

Predicting Responders to Reslizumab after 16 Weeks of Treatment Using an Algorithm Derived from Clinical Studies of Patients with Severe Eosinophilic Asthma

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Abstract

Rationale: Reslizumab is a humanized anti-IL-5 monoclonal antibody used as add-on maintenance treatment for patients with uncontrolled eosinophilic asthma.

Objectives: To predict response and nonresponse to intravenous reslizumab at 52 weeks with an algorithm we developed based on clinical indicators from pivotal clinical trials.

Methods: Patients aged 18 years and older who met Global Initiative for Asthma 4 or 5 criteria and received intravenous reslizumab ($n = 321$) in two trials (www.clinicaltrials.gov identifiers, NCT01287039 and NCT01285323) were selected as the data source. A mathematical model was constructed that was based on change from baseline to 16 weeks in Asthma Control Questionnaire and Asthma Quality of Life Questionnaire scores and FEV₁, and number of clinical asthma exacerbations during the year before enrollment and in the first 16 weeks of treatment, and these measures were evaluated for their ability to predict the outcome at 52 weeks: responder, nonresponder, or indeterminate.

Measurements and Main Results: The algorithm predicted that 276 patients would be classified as responders; in 248 (89.9%), the prediction was correct. In comparison, 26 patients were predicted to be nonresponders; 50.0% of these predictions were correct. Nineteen patients were classified as indeterminate. The algorithm had 95.4–95.5% sensitivity and 40.6–54.1% specificity. Jackknife and cross-study validation confirmed the robustness of the algorithm.

Conclusions: Our algorithm enabled prediction at 16 weeks of treatment of the response to intravenous reslizumab treatment at 52 weeks, but it was not suitable for predicting nonresponse. A positive score at 16 weeks should encourage continued treatment, and a negative score should prompt close monitoring to determine whether discontinuation is warranted.

Keywords: reslizumab; eosinophilic asthma; predictors of response

Severe eosinophilic asthma, characterized by high numbers of eosinophils in sputum and peripheral blood, is a prevalent phenotype associated with reduced lung function, increased risk of severe exacerbations, and

difficulties with asthma symptom control (1, 2). A subset of patients with eosinophilic asthma does not respond adequately to inhaled corticosteroids (ICS) and subsequently requires frequent treatment

with systemic corticosteroids. The frequency of nonresponse to ICS has been reported to be around 20% of patients with eosinophilic asthma (3). Specific therapies targeting the molecular pathways of

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At a Glance Commentary

Scientific Knowledge on the

Subject: Phenotype-guided add-on treatment, such as anti-IL-5 therapy for patients with severe eosinophilic asthma, can improve treatment outcomes. However, the magnitude of response remains difficult to predict, and a minority of patients who qualify for phenotype-based targeted treatments do not respond adequately. Treatment algorithms may facilitate the identification of responders and nonresponders, thus providing evidence to support either continued therapy or the timely cessation of ineffective treatment, respectively.

What This Study Adds to the

Field: Our results indicate that an algorithm based on clinical indicators used in clinical trials (clinical asthma exacerbations, FEV₁, and Asthma Control Questionnaire and Asthma Quality of Life Questionnaire scores, each assessed at 16 wk) can correctly predict a positive response to treatment with intravenous reslizumab at 52 weeks in 90% of cases. The algorithm had a sensitivity of 95.4–95.5% and specificity of 40.6–54.1%, indicating that it is successful in predicting responders but does not reliably predict nonresponders. The methods investigated in this study could potentially help to guide treatment decisions after 16 weeks of intravenous reslizumab therapy, whereby a positive score at 16 weeks should encourage continued treatment.

inflammation have been developed as a means of reducing the degree of dependence on systemic corticosteroids.

