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Original Research

ASTHMA

Monitoring Asthma Control in Children With Allergies by Soft Computing of Lung Function and Exhaled Nitric Oxide

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Background: **Asthma control is emphasized by new guidelines but remains poor in many children. Evaluation of control relies on subjective patient recall and may be overestimated by health-care professionals. This study assessed the value of spirometry and fractional exhaled nitric oxide (FeNO) measurements, used alone or in combination, in models developed by a machine learning approach in the objective classification of asthma control according to Global Initiative for Asthma guidelines and tested the model in a second group of children with asthma.**

Methods: **Fifty-three children with persistent atopic asthma underwent two to six evaluations of asthma control, including spirometry and FeNO. Soft computing evaluation was performed by means of artificial neural networks and principal component analysis. The model was then tested in a cross-sectional study in an additional 77 children with allergic asthma.**

Results: **The machine learning method was not able to distinguish different levels of control using either spirometry or FeNO values alone. However, their use in combination modeled by soft computing was able to discriminate levels of asthma control. In particular, the model is able to recognize all children with uncontrolled asthma and correctly identify 99.0% of children with totally controlled asthma. In the cross-sectional study, the model prospectively identified correctly all the uncontrolled children and 79.6% of the controlled children.**

Conclusions: **Soft computing analysis of spirometry and FeNO allows objective categorization of asthma control status.**

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Abbreviations: $FEF_{25\%-75\%}$ = forced expiratory flow between 25% and 75% of FVC; FeNO = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; PCA = principal component analysis

Asthma guidelines assist physicians in evaluating patients' asthma severity and prescribing appropriate treatment. Earlier guidelines classified asthma by severity, however, it was recognized that asthma symptoms do not always correlate with severity[1] and that asthma severity varies with time.[2] Thus, newer guidelines emphasize not merely asthma severity but also asthma control.[3] Once control has been achieved, ongoing monitoring is essential to establish the minimum necessary treatment as the disease fluctuates.[4] Modern guidelines emphasize the need to measure morbidity using inflammatory markers, symptoms, medication use, exacerbations, and lung function.[3] However, assessment of asthma control relies on patient recall, and this may be complicated by poor symptom perception and, thus, may be unreliable. Objective means of assessing control would be useful as an end point in clinical trials.

Different cutoff values of prebronchodilator FEV_1 were found to be predictive of the risk of asthma exacerbations,[5] but exacerbations and control do not reflect the same aspects of asthma.[6] Fractional exhaled

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nitric oxide (FeNO) measurement, a noninvasive biomarker of airway inflammation,[7] may be used to monitor steroid response and steroid requirements.[8] However, as with spirometry, sensitivity and specificity of FeNO when used to guide treatment in individuals often is not satisfactory. Furthermore, portable spirometers and nitric oxide analyzers are now available, making routine testing a practical possibility.

Basic elements of soft computing and the application of intelligent control have been introduced[9] to help physicians in the interpretation of data and decision making. The term "soft computing" denotes methodologies that try to mimic the human mind, instructing the computer to deal with imprecision, uncertainty, and partial truth and to include all these data in arithmetical algorithms able to counterbalance precision and uncertainty in a way similar to that which is normally done by the human brain. The methodologies used are principal component analysis (PCA), fuzzy logic, neural networks, and genetic algorithms and programming.[10] More details of these methods are provided in e-Appendix 1.

We hypothesized that using a soft computing learning approach[11] applied to spirometry, FeNO, or both would allow the development of models predictive of asthma control. Having generated the model in a longitudinal cohort, we prospectively validated it in a second cohort of children with asthma.

Materials and Methods

Longitudinal Study

The study (discovery) population consecutively enrolled children given a new diagnosis of mild to moderate persistent allergic asthma.[3] At the screening visit, medical history, physical examination, skin prick tests with a panel of standardized allergen extracts, spirometry pre- and postbronchodilator, and FeNO were performed in all patients according to recommended methodologies.[12-14]

Classification of asthma severity according to Global Initiative for Asthma (GINA) guidelines[3] was performed, and treatment was always prescribed by the same investigator (M. P.), who was blinded to the FeNO results. Both parents and children were then asked to participate in a follow-up program that in addition to routine investigations (spirometry and FeNO measurement) and clinical judgment included the use of soft computing. All the participants gave informed consent to participate to the study, which was approved by the Hospital Ethical Committee of Pisa.

