

ORIGINAL RESEARCH

The Asthma Control Test™ (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey

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Submitted 28th May 2008; revised version received 18th September 2008; further revisions received 23rd October 2008; accepted 28th November 2008; online 24th February 2009

Abstract

Aims: To evaluate whether the Asthma Control Test™ (ACT) score is predictive of Global Initiative for Asthma (GINA) guideline-defined classification levels of asthma control. The ACT is a validated, 5-item, patient-completed measure of asthma control with a recall period of four weeks.

Methods: Cross-sectional survey comparing ACT score and GINA classification of asthma control among 2949 patients attending primary care physicians and specialists in France, Germany, Italy, Spain, the UK, and the USA.

Results: The area under the receiver operating characteristics curve for ACT score predicting GINA control was 0.84 (95% CI 0.82–0.85). An ACT score of ≤ 19 (not well-controlled asthma) correctly predicted GINA-defined partly controlled/uncontrolled asthma 94% of the time, while an ACT score of ≥ 20 predicted GINA-defined controlled asthma 51% of the time, with kappa statistic of 0.42, representing moderate agreement.

Conclusions: An ACT score ≤ 19 is useful for identifying patients with poorly controlled asthma as defined by GINA.

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M Thomas, *et al. Prim Care Resp J* 2009; **18**(1): 41-49.

doi:10.4104/pcrj.2009.00010

Keywords asthma, Asthma Control Test, control, GINA, exacerbations, multinational survey, patient-completed outcome assessment, Europe, United States

The full version of this paper, with Appendices and online Tables and Figures, is available online at www.thepcrj.org

Introduction

The 2006 update to the Global Initiative for Asthma (GINA) guideline emphasises the importance of evaluating asthma control, rather than asthma severity, in order to guide asthma management decisions. Classification of disease severity is a static measure that, whilst useful in initiating treatment, is less helpful in guiding subsequent treatment.^{1,2} GINA guidelines suggest that classification of asthma control more directly reflects the effectiveness of therapeutic interventions – and

thus it may be more useful clinically. Current guidelines define asthma control as: no limitations of activities; no nocturnal symptoms; minimal or no daytime symptoms; minimal or no need for rescue therapy; normal lung function; and no exacerbations.³⁻⁵

Guideline-defined asthma control can be attained and maintained for the majority of patients eligible to participate in a controlled trial setting,^{6,7} but it is frequently not achieved in real world practice.⁸⁻¹¹ Poorly controlled asthma accounts for a disproportionate share of the costs of asthma and represents a heavy socioeconomic burden.¹²⁻¹⁵ However, many patients worldwide have sub-optimally controlled asthma,

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and they are often not aware that better control can be achieved; moreover, physicians may overestimate levels of control or the extent of improvement achieved with therapy, often because of inadequate assessment.^{16,17} In addition, selection of asthma control criteria not consistent with current asthma guidelines may hamper assessment.¹⁸

The Asthma Control Test™ (ACT) was developed as a screening tool to address the need for a simple, rapidly-completed assessment tool in clinical practice. The ACT is a validated, patient-completed measure of asthma control comprising five questions that assess activity limitation, shortness of breath, night-time symptoms, use of rescue medication, and patient overall rating of asthma control over the previous four weeks (see Appendix 1 online).¹⁹⁻²¹ The questions are scored from 1 (worst) to 5 (best), and the ACT score is the sum of the responses, giving a maximum best score of 25. An ACT score of 19 demonstrated the highest area under the receiver operating characteristic (ROC) curve, and thus a score of ≥ 20 is the optimal cut-off point defining well-controlled asthma over the previous four weeks^{19,22} – although, as Nathan *et al*¹⁹ describe, the cut-off point can be chosen according to application.

It is important in clinical practice to identify patients whose asthma is not well-controlled, since these patients require review of their therapy as well as assessment of risk factors for poor asthma control.²³ The ACT was designed for use in daily practice as a supplementary measure to the physician's assessment and/or lung function testing, but it has not been validated as a predictor of GINA-defined asthma control. The objective of this multinational cross-sectional survey was to evaluate whether the ACT can predict GINA-defined asthma control, with particular emphasis on the binary split between GINA-defined 'partly controlled'/'uncontrolled' asthma versus 'controlled' asthma.

Methods

Disease Specific Programmes

The Disease Specific Programmes (DSP) are large, multinational observational studies of clinical practice that are conducted every 12 to 18 months by the Adelphi Group in the USA and in five European countries (France, Germany, Italy, Spain, and the UK).²⁴ Designed to survey patients and physicians on their perceptions of treatment effectiveness, symptoms, and impact of common chronic diseases, each DSP is specific to a disease area and includes questionnaires completed by up to 1000 physicians and 12,000 patients. Descriptions of DSP methods for studying asthma and allergic rhinitis have been published.^{25,26}

The respiratory programme was initiated in 2000. Here we summarise the methods specific to patients with asthma included in the sixth wave (Respiratory DSP VI), conducted in the first quarter of 2007.

Respiratory DSP VI survey participants and procedures

Physicians recruited for the Respiratory DSP VI numbered 120 in France, Germany, Italy, and Spain (50 primary care practitioners, 50 pulmonologists or country equivalent, and 20 allergists in each country), 100 in the UK (50 primary care practitioners and 50 chest specialists), and 180 in the US (75 primary care practitioners, 75 pulmonologists, and 30 allergists). Larger samples of physicians were recruited from more densely populated areas. Physicians were asked to collect information for their next six consecutive patients ≥ 12 years of age with physician-diagnosed asthma, irrespective of the reason for the consultation. The physician forms, completed after the consultation with no direct input from the patient, included patient demographic data, disease symptoms and severity, diagnostic and treatment history, and health resource utilisation measures.

Patients included in the survey by their physicians could then be invited to complete a survey form immediately after the consultation. Completion of the survey form was not obligatory, and physicians did not see or influence patient responses. The study protocol followed ethical procedures including verbal informed consent of all physicians and patients for anonymous and aggregated reporting of research findings based on the questionnaires employed.