Treatment decision tools are used widely throughout medicine. Treatment algorithms have been associated with improved clinical outcomes because they can help ensure that patients receive the most effective available treatment(s) at the right time and in the right dose (4, 5). For asthma, selection of treatment is generally based on baseline symptom control and risk factors (6), with exacerbations and use of oral corticosteroids being

key therapeutic considerations. Disease control may be improved by phenotype-guided add-on treatment, such as anti-IL-5 therapy for patients with severe asthma and elevated blood eosinophils (7, 8). However, phenotypes in severe asthma are often complex, and this heterogeneity likely explains the wide variation in clinical responses to biologics (9). In this setting, an ability to predict whether patients are responding relatively early in the course of treatment may be valuable, both for encouraging continued treatment and for those patients who might not be benefiting, thus reducing unnecessary use of medication and cost. Prediction tools may be developed on the basis of analysis of large datasets derived from interventional trials (10–12). Such an approach is used for treatment with anti-IgE antibody using the global evaluation of effectiveness scale (13), but there are no predictive tools for treatment with other biologics currently approved or in development. Buhl and colleagues recently published a consensus statement based on expert opinion that patients with severe eosinophilic asthma prescribed biologics should receive treatment for at least 4 months before a decision is taken to continue treatment for 1 year (14), but they did not propose a validated method of assessing the response to treatment. A tool that could predict a patient's future clinical response would assist physicians in advising their patients with more certainty beyond this initial treatment period.

Reslizumab is a high-affinity, IgG4/k humanized anti-IL-5 monoclonal antibody (15, 16) approved as add-on therapy for patients with severe asthma and an eosinophilic phenotype (17, 18). In two pivotal phase 3 randomized, placebo-controlled trials, intravenous reslizumab 3.0 mg/kg every 4 weeks was compared with standard-of-care treatment. Reslizumab treatment reduced clinical asthma exacerbations (CAEs), increased lung function (FEV₁), and improved Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ)-7 scores (8). Using data from these two pivotal trials, we developed an algorithm with the aim of predicting response to treatment with reslizumab at 52 weeks based on results after the initial 16 weeks of treatment. Some of the results of this analysis were reported previously in the form of an abstract (19).

Methods

Clinical Trials

This study was performed using data from two replicate, multicenter, double-blind, parallel-group, randomized, 52-week, placebo-controlled phase 3 trials (study 3082 [www.clinicaltrials.gov identifier, NCT01287039] and study 3083 [www.clinicaltrials.gov identifier, NCT01285323]). The methods and results of these trials have been published previously (8). The main inclusion criteria and study endpoints are summarized in the online supplement.

Construction of the Mathematical Model

Reslizumab is licensed in Europe for use in adults with severe asthma inadequately controlled despite treatment with a high dose of ICS plus another medicinal product (17), which is equivalent to Global Initiative for Asthma (GINA) 4 or GINA 5 criteria (6). Thus, adult patients (aged ≥ 18 yr) from the pivotal studies who met GINA 4 or 5 criteria and were treated with reslizumab were selected as the data source for constructing the model, using multinomial logistic regression to calculate the probabilities of three different outcomes at 52 weeks: responder, nonresponder, and indeterminate.

Criteria for defining the three outcomes are shown in Table 1 and were informed by an earlier analysis that demonstrated an association between early improvement in lung function and asthma control observed with reslizumab and the annual rate of asthma exacerbations (20). The three probabilities (responder [P_R], nonresponder [P_{NR}], and indeterminate responder [P_I]) were calculated for each patient using the following information at the Week 16 clinical assessment: change from baseline in ACQ-6 score (this score excludes FEV₁ as used in the ACQ-7), change from baseline in AQLQ score, number of CAEs during the year before baseline and during the first 16 weeks of treatment, and FEV₁ at 16 weeks divided by prebronchodilator FEV₁ at baseline (Figure 1). A CAE was defined as worsening lung function or asthma symptoms that required a medical intervention beyond usual care involving any of the following: systemic corticosteroid burst (≥ 3 d), increase

Table 1. Definitions of Responders, Nonresponders, and Indeterminate Outcomes at 52 Weeks

Nonresponders	Responders	Indeterminate
Two or more CAEs at 52 wk unless at least one of the following criteria are met*: • >10% improvement in FEV₁ and ACQ-6 improvement[†] at 52 wk • >10% improvement in FEV₁ and AQLQ improvement[‡] at 52 wk • 50% reduction from historical[§] number of CAEs at 52 wk	At least one CAE at 52 wk and at least one of the following criteria are met: • >10% improvement in FEV₁ at 52 wk • ACQ-6 improvement[†] at 52 wk • AQLQ improvement at 52 wk	Criteria not met for either responders or nonresponders

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; CAE = clinical asthma exacerbation.

*Patients meeting at least one of these criteria were classified as responders.

[†]At least a 0.5-point reduction from baseline in ACQ-6 score, the minimum clinically important difference (27).

[‡]At least a 0.5-point increase from baseline in AQLQ score, the minimum clinically important difference (28).