Follow-up

Ninety days after enrollment and every 3 months during the study period, recent history of asthma symptoms, antiasthma therapy, and spirometry were recorded, and a classification of asthma control (controlled, partly controlled, and uncontrolled, respectively),[3] was always done by the same physician (M. P.). In particular, levels of asthma control were subjectively defined for the presence or absence of daytime symptoms, limitations of activities, nocturnal symptoms or awakening, need for reliever or rescue treatment, and FEV_1 results. Furthermore, any exacerbation (ie, acute episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness or some combinations of those symptoms that required repetitive administration of short-acting inhaled bronchodilators and systemic glucocorticoids)[3] in any week was recorded. The level of asthma control and current therapy determined the adjustment of treatment. An independent investigator (M. D. C.) performed the FeNO measurements at each visit, but the principal investigator (M. P.) remained blinded. FeNO and spirometry (FVC; FEV_1; forced expiratory flow between 25% and 75% of FVC [$FEF_{25\%-75\%}$]; and FEV_1/FVC) together with the clinical judgment were used for soft computing evaluation.

Soft Computing Evaluation

Pattern recognition models (ie, methods that search for structures in data[15]) were applied to quantify the potential of the extracted values of FeNO and spirometry (FVC, FEV_1, $FEF_{25\%-75\%}$, FEV_1/FVC) in discriminating among the three levels of asthma control as reported in GINA. Finally, a model based on artificial neural networks (ie, a mathematical model that tries to simulate the structure and/or functional aspects of biologic neural networks[16]) was developed for the classification of patients on the basis of FeNO and spirometry, alone or in combination, into the categories of controlled, partly controlled, and uncontrolled asthma.[3] Full details of the methods are provided in e-Appendix 1.

Cross-sectional Study

The model was then prospectively tested in another cohort (validation) of children. Clinical evaluation was always by the same investigator (A. L. B.), who was unaware of FeNO results. FeNO and spirometry always were performed by a different investigator (I. C.), using exactly the same methodology as the longitudinal study.

Statistical Analysis

Baseline variables were described as group mean ± SD, with the exception of FeNO values, which were expressed as median and interquartile range. Differences between means and distributions of FEV_1, FVC, $FEF_{25\%-75\%}$, and FEV_1/FVC measurements were evaluated by the two-tailed Student *t* test. Differences among FeNO medians were assessed by Mann-Whitney (Wilcoxon) *U* test.

Sample size was evaluated using the rule of thumb that a predictive logistics model should be used with a minimum of 10 events per predictor variable.[17] Because the outcome has three levels (controlled, partially controlled, and uncontrolled asthma) and there are five predictor variables (FVC, FEV_1, FEV_1/FVC, $FEF_{25\%-75\%}$, FeNO), the minimum number of necessary visits is $50 + 50 + 50 = 150$ observations.

Results

Fifty-three children (40 boys, 13 girls) aged 11.5 ± 2.4 years (range, 7.5 to 17 years) were included in the longitudinal study. All were nonsmokers and had at least one positive skin prick test. All had persistent asthma that was considered mild in 28 (52.8%), moderate in 14 (26.5%), and severe in 11 (20.7%) by GINA classification of severity.

Patients had from two to six follow-up visits. Fifty (94.3%) patients had at least four visits, and 41 (77.4%) had all the six visits. Mean lung function values and

FeNO measurements are reported in Table 1. After 3 months of guideline-driven pharmacologic treatment (visit 2) (Table 1), there were statistically significant increases in FEV_1 ($P = .03$) and $FEF_{25\%-75\%}$ ($P = .004$) and a significant decrease in FeNO ($P = .01$). There were nonsignificant changes in FVC ($P = .2$) and FEV_1/FVC ($P = .09$). In a total of 294 subsequent visits, there generally were no significant changes between successive evaluations. During follow-up, asthma was controlled in 169 (57.5%) occasions, partly controlled on 95 (32.3%), and uncontrolled on 30 (10.2%). The 30 visits with uncontrolled asthma occurred in 20 different children, but only six children had an exacerbation during follow-up. Because the number is so low, exacerbations were not analyzed further. Mean ± SD lung function, percent-predicted values, and median and interquartile range for FeNO values on the occasions of controlled, partially controlled, and uncontrolled asthma and during exacerbations are reported in Figure 1. As can be seen, lung function parameters were higher and FeNO values lower on occasions when asthma was controlled than on those of partially controlled and uncontrolled asthma, but there was a considerable overlap among the three different conditions.