The patient survey included questions on asthma symptoms and severity, the impact of asthma and any measures taken by the patient to control their asthma, as well as satisfaction and compliance with medication, expectations of therapy, and health resource utilisation. Physicians were provided with an honorarium for study completion. Patient compensation depended on local country regulations (some were not compensated, some received vouchers, some received payment).

Outcome measures

Included in the Respiratory DSP VI survey were the ACT tool and variables to identify asthma control level as per GINA classification (other survey data not reported here). The ACT was included as part of the patient-completed form, and GINA-defined asthma control was determined primarily from patient responses.

Translations of the ACT were validated. The translations of the Respiratory DSP VI survey were made using forward-backward translation and were not validated. Specific cognitive debriefing was not done before initiating the survey; however, the forms were piloted to see how they were completed, given that patients would be completing them alone.

The GINA classification and our survey definitions of GINA asthma control are summarised in Table 1, with differences between the two noted (all relate to time frame). Questions relating to the first four items in the GINA classification – daytime symptoms, limitations of activities, nocturnal

symptoms, and need for rescue medication – were included on both physician and patient forms with reference to the previous four weeks, as in the ACT (online Appendices 1, 2, and 3). Questioning on the fifth item in the GINA classification – lung function – was included on the physician form with reference to the previous 12 months.

Questioning about the sixth item in the GINA control definition – asthma exacerbations – was with reference to the preceding 12 months on both physician and patient forms; however, the timing of the exacerbation was enquired about on (and thus data derived from) only the physician-completed forms (see Appendices 2 and 3 online). Of note, the GINA definitions for partly controlled and uncontrolled categories are not mutually exclusive based on the exacerbation item because the time period for an exacerbation is not specified (see Table 1).³ We therefore elected to specify an exacerbation

in the preceding seven days as defining uncontrolled asthma, and an exacerbation within the preceding year (but not in the previous seven days) to define partly controlled asthma in terms of the GINA classification.

Analysis

Physicians and their patients were linked by assigned study numbers, and data included in the analyses were anonymised and restricted to those from matched and fully completed patient and physician forms. The primary analyses were performed including all patients as well as by country.

The analyses evaluated the relationship between ACT scores and GINA-defined asthma control, taking the GINA classification as the “true” classification and the ACT score as the “predictor” classification. Our primary analyses evaluated the relationship between ACT scores and GINA-defined partly controlled/uncontrolled versus controlled asthma. In

Table 1A. Levels of asthma control according to the Global Initiative for Asthma (GINA).³ Reprinted with permission.

Levels of Asthma Control			
Characteristic	Controlled (All of the following)	Partly controlled (Any measure present <i>in any week</i>)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	
Limitations of activities	None	Any	Three or more
Nocturnal symptoms/awakening	None	Any	features of partly
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	controlled asthma
Lung function (PEF or FEV ₁) [†]	Normal	<80% predicted or personal best (if known)	present <i>in any week</i>
Exacerbations	None	One or more/year*	One <i>in any week</i> [‡]

FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.
 *Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.
[‡]By definition, an exacerbation in any week makes that an uncontrolled asthma week.
[†]Lung function is not a reliable test for children 5 years and younger.

Table 1B. Working definition of GINA-defined asthma control used in the survey.

Levels of Asthma Control			
Characteristic	Controlled (All of the following)	Partly controlled (Any measure present <i>in previous 4 weeks</i> [‡])	Uncontrolled
Daytime symptoms*	None (twice or less/week)	More than twice/week	
Limitations of activities*	None	Any	Three or more
Nocturnal symptoms/awakening*	None	Any	features of partly
Need for reliever/rescue treatment*	None (twice or less/week)	More than twice/week	controlled asthma
			present in any week <i>of the last 4 weeks</i>
Exacerbations [†]	None	One or more in prior year	One or more <i>in the previous 7 days</i>

*Data derived from patient-completed forms
[†]Data derived from physician-completed forms
[‡]Text in bold italics signifies differences from GINA definitions in Table 1A

sensitivity analyses, we examined the effect of including exacerbations for the GINA definitions of uncontrolled and partly controlled asthma; thus, we re-ran the analyses: firstly with all exacerbation data taken out; and secondly with exacerbations defining partly controlled asthma taken out (i.e., exacerbations >7 days to 1 year) but leaving them in for defining uncontrolled asthma. An additional sensitivity analysis, with all exacerbations removed, focused on uncontrolled asthma (thus, uncontrolled versus partly controlled/controlled asthma). We calculated the sensitivity, specificity, positive predictive value (predictive value of a positive test), negative predictive value (predictive value of a negative test), and percentage of patients correctly classified overall using each ACT score as the cut-off point for GINA-defined controlled asthma and, in the sensitivity analysis, the cut-off point for GINA-defined uncontrolled asthma.

For the primary analysis, we plotted ROC curves (sensitivity versus 1 – specificity) for the full range of ACT cut-off points. From these we determined the area under the curve (AUC), with 95% confidence intervals (CI). The AUC summarises the relationship between the two measures by incorporating information from all ACT values. If the ACT score were a perfect predictor this area would equal 1; if it were no better than random chance it would equal 0.5 (the straight line drawn on the ROC curves). We tested for differences in the AUC between countries using the Wald X^2 test.

The kappa statistic was used to measure agreement between an ACT cut-off point of ≥ 20 defining well-controlled asthma and the GINA binary split of partly controlled/uncontrolled versus controlled asthma.²⁷ In addition, we evaluated the kappa statistic for defining uncontrolled asthma in the sensitivity analysis.

Descriptive statistics were used to summarise ACT scores relative to the three GINA classifications of asthma control including the exacerbation criterion. As ACT scores were non-

normally distributed across all GINA as well as GINA partly controlled and uncontrolled categories, we report median ACT scores with interquartile ranges (IQR) for each category. The Kruskal-Wallis test was used to test for differences in ACT medians among GINA categories. Pairwise comparisons were made using the Mann-Whitney U test with Bonferroni adjustments for multiple testing.

