially for uncommon outcomes. We thus chose to develop the tool based on prior year information and test it based on subsequent year information. We assessed both prior year markers of impairment (SABA ≥ 7) and risk (≥ 2 SCS) in developing the score since these are considered as two separate but important domains of asthma severity (or control) (1). Although we could have determined data-based optimal cutoffs for each potential element of the tool empirically using ROC curve analyses of various cutoffs, we felt that using previously defined cutoffs for the various elements would increase generalizability, since the data-based cutoffs would have been specific for the current sample. We used ACT < 16 (the cutoff for poorly controlled asthma) because we have shown that such patients are at particularly increased risk of subsequent adverse outcomes (13). In addition, ACT < 19 (the cutoff for not well-controlled asthma) was not independently related to prior exacerbations in this study (data not shown), while ACT < 16 was (Table 3).

Our study shows that the AIMS predicts the risk of future exacerbations. It has been previously shown that two of the AIMS elements, FEV₁ and FENO, independently predict asthma exacerbations (14). Many other studies have identified independent risk factors for asthma exacerbations, including some studies that have produced risk scores using clinical data (15–17). The main purpose of these scores, to identify patients at increased risk of asthma exacerbations, is different from the purpose of the AIMS, which is to assess intrinsic disease intensity/severity. Consequently, the prior clinical risk scores have included predictors such as demographic and socioeconomic factors, comorbidities, and prior utilization

(15–17). Although these factors may indirectly reflect or affect asthma severity or control, they are not direct measures of disease intensity as the AIMS is meant to be.

We believe that the AIMS could be clinically useful for individual patients and for research. For individual patients, higher scores indicate the need for more intense management, including addressing triggers, treating comorbidities, and assuring adherence to appropriate medications. The predictive properties of the AIMS suggest that a score ≥ 2 indicates a 38% likelihood of future impairment or risk compared to 16% for patients with scores of 0 or 1 (Table 5). However, a score of 3 or more indicates more than a 50% likelihood of subsequent uncontrolled asthma based on impairment or risk (Table 4), even in the actively managed patients in this study. Conversely, the high NPVs (80–98% for both the three-component and four-component tools) demonstrated in this study suggest that patients with AIMSs < 2 may generally be safely considered for step-down therapy.

Common outcomes in asthma clinical trials include symptoms, rescue therapy use, composite control scores, quality of life, pulmonary function, and exacerbations (18). Presumably, all of these outcomes are influenced by inherent disease severity. Although it would be hoped that randomization in a clinical trial would balance treatment groups for inherent severity, such a balance is never guaranteed. The AIMS provides a potential tool to test the baseline balance of inherent severity or adjust for it if the treatment groups are not balanced. Presenting the distribution of baseline AIMSs as part of the sample description should also allow improved comparisons of samples and results between studies. Finally, AIMSs should be useful in observational research studies as population descriptors or risk adjusters.

An important issue is the generalizability of the current results. As noted above, the use of standard cutoffs for the elements of the AIMS increases the generalizability of the tool. However, the study sample was a convenience sample of atopic patients treated with inhaled corticosteroids by asthma specialists. Generalizability to nonatopic patients, to patients with persistent asthma not on inhaled corticosteroids, and to patients managed by generalists needs to be established.

This study does have other potential limitations. The AIMS is based on clinical findings, but the outcomes used in this study for development and validation were based on administrative data. Although these administrative data have been shown to be related to patient-reported outcomes (9), demonstration of the relationships of the AIMS to future clinical outcomes will be welcome. AIMS does not directly assess *responsiveness*, which, along with inherent severity, is important in determining asthma outcomes such as control (1). Thus, high AIMSs cannot differentiate increased inherent severity from decreased responsiveness. Responsiveness could be indirectly assessed by changes in the three-component tool (ACT, FEV₁, and FENO) after initiation of a uniform therapy. The three-component tool (Tables 6 and 7) would also be used for severity assessment in patients not

currently on controller therapy or in patients whose report of current controller therapy is considered unreliable.

CONCLUSION

This study developed and preliminarily validated a four-component disease intensity scale as a surrogate for inherent severity that has been shown to be related to subsequent markers of asthma risk and impairment. It could be applied to the care of individual asthmatic patients and to interventional and observational clinical research. Further studies will be necessary to provide additional validation data using other outcomes and samples and to confirm the proposed usefulness of this tool in clinical and research settings.