PCA was successively applied to this data set. First, a subset consisting of only the four lung function variables (FVC, FEV_1, $FEF_{25\%-75\%}$, FEV_1/FVC) was analyzed. Figure 2 is a three-dimensional scatterplot of the first three principal components from this analysis. There is no cluster that corresponds with any GINA classification of asthma control; thus, it is impossible to discriminate among levels of control. Next, PCA was performed on the FeNO data. Again, the analysis cannot discriminate levels of asthma control (Fig 3). Finally, the whole data set (ie, the four lung function variables of FVC, FEV_1, $FEF_{25\%-75\%}$, and FEV_1/FVC and FeNO were analyzed. The PCA topologic map is shown in Figure 4. For each GINA classification of asthma control, there is a corresponding, minimally overlapping cluster. Furthermore, although the numbers are small, the six children with an asthma exacerbation are the outliers.

To explore the discriminatory power of the lung function variables and FeNO, models based on multilayer perception were identified. A threefold cross-validation procedure was applied to test the performance of each model. We developed three different models that input variables as follows:

A. the values of lung function parameters;
B. the values of FeNO;
C. the values of lung function parameters and FeNO.

The mean ± SD percentages of the confusion matrices obtained for the models A, B, and C are reported in Table 2. The model based on lung function alone is able to recognize all patients with uncontrolled asthma but overestimates partial control as controlled and minimally underestimates patients who are controlled. The model based on only FeNO identifies 99% of patients with controlled asthma but overestimates control in patients who are completely uncontrolled. Finally, the use of the combined parameters correctly identifies all patients with uncontrolled asthma, 99.0% of those with total control, and 74% of those with partial control.

Next, we evaluated this model in a new (validation) cohort of patients (Table 3). Seventy-seven children (44 boys) aged 10.0 ± 2.0 years (range, 6-15 years) were recruited. Thirty-five had persistent asthma, and 42 had intermittent asthma.[3] Patients with intermittent asthma had a written plan to use short-acting bronchodilators and inhaled or oral corticosteroids when needed. Of the patients with persistent asthma, 21 were prescribed fluticasone propionate metered-dose inhaler 100 μg bid, and 14 were using regular treatment with combined salmeterol/fluticasone 25/50 μg bid plus montelukast 5 mg optimal dose. Of the 42 children with intermittent asthma, six (14.3%) had uncontrolled asthma, 19 (45.2%) partially controlled, and 17 (40.5%) controlled. In children with persistent asthma, the disease was uncontrolled in four (11.4%), partially controlled in 10 (28.6%), and controlled in 21 (60%). Spirometry and FeNO values are reported in Table 3. The mean ± SD percentages of the obtained

Table 1—*Lung Function and FeNO Values During Longitudinal Evaluations*

Parameters Evaluated	Follow-up Visits					
	1	2	3	4	5	6
No. subjects (male/female sex)	53 (36/17)	53 (36/17)	51 (35/16)	50 (34/16)	46 (30/16)	41 (26/15)
FEV_1 %	95.9 ± 17.9	102.8 ± 14.8	102.1 ± 13.9	101.6 ± 14.0	99.3 ± 15.2	100.8 ± 15.3
FVC %	93.6 ± 16.6	97.7 ± 13.7	97.2 ± 14.1	96.9 ± 14.6	93.7 ± 14.0	95.7 ± 14.4
$FEF_{25\%-75\%}$	82.1 ± 28.5	97.8 ± 27.6	95.9 ± 22.5	96.5 ± 21.9	98.4 ± 27.8	97.9 ± 24.1
FEV_1/FVC %	101.9 ± 9.3	104.7 ± 7.9	104.9 ± 6.9	105.0 ± 7.4	105.8 ± 8.0	105.4 ± 7.7
FeNO, ppb	20.2 (32)	14.9 (10.4)	14.8 (11.3)	13.6 (11.5)	15.8 (17.7)	17.7 (23.0)

Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated. $FEF_{25\%-75\%}$ = forced expiratory flow, between 25% and 75% of FVC; FeNO = fractional exhaled nitric oxide; ppb = parts per billion.