All statistical analysis was carried using STATA® Version 10 (StataCorp LP, College Station, Texas, US).

Results

Survey participants

Physicians completed asthma patient record forms for 3503 patients in Europe and 1080 patients in the USA. Eighty-five percent of these forms (3877/4583) could be matched with a corresponding patient self-completed form. A total of 2949 of the 3877 (76%) patient forms, corresponding to 64% of physician forms, had complete responses for the ACT- and GINA-related questions and were included in the analyses. Patient numbers by country are summarised in Table 2.

Patients ranged in age from 12 to 93 years (mean [SD], 42 [17]), and 56% (1657/2941) were female (a few demographic data were missing). Most patients were white (2598/2930 or 89%); patients of Hispanic (102, 3%) and African-American descent (98, 3%) were equally represented, with smaller numbers who described themselves as Afro-Caribbean (62, 2%), Asian (55, 2%), and other (15, <1%). Twelve percent were current smokers, 24% were ex-smokers, and 64% had never smoked.

Respiratory DSP VI Survey results

Lung function data were available from only 539 of 2949 (18%) matched physician-completed forms and thus were not included in the main analyses. However, analyses incorporating lung function data gave results very similar to those obtained when the data were excluded, both for the overall study population as well as for the subgroup with lung function data (online Tables 1–3, see www.thepcrj.org).

GINA partly controlled/uncontrolled versus controlled asthma as defined by ACT score

With a cut-off point of ≥ 20 for the ACT score defining well-controlled asthma, and a binary split for GINA classification (partly controlled/uncontrolled versus controlled asthma), an ACT score of ≤ 19 (not well-controlled asthma) correctly predicted GINA-defined partly controlled/uncontrolled asthma 93.9% of the time (Table 3). An ACT score of ≥ 20 predicted GINA-defined controlled asthma 51.3% of the time. Table 4 summarises the positive and negative predictive values, as well as sensitivity and specificity, of the ACT score cut point of ≥ 20 for all patients and by country.

The area under the ROC curve for the ACT score predicting the GINA control classification was 0.84 (95% CI

Table 2. Number of physician-completed patient record forms (PRF) and patient self-completed (PSC) responses available for analysis, by country.

	PRF (n=4583)	Matched PSC (n=3877)	Matched PSC for analysis* (n=2949)
France	741	732 (99%)†	697 (94%)†
Germany	720	710 (99%)	495 (69%)
Italy	720	702 (98%)	495 (69%)
Spain	726	573 (79%)	395 (54%)
United Kingdom	596	200 (34%)	154 (26%)
United States	1080	960 (89%)	713 (66%)

*No. forms with corresponding PRF as well as complete responses for inclusion in the analyses.

†Percentages are relative to number of PRFs for that country.

0.82–0.85) for all countries combined. This AUC can be interpreted as the probability that the ACT score for a randomly selected patient with partly controlled/uncontrolled asthma will be less than that for a randomly selected patient with controlled asthma. Among individual countries, the area under the ROC curve varied significantly (Wald X^2 $p=0.0048$), from 0.80 (Italy) to 0.89 (UK) – see Figure 1.

Using the cut-off point of ≥ 20 for ACT well-controlled asthma, the kappa level of agreement for the entire patient population was 0.42. The kappa statistic is a means of measuring agreement beyond chance between two sets of observations using categorical data and is interpreted as follows: 0.81–1.0, almost perfect; 0.61–0.80, substantial; 0.41–0.60, moderate; 0.21–0.40, fair; and 0.0–0.20, slight; and <0 , poor agreement.²⁷ Individual country kappa scores (0.29–0.52) represented fair to moderate agreement (Table 5).

Sensitivity analyses

In sensitivity analyses, when we removed all exacerbations as a criterion, more patients were defined as having GINA-controlled asthma. The positive predictive value of the ACT remained similar while the negative predictive value improved: an ACT score of ≤ 19 correctly predicted GINA-defined partly controlled/uncontrolled asthma 88.4% of the time, and an ACT score of ≥ 20 predicted GINA-defined controlled asthma 71.6% of the time (online Table 4). The area under the ROC curve improved to 0.89 and the kappa statistic improved substantially to 0.58. When we removed only exacerbations occurring >7 days to 1 year previously, the results were virtually identical (same kappa and area under ROC curve to two digits; data not shown).

Online Table 5 and Figures 1 and 2 report the results of sensitivity analyses using the binary split of GINA uncontrolled versus partly controlled/controlled asthma and removing exacerbations as a criterion. As compared with the primary analyses, the positive predictive value fell substantially (33.6%) while the negative predictive value of an ACT score ≥ 20 rose to almost 99%, i.e. correctly predicting GINA-defined partly controlled/controlled asthma 99% of the time. At the cut-off point of ACT ≥ 20 , the overall kappa statistic was 0.35, while the maximum kappa values for predicting uncontrolled asthma occurred at ACT scores of ≤ 14 (kappa 0.55) and ≤ 15 (kappa 0.53).

GINA control categories and ACT scores

The distributions of the three GINA control categories relative to ACT scores are depicted in Figure 2 for all patients.