ACKNOWLEDGEMENTS

The authors thank Kjell Alving, M.D., for his helpful suggestions regarding this manuscript. The study was supported by investigational grants to the Southern California Permanente Medical Group Research and Evaluation Department from Aerocrine AB, Solna, Sweden, and Panasonic Shikoku Electronics Co., Ltd., Tōon City, Ehime, Japan.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

- Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol* 2007; 120: S94–S138.
- Zeiger RS, Schatz M, Zhang F, Crawford WW, Kaplan MS, Roth RM, Chen W. Association of exhaled nitric oxide to asthma burden in asthmatics on inhaled corticosteroids. *J Asthma* 2011; 48:8–17.
- Zeiger RS, Schatz M, Zhang F, Crawford WW, Kaplan MS, Roth RM, Chen W. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatics on inhaled corticosteroids. *J Allergy Clin Immunol* 2011; 128:412–414.
- Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. *Eur Respir J* 2004; 23:287–291.
- Holt EW, Cook EF, Covar RA, Spahn J, Fuhlbrigge AL. Identifying the components of asthma health status in children with mild to moderate asthma. *J Allergy Clin Immunol* 2008; 121:1175–1180.
- Rodrigo GJ, Arcos JP, Nannini LJ, Neffen H, Broin MG, Contrera M, Pineyro L. Reliability and factor analysis of the Spanish version of the Asthma Control Test. *Ann Allergy Asthma Immunol* 2008; 100:17–22.
- Dweik RA, Boggs PB, Erzurum SC, Irvin CS, Leigh MW, Lungberg JO, Olin AC, Plummer AL, Taylor DR. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FE_{NO}) for clinical application. *Am J Respir Crit Care Med* 2011; 184:602–615.
- Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152(3):1107–1136.
- Schatz M, Zeiger RS, Vollmer WM, Mosen D, Apter AJ, Stibolt TB, Leong A, Johnson MS, Mendoza G, Cook EF. Validation of a beta-agonist long-term asthma control scale derived from computerized pharmacy data. *J Allergy Clin Immunol* 2006; 117(5):995–1000.
- National Heart Lung and Blood Institute. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Bethesda, MD: National Institutes of Health, 1995. NHLBI Publication Number 95-3659.
- Liard R, Leynaert B, Zureik M, Beguin F-X, Neukirch F. Using Global Initiative for Asthma guidelines to assess asthma severity in populations. *Eur Respir J* 2000; 16:615–620.
- Antonicevici L, Bucca C, Neri M, De Benedetto F, Sabbatani P, Bonifazi F, Eichler HG, Zhang Q, Yin DD. Asthma severity and medical resource utilization. *Eur Respir J* 2004; 23:723–739.
- Schatz M, Zeiger RS, Drane A, Harden K, Cibildak A, Oosterman JE, Kosinski M. Reliability and predictive validity of the Asthma Control Test™ administered by telephone calls using speech recognition technology. *J Allergy Clin Immunol* 2007; 119:336–343.
- Gelb AF, Taylor CF, Shinar CM, Gutierrez C, Zamel M. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. *Chest* 2006; 129:1492–1499.
- Miller MK, Lee JH, Blanc PD, Pasta DJ, Gujrathi S, Barron H, Wenzel SE, Weiss ST; TENOR Study Group. TENOR risk score predicts health-care in adults with severe or difficult-to-treat asthma. *Eur Respir J* 2006; 28:1145–1155.
- Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, Vollmer WM. Assessing future need for acute care in adult asthmatics. *Chest* 2007; 132:1151–1161.
- Forno E, Fuhlbrigge A, Soto-Quirós ME, Avila L, Raby BA, Brehm J, Sylvia JM, Weiss ST, Celedón JC. Risk factors and predictive clinical scores for asthma exacerbations in childhood. *Chest* 2010; 138: 1156–1165.
- Reddel HK, Taylor R, Bateman ED, Boulet LP, Busse WW, Casale TB, Chaney P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HA, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stollhoff SW, Sullivan SD, Szeffler SJ, Thomas MD, Wenzel SE. An official American Thoracic Society/European Respiratory Society Statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180:59–99.

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