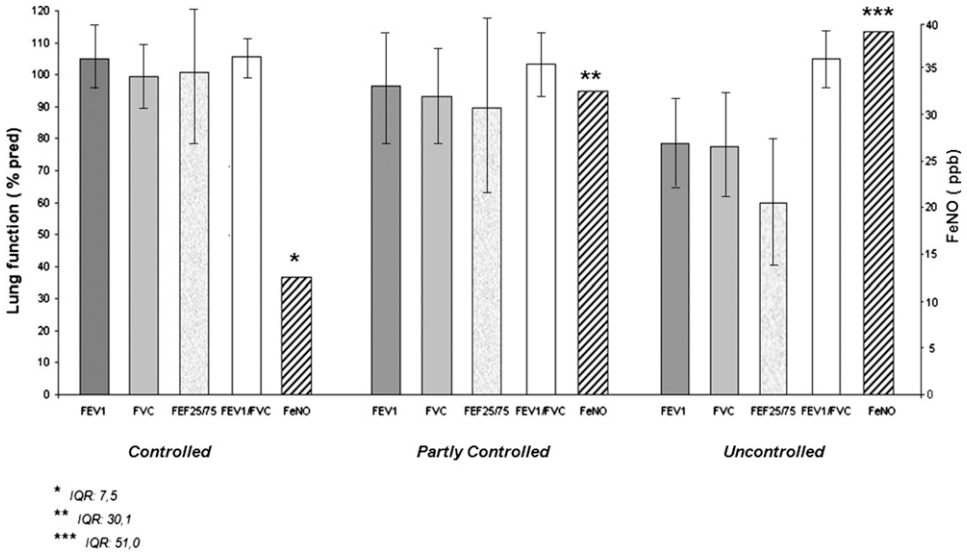

FIGURE 1. Mean ± SD lung function, percent-predicted values, and median and IQR of fractional exhaled nitric oxide values in occasions of controlled, partially controlled, uncontrolled asthma. Exacerbations are included in the uncontrolled asthma group. FEF25/75 = forced expiratory flow between 25% and 75% of FVC; FeNO = fractional exhaled nitric oxide; IQR = interquartile range; ppb = parts per billion.

confusion matrices for the models A, B, and C are reported in Table 4. The model based on lung function alone is able to recognize all the patients with uncontrolled asthma but underestimates control and does not distinguish partial control. The model based only on FeNO does not identify patients who are uncontrolled at all. Finally, the use of the combined parameters (Fig 5, Table 4) correctly identifies all the patients with uncontrolled asthma and almost 80% of those with total and partial control.

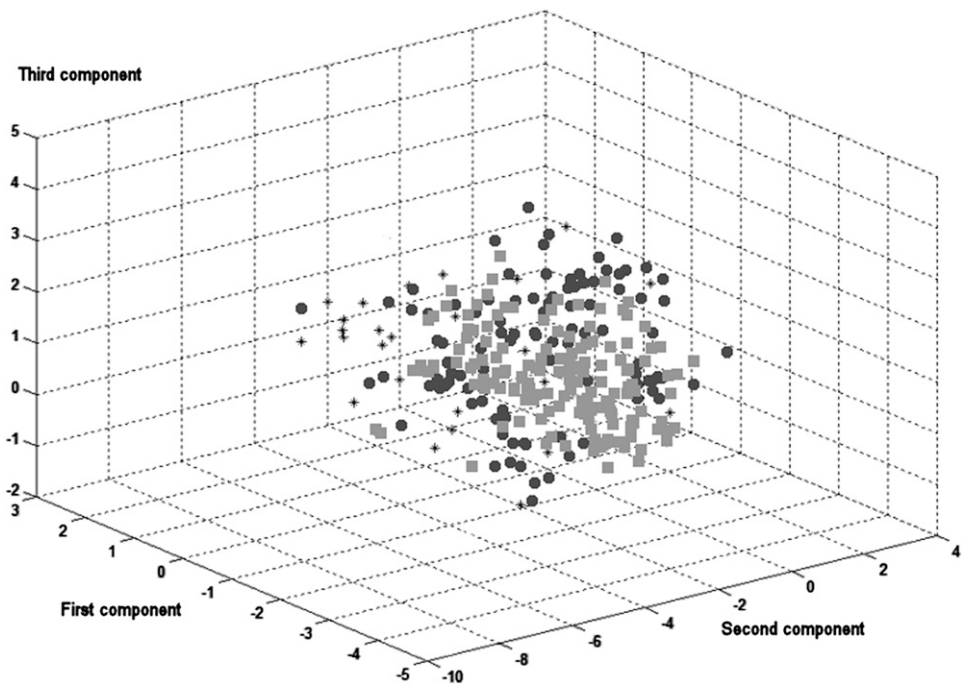

FIGURE 2. Principal component analysis (PCA) on lung function variables for each Global Initiative for Asthma (GINA) classification. The three components are generated by a mathematical procedure that selects the three components that explain as much of the variance in the data as possible. See e-Appendix 1 for further explanations. ∗ = uncontrolled; ● = partially controlled; ■ = controlled.