The median (IQR) ACT scores for GINA categories were 14 (11–17), 20 (17–22), and 23 (21–25) for uncontrolled, partly controlled, and controlled asthma, respectively ($p<0.001$). The median ACT scores for each GINA category varied significantly within each country ($p<0.001$), with significant

Table 3. Performance of the ACT score at different cut-off points in predicting GINA categories of asthma control (controlled versus partly controlled/ uncontrolled) for all patients (n=2949)

	Sensitivity	Specificity	Correctly classified	Positive predictive value	Negative predictive value
≥ 5	0	100	32	--	32
≥ 6	0	100	32	100	32
≥ 7	1	100	32	100	32
≥ 8	2	100	33	100	32
≥ 9	3	100	34	100	32
≥ 10	6	100	36	100	33
≥ 11	8	100	37	100	34
≥ 12	11	100	39	100	34
≥ 13	15	100	42	100	35
≥ 14	18	100	44	99	36
≥ 15	23	99	47	99	37
≥ 16	28	99	51	98	39
≥ 17	34	98	55	97	41
≥ 18	42	97	59	97	44
≥ 19	51	95	65	96	47
≥ 20	60	92	70	94	51
≥ 21	70	84	75	91	57
≥ 22	79	74	78	87	63
≥ 23	87	59	78	82	67
≥ 24	91	42	76	77	69
≥ 25	94	27	73	74	68

All data are percentages.

For each ACT score cut-off point, the:

- * Sensitivity is defined as the percentage of patients with GINA-defined partly controlled/uncontrolled asthma who were identified by the ACT as belonging to this group.
- † Specificity is defined as the percentage of patients with GINA-defined controlled asthma who were identified by ACT as belonging to this group.
- ‡ Positive predictive value, or the predictive value of a positive test, is the percentage of patients whom ACT predicts correctly to have partly controlled/uncontrolled asthma based on the GINA classification.
- ** Negative predictive value, or the predictive value of a negative test, is the percentage of patients whom ACT predicts correctly to have controlled asthma based on the GINA classification.

differences ($p<0.001$) for all pairwise comparisons; median ACT scores were numerically similar for any given GINA category among countries (see Table 6).

Table 7 summarises the numbers of patients meeting each GINA criterion for all patients who did not have controlled asthma by the GINA definition but who had an ACT score ≥ 20 (well-controlled asthma). A total of 56 patients were classified as having GINA uncontrolled asthma with an ACT score ≥ 20 , including 36 (64%) with an exacerbation in the previous seven days, and 21 (38%) with three or more symptoms in any one week of the preceding four weeks (one

Table 4. Specificity, sensitivity, positive and negative predictive values for ACT score cut-off point of ≥ 20 for well-controlled asthma and GINA binary split of controlled vs partly controlled/uncontrolled asthma, globally and by country

	Sensitivity	Specificity	Correctly classified	Positive predictive value	Negative predictive value
Global (n=2949)	60	92	70	94	51
France (n=697)	58	93	72	93	58
Germany (n=495)	59	93	73	93	60
Italy (n=495)	56	85	63	93	38
Spain (n=395)	55	97	65	98	41
UK (n=154)	73	88	77	94	56
US (n=713)	64	91	72	94	51

All data are percentages.

Table 6. GINA classifications and corresponding median ACT scores for all patients and by country

	N	ACT median* (IQR)	ACT range
GINA controlled			
All	934	23 (21–25)	11–25
France	270	23 (22–25)	14–25
Germany	198	23 (21–24)	15–25
Italy	117	23 (21–24)	13–25
Spain	98	23 (22–24)	18–25
UK	43	23 (21–24)	17–25
US	208	23 (22–25)	11–25
GINA partly controlled			
All	1439	20 (17–22)	5–25
France	323	20 (17–22)	6–25
Germany	208	20 (18–22)	9–25
Italy	298	20 (18–21)	9–25
Spain	237	20 (17–22)	9–25
UK	66	19 (16–21)	5–25
US	307	20 (17–22)	8–25
GINA uncontrolled			
All	576	14 (11–17)	5–25
France	104	13 (10–16)	5–24
Germany	89	14 (11–16)	6–23
Italy	80	15 (13–18)	8–24
Spain	60	15 (13–17.5)	5–25
UK	45	12 (10–16)	5–23
US	198	14 (11–17)	5–25

* $p < 0.001$ (Kruskal-Wallis) for all between-group comparisons for each country; $p < 0.001$ (Mann-Whitney with Bonferroni adjustment) for all pairwise comparisons for each country.

Table 5. Kappa level of agreement at ACT score cut-off point of ≥ 20 for well-controlled asthma and GINA binary split of controlled vs partly controlled/uncontrolled asthma

Country	GINA classification	ACT ≥ 20 N (%)	ACT < 20 N (%)	Kappa statistic
All	Controlled	856 (92)	78 (8)	0.42
	Partly/uncontrolled	812 (40)	1203 (60)	
France	Controlled	250 (93)	20 (7)	0.46
	Partly/uncontrolled	178 (42)	249 (58)	
Germany	Controlled	184 (93)	14 (7)	0.48
	Partly/uncontrolled	122 (41)	175 (59)	
Italy	Controlled	100 (85)	17 (15)	0.29
	Partly/uncontrolled	166 (44)	212 (56)	
Spain	Controlled	95 (97)	3 (3)	0.36
	Partly/uncontrolled	134 (45)	163 (55)	
UK	Controlled	38 (88)	5 (12)	0.52
	Partly/uncontrolled	30 (27)	81 (73)	
US	Controlled	189 (91)	19 (9)	0.45
	Partly/uncontrolled	182 (36)	323 (64)	

Table 7. Patients who did not have controlled asthma by the GINA definition but who had an ACT score ≥ 20 (well-controlled asthma): numbers meeting each GINA criterion for partly controlled or uncontrolled asthma*

	GINA partly controlled (n=756)	GINA uncontrolled (n=56)
Daytime symptoms, $>2/wk$	123 (16%)	23 (41%)
Limitations of activities, any	155 (21%)	23 (41%)
Nocturnal symptoms, any	242 (32%)	35 (63%)
Need for rescue inhaler, $>2/wk$	86 (11%)	23 (41%)
≥ 3 of above issues in 1 week of prior 4	N/A	21 (38%)
Asthma exacerbation [†]	499 (66%)*	36 (64%)*

N/A = not applicable

*Patients could meet ≥ 1 criterion.