[§]Self-reported exacerbations during the year before enrolment.

(doubling or more) in the dose of ICS or systemic corticosteroids (≥ 3 d), or the need for urgent asthma treatment (unscheduled visit to a doctor's office, emergency room visit, or hospitalization for asthma). Further details of the methodology are provided in the online supplement. The 16-week time point was chosen for the analysis because responses to asthma treatment (improvements in lung function and asthma control) tend to plateau by then (21).

This time point for assessment is similar to that suggested by the expert group of the consensus statement (14). P_R , P_{NR} , and P_I represent the probabilities of mutually exclusive outcomes, and patients cannot be classified as anything other than responder, nonresponder, or indeterminate. Consequently, the sum of the three probability values must be equal to 1. The three probabilities can be shown graphically using a triangular simplex plot (Figure 2). A patient with a responder probability of 1 would be seen as a data point at the apex of the triangle, whereas a patient with a nonresponder probability of 1 would be placed at the lower right vertex of the triangle. An example of a patient with all three probabilities between 0 and 1 is shown in Figure 2B; values are plotted at a distance from the side of the triangle opposite to the vertex representing the outcome in question.

The model was applied to the best fit of the clinical data to calculate threshold probabilities for identifying each patient's predicted outcome at 52 weeks. These criteria were then applied to the patient population. Lin's concordance correlation coefficient was used to measure

overall agreement between responder/indeterminate/nonresponder status at 52 weeks with the predicted status. The sensitivity and specificity of the algorithm are expressed as ranges, calculated by categorizing indeterminate patients as either responders or nonresponders.

Jackknife resampling was used to validate the algorithm. In this approach, the analysis is run " n " times (i.e., 321 times, once for each patient), where each observation is systematically left out of the data one at a time, and the mathematical model is fit to the remaining " $n - 1$ " ($n = 320$) observations. Cross-study validation was also performed to assess how successfully the algorithm could be applied to data that were not used in the development process. Analysis of data from only one of the two studies (training set) was used as the basis for estimating outcomes from the other study (validation set) and vice versa, and the results were compared with those obtained using the full algorithm.

Results

Early Response to Reslizumab

Changes from baseline scores for FEV₁, ACQ-6, and AQLQ at Week 16 are presented in the online supplement, together with the frequency of CAEs during the first 16 weeks of treatment (see Tables E1 and E2 in the online supplement). For all three parameters, the majority of the change from baseline over the course of 52-week treatment had occurred by Week 16 (Table E3).

Predicting Response to Reslizumab

Application of the model to the best fit of the clinical data indicated that responders by Week 16 may be identified by P_R greater than 0.6 and an indeterminate outcome by P_I greater than 0.4. These results are illustrated as a simplex plot in Figure 3A. Figure 3B shows the application of these criteria to an example patient (the same example as that considered above in Figure 2B), whereby the patient was predicted to be a nonresponder.

The criteria for identifying response at 52 weeks were applied to the patient population from the two pivotal studies. In total, 383 patients met the inclusion criteria, of whom 321 were aged 18 years and older and had data available for all time points (Figure E1). A comparison of predictions obtained from the algorithm and actual outcomes is shown in Table 2. Two hundred seventy-six patients were predicted to be responders at Week 52, and in 248 of these cases (89.9%), the prediction was correct. In comparison, 26 patients were predicted to be nonresponders, and 50.0% of these predictions were correct.

In the sensitivity and specificity analysis, in which indeterminates were pooled with either responders or nonresponders, the algorithm demonstrated a sensitivity range of 95.4% (95% confidence interval [CI], 92.1–97.6%) to 95.5% (95% CI, 92.4–97.6%) and a specificity range of 40.6% (95% CI, 23.7–59.4%) to 54.1% (95% CI, 40.9–66.9%). The positive predictive value ranged from 89.9% (95% CI, 87.1–92.1%) to 93.6% (95% CI, 91.6–95.1%), and the negative predictive value ranged from 50.0% (95% CI, 33.7–66.3%) to 73.3% (95% CI,