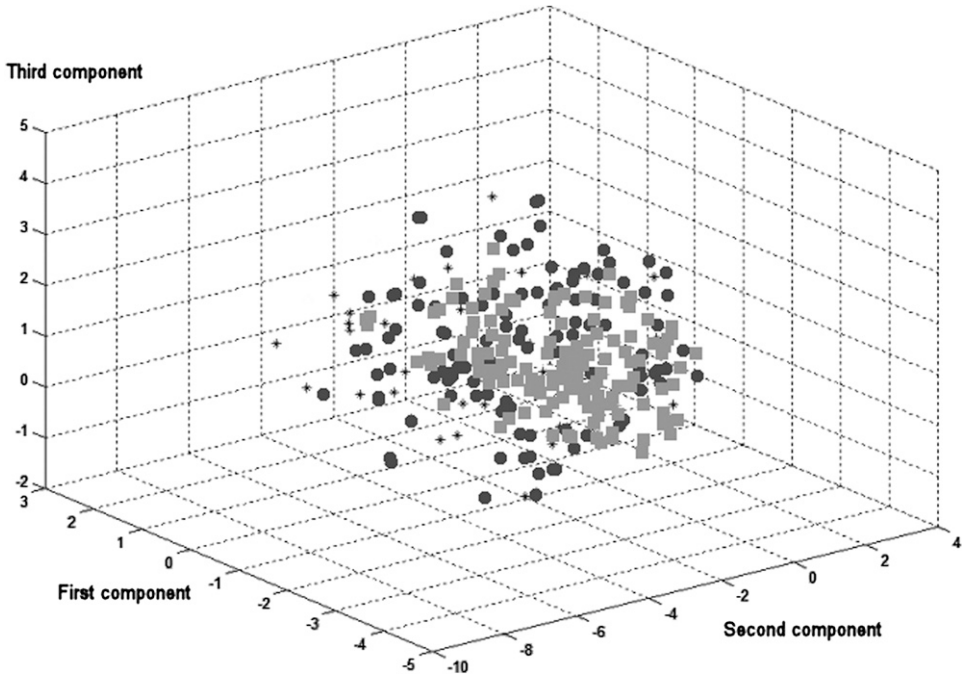

FIGURE 3. PCA on fractional exhaled nitric oxide (FENO) for each GINA classification. ∗ = uncontrolled; ● = partially controlled; ■ = controlled. See Figure 2 legend for expansion of abbreviations.

DISCUSSION

We have used soft computing to develop a model to discriminate level of asthma control.[3] The model required only two simple measurements, namely spirometry and FENO, and performs better than the use of either measurement alone. Furthermore, we have prospectively validated the model in a second cohort of patients with asthma. Thus, soft computing of spirometry and FENO may allow objective monitoring of control status in patients with allergic asthma.