[†]Exacerbation recorded in prior 7 days for GINA uncontrolled asthma and at any time in >7 days and prior 12 months for GINA partly controlled asthma.

patient met both criteria). Of the 756 patients who were classified as having GINA partly controlled asthma with an ACT score ≥ 20 , 322 (43%) had had ≥ 1 exacerbation in the preceding 12 months and no other issues, while 176 (23%) had had no exacerbation and just one issue during the previous four weeks causing them to meet the criteria for GINA partly controlled asthma.

Figure 1. Receiver operating characteristics (ROC) curves for the Asthma Control Test score predicting the Global Initiative for Asthma (GINA) control classification for the six countries included in the survey. The legend shows area under the ROC curve (95% CI) for each country.

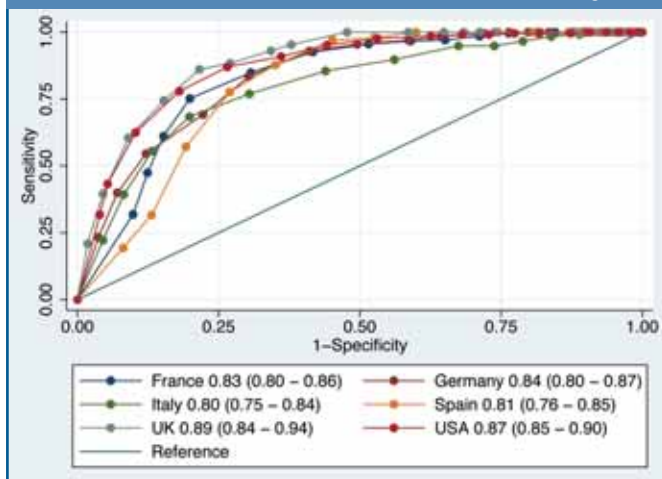
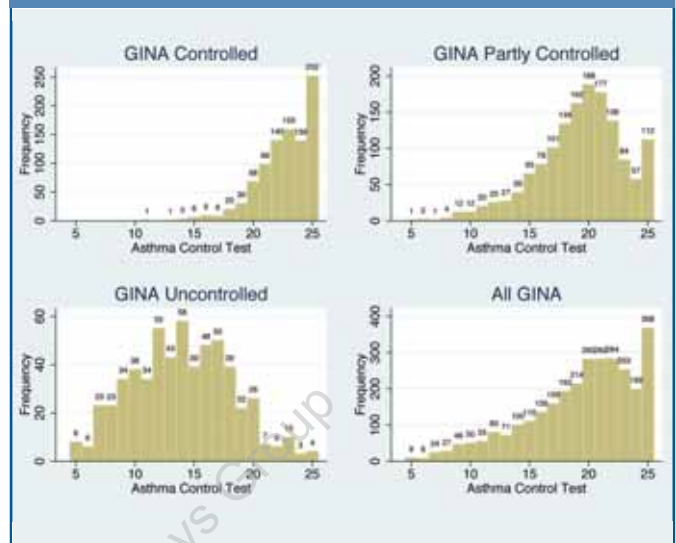


Figure 2. Distribution of GINA control categories relative to ACT scores for outpatients with asthma (n=2949) in five European countries and the US.



Discussion

In this multinational survey, the ACT was useful in predicting GINA-defined asthma control categories and was particularly useful in confirming patients whose asthma was not controlled according to the GINA classification. We found that an ACT score of ≤ 19 correctly predicted GINA 'partly controlled' or 'uncontrolled' asthma 94% of the time overall and $\geq 93\%$ of the time in each country. The area under the ROC curve, the single measure incorporating the most information on the relationship between ACT predicting GINA, was quite adequate at 0.84 and of a similar magnitude to prior findings for the ACT as well as other case identification instruments for asthma, allergy, and chronic obstructive pulmonary disease.²⁸⁻³⁰

An ACT score ≥ 20 predicted GINA-defined controlled asthma 51% of the time, and the kappa statistic (0.42) suggested a moderate agreement using the cut-off point of ≥ 20 for 'well controlled' asthma. This is largely because substantial numbers of patients with an ACT score ≥ 20 had GINA 'partly controlled', and a few GINA 'uncontrolled', asthma. Many of the discrepancies could be explained by either the timing of exacerbations or by variability in item content and grading between the ACT and GINA definitions. Overall, 66% of patients with GINA partly controlled asthma and an ACT score ≥ 20 failed to meet the GINA definition of controlled asthma either because of an old exacerbation or isolated symptoms, with nocturnal symptoms reported in isolation most commonly. The ACT lists specific symptoms (for example, shortness of breath, night-time wheezing), while the GINA categories are less specific (namely, daytime or night-time symptoms), perhaps capturing symptoms outside

the ACT definition. Moreover, some discrepancies likely arose from faulty questionnaire completion, not uncommon in a large survey of this nature.

There is no gold standard for measuring asthma control; even the GINA classification is described as a "working scheme based on current opinion [that] has not been validated."³ The GINA classification does not include a timeframe and thus can be used to define long- or short-term control. The fact that exacerbations and any symptoms during the preceding year are captured, provides a long-term picture of asthma control that can be useful in determining optimal asthma therapy.

The ACT was developed and validated, using a criterion measure of control (specialists' rating of asthma control after spirometry), to serve as a screening tool for assessing short-term asthma control over the preceding four weeks.^{19,20} Patients' recall of asthma symptoms decreases over time and thus a short recall period (2–4 weeks) is recommended for patient-reported symptom history.⁴ The ACT is rapidly completed by patients, and the dichotomous scoring system is convenient for busy clinicians. However, reliance on a single questionnaire could result in the potential for over- or under-treatment. No questionnaire is a perfect replacement for a thorough medical history and clinical judgement.

Results of sensitivity analyses support the robustness of our primary analyses and help to characterise further the relationship between the ACT and GINA control classifications. When we removed exacerbations as a criterion, more patients were defined as having controlled asthma by the GINA definition, and the negative predictive value of the ACT score improved substantially to 72%, with

kappa improved to 0.58. For predicting uncontrolled asthma, the maximum kappa values were at ACT scores of ≤ 14 (0.55) and ≤ 15 (0.53). Of note, an ACT score of ≤ 15 was identified previously by Schatz and coworkers²⁰ as the optimal cut-off point defining uncontrolled asthma.