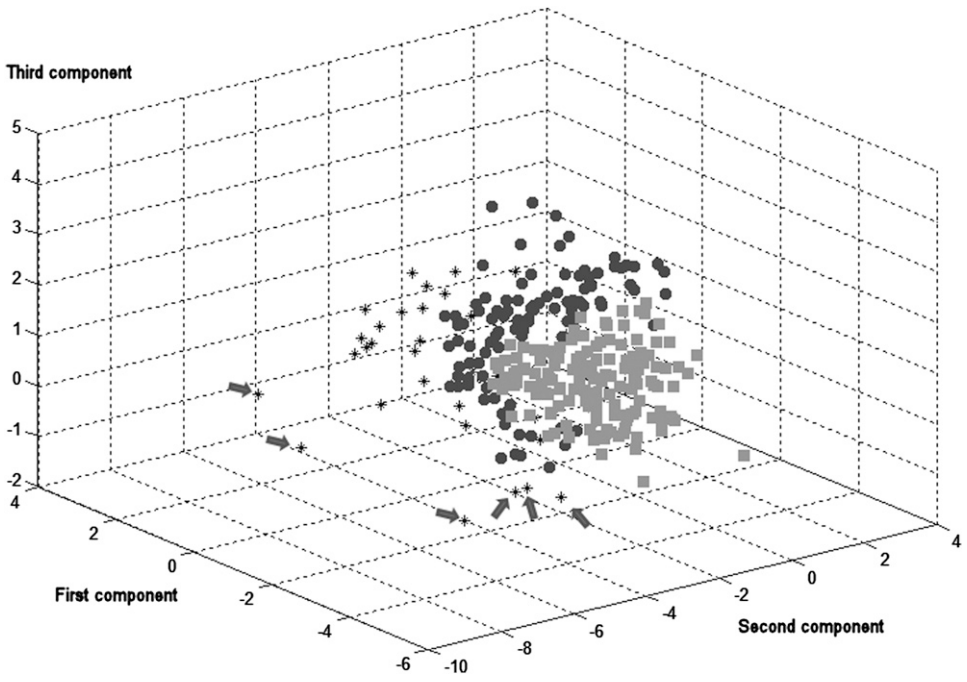

FIGURE 4. PCA on lung function variables and FENO for each GINA classification. Arrows identify occasions with exacerbations. ∗ = uncontrolled; ● = partially controlled; ■ = controlled. See Figure 2 and 3 legends for expansion of abbreviations.

Table 2—*A, B, and C Models: Percentages of Correct Classification of Asthma Control as Reported in GINA*

Model	Asthma Control by GINA		
	Controlled	Partially Controlled	Uncontrolled
Model A: asthma control by an MLP model based on lung function variables			
Controlled	90.0 ± 0.6	8.5 ± 0.5	1.5 ± 0.1
Partially controlled	64.1 ± 0.3	4.9 ± 0.5	31.0 ± 0.2
Uncontrolled	0.0 ± 0.0	0.0 ± 0.0	100.0 ± 0.0
Model B: asthma control by an MLP model based on FeNO			
Controlled	99.0 ± 0.2	1.0 ± 0.2	0.0 ± 0.0
Partially controlled	32.5 ± 0.5	67.5 ± 0.5	0.0 ± 0.0
Uncontrolled	23.5 ± 0.4	76.5 ± 0.5	0.0 ± 0.0
Model C: asthma control by an MLP model based on lung function variables and FeNO			
Controlled	99.0 ± 0.3	1.0 ± 0.1	0.0 ± 0.0
Partially controlled	20.0 ± 0.2	73.8 ± 0.5	6.2 ± 0.4
Uncontrolled	0.0 ± 0.0	0.0 ± 0.0	100.0 ± 0.0

Data are presented as mean ± SD. GINA = Global Initiative for Asthma; MLP = multilayer perception. See Table 1 legend for expansion of other abbreviation.

All the children in our study were atopic, and thus, our results should not be extrapolated to children with nonatopic, viral-triggered asthma. However, the allergic asthma phenotype is the most common in the age range in which high-quality spirometry and accurate measurement of FeNO can be obtained. Furthermore, it should be noted that the children we studied were relatively mildly affected. Thus, the findings should not be extrapolated to children with more severely atopic conditions.

Noninvasive biomarkers increasingly are used as adjuncts to clinical judgment and lung function to adjust therapy.[18] Among these, FeNO is particularly attractive because it is readily measured, provides reproducible results, and changes with treatment and disease fluctuations. Furthermore, FeNO can be measured with hand-held monitoring devices.[19] The use of PCA and other computing tools is increasingly being used to evaluate combinations of measurements. The major novel finding of this study is that a machine learning approach (soft computing) based on four spirometric variables and FeNO evaluation can be used objectively to classify asthma control in children. The combination of measurements was superior to either alone.

Table 3—*Spirometry and FeNO Values of Children With Asthma Evaluated in the Cross-sectional Study*

Parameters Evaluated	Intermittent Asthma	Persistent Asthma	*P* Value
Subjects, No. (%)	42 (54.5)	35 (45.5)	…
Age, y	10.1 (6-15)	10.2 (6-15)	…
Male (female) sex	25 (17)	19 (16)	…
FVC %	103.3 ± 17.5	101.5 ± 12.2	.613
FEV_1 %	100.7 ± 18.9	100.9 ± 14.0	.948
FEV_1/FVC %	97.1 ± 10.6	99.3 ± 9.6	.344
$FEF_{25\%-75\%}$ %	77.7 ± 26.7	82.5 ± 25.6	.422
FeNO, ppb	23.5 (36.9)	21.5 (18.6)	.308

Data are presented as mean ± SD, mean (range), or median (interquartile range), unless otherwise indicated. See Table 1 legend for expansion of abbreviations.