Nonetheless, the use of prior exacerbations in identifying at-risk patients is supported by results of enquiries into asthma deaths³¹ and by the GINA guidelines, which include "no exacerbations" as a criterion for asthma control.³ Asthma control is a complex concept, and as no single measure encompasses the full complexity of asthma, composite outcome measures that include measures of current symptom control and disease impact as well as future risk are advocated.³²

In the clinic (or consulting room) it may be difficult to evaluate exacerbations, and the relevance of a prior exacerbation with regard to asthma control may be difficult to judge; for example, the relevance will vary according to whether there is a seasonality to exacerbations or whether treatment had been changed since an exacerbation. Nevertheless, to ignore exacerbations is to miss an important facet of the disease. Our study was a real world study and thus reflective of real world hurdles that clinicians face in interpreting GINA guidelines. Indeed, applying any guideline criterion can be difficult in a real world setting.

A survey of this nature has several limitations, including the possibility of patient selection bias, since the participants represent a convenience sample and may not be representative of the overall population of patients with asthma – although they may be representative of the consulting population in whom these instruments are often used. We recruited larger numbers of physicians in densely populated areas, and physicians were asked to invite consecutive patients to participate, with the goal of collecting cross-sectional data from an unselected real world sample. In most countries, over two-thirds of patients returned completed surveys that could be matched to their physicians' forms. The two exceptions were Spain and the UK, where only 54% and 26% of patients, respectively, completed their surveys, raising the possibility of non-response bias for those countries. Poor UK response rates appear to have resulted from a combination of physicians not asking patients to complete the surveys, combined with low response rates from patients. Another limitation of this survey is that the quality of data relied on provision of accurate data from physicians and patients. In addition, some of the survey questions were not directly equivalent to the GINA criteria; for example, the question on the patient-completed form for exercise limitation ("[has] your asthma ... stopped you taking part in every day activities?") could be interpreted differently from the wording used in the actual GINA table ("limitations of

activities"). Moreover, the Respiratory DSP VI questionnaire was not validated. Finally, we cannot rule out recall bias on the part of participating patients.

A strength of this survey is its inclusion of a large multinational patient population from both primary and specialist care. The greater percentage of women than men (56% vs. 44%) in our survey mirrors the greater prevalence of asthma among adult women worldwide.¹ Moreover, our findings confirm the prevalence of uncontrolled asthma among consulting patients,^{9,10} with only 934/2949 (32%) of patients categorised as having GINA controlled asthma and 1668/2949 (57%) having an ACT score of ≥ 20 , the cut-off point for well-controlled asthma.

In conclusion, we found that an ACT score ≤ 19 is useful to identify patients with poorly controlled asthma for whom a full clinical review is needed. Further studies are needed to evaluate the benefits of the ACT over time in a real world setting. The ACT is easily and rapidly completed by patients and can serve as a useful tool in the clinic to assess asthma control, ideally in conjunction with a complete medical history and lung function testing.

Discussion Summary

a) Difficulties

Low patient yield in UK

b) Alternative methodologies

A reverse approach, in which the GINA classification, which has not been validated, is tested against the ACT as the gold standard could have been of interest

c) New questions arising

Need to test ACT in a real world clinical setting, adjusting therapy according to score, to evaluate outcomes

d) Lessons for clinical practice

ACT score ≤ 19 useful clinically in identifying patients with poorly controlled asthma

Data from this study were presented as a late breaker abstract at the International Primary Care Respiratory Group conference, 28-31 May 2008, Seville, Spain.

Conflicts of interest

Elizabeth V Hillyer has received freelance writing assignments from Merck and Aerocrine. She has no shares in any pharmaceutical company.

Professor David Price has consultant arrangements with: Altana, Boehringer-Ingelheim, GlaxoSmithKline, Ivax and Pfizer. He or his team have received grants and research support for research in respiratory disease from the following organisations: UK National Health Service, Altana Pharma, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Ivax, Merck Sharpe and Dohme, Novartis, Pfizer, and Schering Plough. Professor Price has also spoken for: Altana Pharma, Boehringer-Ingelheim, GlaxoSmithKline, Merck, Sharpe and Dohme and Pfizer.

Angela E. Williams and Jacqueline R Carranza Rosenzweig are employees of GlaxoSmithKline.

Neither Mike Thomas nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years he has received fees for acting as a consultant for MSD, Schering and GSK, has received speaker's honoraria for

speaking at sponsored meetings from the following companies marketing respiratory and allergy products: AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Teva. He has received honoraria for attending advisory panels with: Altana, Astra Zeneca, BI, GSK, MSD, Merck Respiratory, Schering-Plough, Teva. He has received sponsorship to attend international scientific meetings from: GSK, MSD, Astra Zeneca. He has received funding for research projects from: GSK, MSD, Astra Zeneca. He holds a research fellowship from Asthma UK.

Funding

Funding support was provided by Global Health Outcomes, GlaxoSmithKline R&D Building 11, 1st Floor, Stockley Park West, Uxbridge, Middlesex UB11 1BU, UK.

Acknowledgement

The authors would like to acknowledge the help of Victoria Higgins in these analyses.

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Available online at <http://www.thepcrj.org>

Appendices and Online Tables and Figures

Appendix 1. Asthma Control Test™ as included in the Respiratory DSP VI survey

Asthma Control Test™

The following test can help people with asthma (12 years or older) assess their asthma control. Please circle the appropriate score for each question. There are FIVE questions in total. Please answer the questions as honestly as possible.

35a. During the past **4 weeks**, how often did your **asthma** prevent you from getting as much done at work, school or home?

- 1 All the time 2 Most of the time 3 Some of the time 4 A little of the time 5 None of the time

35b. During the past **4 weeks**, how often have you had shortness of breath?