It is well known that FeNO and spirometry provide complementary information; previous work has shown no relationship between FeNO and the degree of airway obstruction despite correlations with airway reactivity, atopic status, allergen exposure,[20,21] the risk of exercise-induced bronchoconstriction,[22] and the presence of nocturnal symptoms.[23] All are important contributors to asthma control for which FeNO may be a partial biomarker. Notwithstanding, that the majority of children with asthma have a normal FEV_1 despite significant asthma symptoms, the different variables derived from the flow-volume curve may provide additional and complementary information, despite the known colinearity between them. FEV_1 may improve the classification of asthma severity in children[5] and may be predictive of subsequent asthma attacks.[24] FVC is a good measure of excessive airway narrowing.[25] Low $FEF_{25\%-75\%}$ value is a risk factor for the persistence of respiratory symptoms,[26] and wheezing is associated with abnormal $FEF_{25\%-75\%}$ values more often than with abnormal FEV_1 or peak expiratory flow in patients with asthma.[27] The FEV_1/FVC ratio should be used to reduce misclassification of airway obstruction.[28] Adding FEV_1/FVC to symptom history may be a more-sensitive and -discriminating parameter.[29]

Thus, it is not surprising that combinations of markers are more useful than a single measurement. Randomized studies of using FeNO alone to guide therapy are conflicting.[8] There are several possible reasons for this conflict, including the relatively poor relationship of FeNO to eosinophilic inflammation in

Table 4—*A, B, and C Models: Percentages Correct Classification of Asthma Control as Reported in GINA in the Cross-sectional (Validation) Cohort*

Model	Asthma Control by GINA		
	Controlled	Partially Controlled	Uncontrolled
Model A: asthma control by an MLP model based on lung function variables			
Controlled	65.1 ± 1.1	21.5 ± 0.5	13.4 ± 0.1
Partially controlled	38.3 ± 0.5	35.0 ± 1.6	26.7 ± 0.2
Uncontrolled	0.0 ± 0.0	0.0 ± 0.0	100.0 ± 0.0
Model B: asthma control by an MLP model based on FeNO			
Controlled	63.2 ± 1.0	36.8 ± 1.1	0.0 ± 0.0
Partially controlled	44.1 ± 1.1	55.9 ± 1.9	0.0 ± 0.0
Uncontrolled	40.0 ± 0.5	60.0 ± 1.2	0.0 ± 0.0
Model C: asthma control by an MLP model based on lung function variables and FeNO			
Controlled	79.6 ± 1.2	20.4 ± 1.0	0.0 ± 0.0
Partially controlled	20.5 ± 0.8	79.5 ± 0.8	0.0 ± 0.0
Uncontrolled	0.0 ± 0.0	0.0 ± 0.0	100.0 ± 0.0

Data are presented as mean ± SD. See Table 1 and 2 legends for expansion of abbreviations.

nonsteroid-naive children,[30] the different study designs, and the dissimilar algorithms used.[31] Nonetheless, whatever the theoretical arguments for or against the use of these different spirometric parameters, the fact remains that their use has allowed us to generate a robust predictive model.

Another group used factor analysis to explore the relationships between different measures of asthma morbidity, such as lung function, symptoms, health-care utilization, serum IgE levels, total eosinophil count, skin test positivity, airway hyperresponsiveness, FeNO, and sputum eosinophil cationic protein. They showed that each of these factors provides independent information in the assessment of asthma.[32] However, the advantage of the approach reported in this article is that we have been able to model control using only two simple measurements that can be performed easily, quickly, and repeatedly in the clinic.

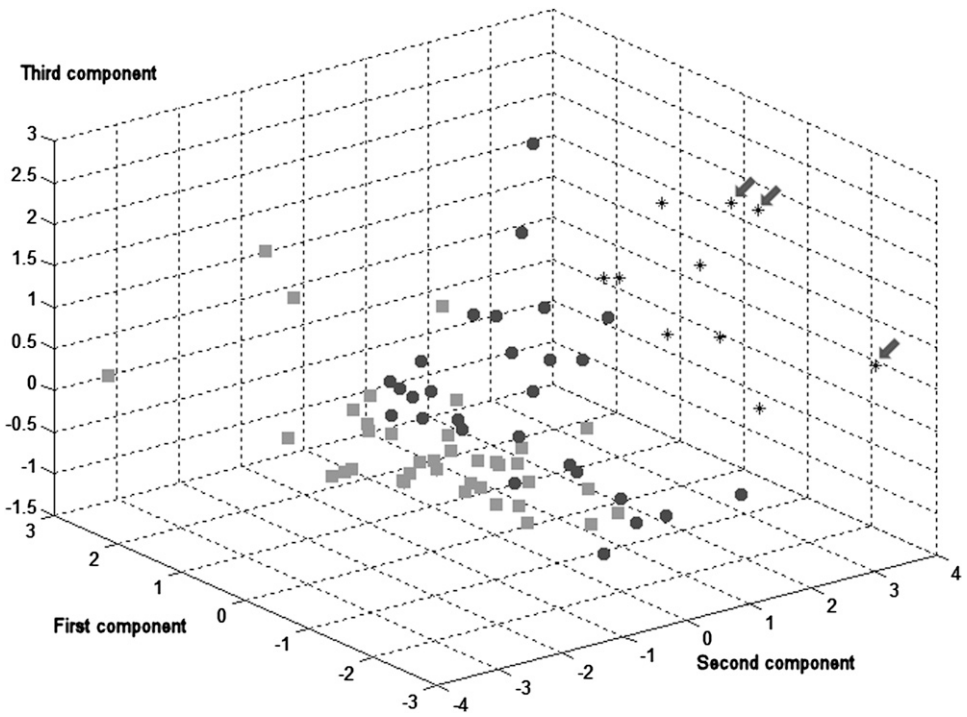

FIGURE 5. PCA on lung function variables and FeNO for each GINA classification of patients in the cross-sectional study. Arrows identify occasions with exacerbations. ∗ = uncontrolled; ● = partially controlled; ■ = controlled. See Figure 2 and 3 legends for expansion of abbreviations.

The main problem with this sort of study is the lack of a gold standard for asthma control. We derived our model from the assessment of control in a specialized asthma clinic. Given current techniques and understanding, it is difficult to think of a better comparator. We suggest that our model will allow objective assessment of control in less-specialized settings, and the model has the further advantage of being based on measurements readily made in the primary-care setting. Furthermore, it allows control to be objectively monitored in the setting of clinical trials.

Another problem with our study is that the number of children who had an asthma exacerbation (n = 3) was too small to reach any conclusions. However, it should be noted that exacerbations and baseline control reflect different facets of asthma severity.[6] A reanalysis of the Pediatric Asthma Controller Trial showed that there was no relationship between risk of exacerbation and baseline control or FeNO levels,[33] which suggests that different tools would be required to predict exacerbations. In this context, it is interesting to note that a mathematical model studying longitudinal short-term fluctuations in lung function can predict the risk of asthma exacerbations.[34]

In conclusion, asthma control remains suboptimal despite clinical practice guidelines and effective asthma treatments.[35] Our model required sophisticated mathematical analyses and computing to develop, but it is simple to use and able to objectively predict asthma control. The model should improve treatment in clinical practice as well as be useful in randomized controlled trials of new therapies. The model has the further advantage of not relying on patient recall of symptoms, which is notoriously subjective.

Acknowledgments

Author contributions: Dr Pifferi had full access to all data and takes full responsibility for their integrity and the accuracy of the data analysis.
Dr Pifferi: contributed to the study design, data evaluation, and drafting of the submitted manuscript.
Dr Bush: contributed to the data evaluation and drafting and revising of the submitted manuscript.
Dr Pioggia: contributed to the data analysis and drafting of the submitted manuscript.
Dr Di Cicco: contributed to the data collection.
Dr Chinellato: contributed to the data collection.
Dr Bodini: contributed to the data collection.
Dr Macchia: contributed to the study design.
Dr Boner: contributed to the study design, data evaluation, and drafting and revising of the submitted manuscript.
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Other contributions: The work was performed at the Department of Pediatrics, University Hospital of Pisa and Verona, and at Institute of Clinical Physiology, CNR, Pisa, Italy. We thank Dr Marco Sandri for the statistical suggestions.
Additional information: The e-Appendix can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/139/2/319/suppl/DC1.

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