- 1 More than once a day 2 Once a day 3 3-6 times a week 4 1-2 times a week 5 Not at all

35c. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

- 1 4 or more nights a week 2 2 to 3 nights a week 3 Once a week 4 Once or twice 5 Not at all

35d. During the past **4 weeks**, how often have you used your rescue inhaler (such as salbutamol)?

- 1 3 or more times a day 2 1 or 2 times a day 3 2 or 3 times a week 4 Once a week or less 5 Not at all

35e. How would you rate your **asthma** control during the past **4 weeks**?

- 1 Not controlled 2 Poorly controlled 3 Somewhat controlled 4 Well controlled 5 Completely controlled

Appendices and Online Tables and Figures

Appendix 2. Questions on physician-completed survey form used to derive GINA control classification in the Respiratory DSP VI survey

D SYMPTOMS -continued

3. Thinking about this patient over the past 4 weeks, how often has this patient experienced any of the following? (please tick one box for each characteristic)

	A		B
a) Daytime symptoms	<input type="checkbox"/> Twice a week or less	or	<input type="checkbox"/> More than twice a week
b) Nocturnal symptoms or awakening	<input type="checkbox"/> None of the time	or	<input type="checkbox"/> One or more times
c) Need for rescue treatment	<input type="checkbox"/> Twice a week or less	or	<input type="checkbox"/> More than twice a week
d) Limitation of activities	<input type="checkbox"/> None of the time	or	<input type="checkbox"/> One or more times

4. If this patient has three or more ticks in column B above, have 3 or more of these occurred in any one week during the last 4 weeks?

Yes No

C DIAGNOSTIC HISTORY

- 1a. Please tick if the following spirometry tests have been measured in this patient in the last 12 months
- 1b. When was this patient's last spirometry test?
- 1c. What was the most recent level recorded in the patient (if known)?
- 1d. What was the most recent percentage predicted value recorded in this patient (if known)?
- 1e. Was this most recent test performed pre or post bronchodilator?

	(a) Test measured in last 12 months?			(b) Last test?			Results		(e) Pre or post bronchodilator		
	Yes 1	No 2	Dk 3	last 3 mths 1	4-12 mths ago 2	Over 12 mths ago 3	(c) level recorded	(d) % predicted (if known)	Pre 1	Post 2	Dk 3
FEV ₁ (Forced Expiratory Volume in 1 second)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____ (litres)	_____ %	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PEFR (Peak Expiratory Flow rate)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____ (litres)	_____ %	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
FVC (Forced Vital Capacity)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____ (litres)	_____ %	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
FEV ₁ /FVC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____ %	n/a	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3a. How many exacerbations has this patient suffered in the last 12 months? _____

3b. How long ago did this patient suffer their last exacerbation? _____ days ago _____ weeks ago _____ months ago

Appendices and Online Tables and Figures

Appendix 3. Questions on patient-completed form used to derive GINA control classification in the Respiratory DSP VI survey

8a. In the last **4 weeks**, have you experienced any of the following in the list below? (please tick **one** box for each point listed)

	Column (A)	or	Column (B)
a) Daytime symptoms	<input type="checkbox"/> Twice a week or less		<input type="checkbox"/> More than twice a week
b) Night time symptoms or waking up earlier in the morning than usual	<input type="checkbox"/> None of the time		<input type="checkbox"/> One or more times
c) Your asthma has stopped you taking part in every-day activities	<input type="checkbox"/> None of the time		<input type="checkbox"/> One or more times
d) The need to take your rescue inhaler such as salbutamol	<input type="checkbox"/> Twice a week or less		<input type="checkbox"/> More than twice a week

8b. If you have 3 or more ticks in column (B), did these happen in any one week during the last 4 weeks?

Yes No

17. Have you ever had times in the last 12 months when you had to seek further medical help for your increased asthma symptoms?

Yes → (Go to question 18) No → (Go to question 21)

Appendices and Online Tables and Figures

Online Table 1. Performance of the ACT score at different cut-off points in predicting GINA categories of asthma control (controlled versus partly controlled/uncontrolled) for all patients (n=2949), with lung function criterion included for those patients who had lung function data (n=539)

	Sensitivity	Specificity	Correctly classified	Positive predictive value	Negative predictive value
≥5	0	100	30	--	30
≥6	0	100	30	100	30
≥7	1	100	30	100	30
≥8	2	100	31	100	30
≥9	3	100	32	100	31
≥10	6	100	34	100	31
≥11	8	100	35	100	32
≥12	11	100	37	100	32
≥13	14	100	40	100	33
≥14	18	100	42	99	34
≥15	22	99	45	99	35
≥16	28	99	49	98	37
≥17	34	98	53	97	39
≥18	41	97	58	97	41
≥19	49	95	63	96	44
≥20	58	92	68	94	49
≥21	69	86	74	92	54
≥22	79	75	78	88	60
≥23	86	60	78	83	65
≥24	91	43	76	79	66
≥25	94	28	74	75	66

All data are percentages.
 Area under ROC = 0.84 (95% CI 0.82–0.85)
 For each ACT score cut point, the:
 * Sensitivity is defined as the percentage of patients with GINA-defined partly controlled/uncontrolled asthma who were identified by the ACT as belonging to this group.
 † Specificity is defined as the percentage of patients with GINA-defined controlled asthma who were identified by ACT as belonging to this group.
 ‡ Positive predictive value, or the predictive value of a positive test, is the percentage of patients whom ACT predicts correctly to have partly controlled/uncontrolled asthma based on the GINA classification.
 ** Negative predictive value, or the predictive value of a negative test, is the percentage of patients whom ACT predicts correctly to have controlled asthma based on the GINA classification.

Online Table 2. Performance of the ACT score at different cut-off points in predicting GINA categories of asthma control (controlled versus partly controlled/uncontrolled) for patients with lung function data (n=539) - lung function criterion applied in GINA definition

	Sensitivity	Specificity	Correctly classified	Positive predictive value	Negative predictive value
≥5	(no 5 responses)				
≥6	0	100	17	--	17
≥7	0	100	17	100	17
≥8	2	100	19	100	18
≥9	3	100	20	100	18
≥10	6	100	22	100	18
≥11	9	100	24	100	19
≥12	12	100	27	100	19
≥13	17	100	32	100	20
≥14	21	100	35	100	21
≥15	26	100	39	100	22
≥16	30	100	42	100	23
≥17	38	100	48	100	25
≥18	44	100	54	100	27
≥19	51	98	59	99	30
≥20	59	96	65	98	32
≥21	68	87	71	96	36
≥22	76	81	77	95	41
≥23	83	66	80	92	45
≥24	89	51	82	90	48
≥25	94	29	83	86	51

All data are percentages.
 Area under ROC = 0.85 (95% CI 0.82–0.89)

Appendices and Online Tables and Figures

Online Table 3. Performance of the ACT score at different cut-off points in predicting GINA categories of asthma control (controlled versus partly controlled/uncontrolled) for patients with lung function data (n=539)—lung function criterion not applied in GINA definition

	Sensitivity	Specificity	Correctly classified	Positive predictive value	Negative predictive value
≥5	0	100	46	--	46
≥6	1	100	46	100	46
≥7	1	100	46	100	46
≥8	3	100	47	100	46
≥9	4	100	48	100	47
≥10	7	100	49	98	47
≥11	10	100	51	98	48
≥12	13	100	53	97	49
≥13	18	99	55	98	50
≥14	23	99	58	98	52
≥15	28	99	61	97	54
≥16	35	98	63	96	56
≥17	42	97	67	94	58
≥18	51	96	71	94	62
≥19	61	94	76	92	67
≥20	71	89	79	88	72
≥21	81	80	81	83	78
≥22	89	69	80	78	84
≥23	95	55	77	72	90
≥24	98	39	71	66	93
≥25	99	26	65	61	93

All data are percentages.
Area under ROC = 0.85 (95% CI 0.81–0.88)

Online Table 4. Performance of the ACT score at different cut-off points in predicting GINA categories of asthma control (controlled versus partly controlled/uncontrolled) for all patients (n=2949)—exacerbation criterion removed from GINA definition

	Sensitivity	Specificity	Correctly classified	Positive predictive value	Negative predictive value
≥5	0	100	46	--	46
≥6	1	100	46	100	46
≥7	1	100	46	100	46
≥8	3	100	47	100	46
≥9	4	100	48	100	47
≥10	7	100	49	98	47
≥11	10	100	51	98	48
≥12	13	100	53	97	49
≥13	18	99	55	98	50
≥14	23	99	58	98	52
≥15	28	99	61	97	54
≥16	35	98	63	96	56
≥17	42	97	67	94	58
≥18	51	96	71	94	62
≥19	61	94	76	92	67
≥20	71	89	79	88	72
≥21	81	80	81	83	78
≥22	89	69	80	78	84
≥23	95	55	77	72	90
≥24	98	39	71	66	93
≥25	99	26	65	61	93

All data are percentages.
Area under ROC curve = 0.89 (95% CI 0.88 –0.90)

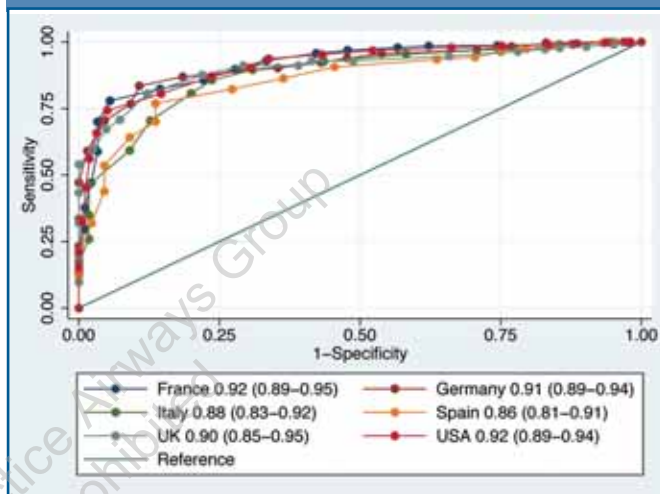
Appendices and Online Tables and Figures

Online Table 5. Performance of the ACT score at different cut-off points in predicting GINA categories of asthma control with the binary split of uncontrolled versus partly controlled/controlled (exacerbation criterion removed from GINA definition) for all patients (n=2949)

	Sensitivity	Specificity	Correctly classified	Positive predictive value	Negative predictive value
≥5	0	100	85	85	85
≥6	2	100	85	89	85
≥7	3	100	85	82	85
≥8	8	100	86	85	86
≥9	12	99	86	78	86
≥10	18	99	86	73	87
≥11	27	98	87	73	88
≥12	33	97	87	69	89
≥13	45	96	88	68	91
≥14	53	95	88	65	92
≥15	63	93	88	61	93
≥16	69	89	86	54	94
≥17	78	86	84	49	96
≥18	86	81	81	45	97
≥19	92	74	77	39	98
≥20	95	66	70	34	99
≥21	98	55	62	28	99
≥22	98	44	52	24	99
≥23	99	33	43	21	100
≥24	100	23	34	19	100
≥25	100	15	28	18	100

All data are percentages.
Area under ROC curve = 0.91 (95% CI 0.89–0.92)

Online Figure 1. Receiver operating characteristics (ROC) curves for the Asthma Control Test score predicting the Global Initiative for Asthma (GINA) control classification—using GINA binary split of uncontrolled vs partly controlled/controlled asthma and the exacerbation criterion removed from GINA definition—for the six countries included in the survey. The legend shows area under the ROC curve (95% CI) for each country.



Online Figure 2. Distribution of GINA control categories relative to ACT scores for outpatients with asthma (n=2949) in five European countries and the US - exacerbation criterion removed from GINA definition.