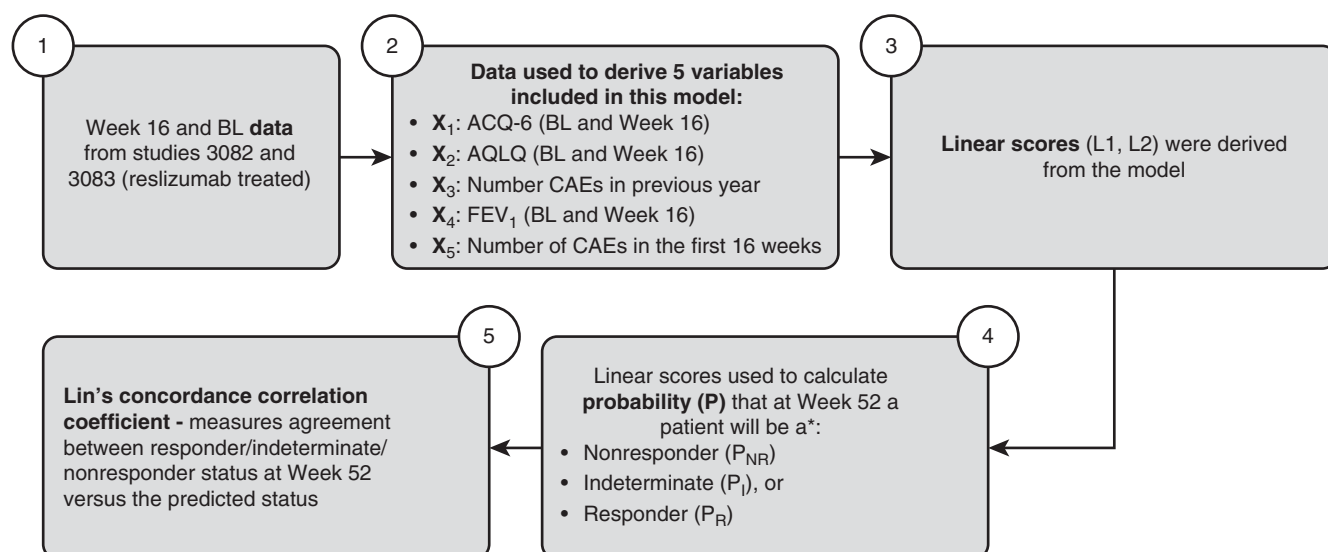


Figure 1. Overview of construction of the mathematical model. Multinomial regression analysis was used to predict the probability of a patient being a responder, nonresponder, or indeterminate at Week 52. *Decision rule. ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BL = baseline; CAE = clinical asthma exacerbation.

60.2–83.4%). Lin's correlation coefficient for the algorithm was calculated as 0.56.

Validation Studies

The results of jackknife validation showed a pattern similar to the initial response prediction: 230 of 260 responders were correctly predicted, compared with 10 of 32 nonresponders. In the cross-study validation analysis, of the 162 patients in study 3082, 123 (76%) were predicted correctly for the model parameters estimated using the study 3083 data alone. Similarly, of the 159 patients in study 3083, 138 (87%) were predicted correctly for the model parameters estimated using the study

3082 data alone. When study 3082 was used as the training set and study 3083 as the validation set, the predicted values for the study 3083 patients were 100% in agreement with the predictions obtained using the full algorithm (i.e., based on both studies). When study 3083 was used as the training set and study 3082 as the validation set, the predicted values for the study 3082 patients were 93.7% (149 of 159) in agreement with the full-algorithm predictions.

Discussion

The intention of our study was to develop a tool that, if used after 16 weeks of treatment

with a biologic, predicts response to treatment at 52 weeks based on change in FEV₁, ACQ-6, and AQLQ compared with baseline and CAE status over the first 16 weeks of treatment. The majority of reslizumab-treated patients were categorized as responders by the criteria specified. In 90% of patients predicted to be responders at Week 52, the prediction was correct, providing confidence that patients who respond at 16 weeks are unlikely to deteriorate later while receiving continued therapy. However, the algorithm was less effective at predicting patients with nonresponse or indeterminate responses. This conclusion was supported by the results of the jackknife methodology. Given the low specificity and negative predictive value of this analysis, it is clear that nonresponse based on the definition used in this algorithm may be concluded only from results of continued monitoring over a longer period, during which a late response may occur.

The present study is not unique in attempting to predict clinical outcomes in asthma and other chronic pulmonary diseases and the impact of different treatments. Bateman and colleagues identified clinical factors associated with an increased risk for severe asthma exacerbations based on a large dataset from three clinical studies (22). Five dominant baseline predictors were identified (GINA treatment step, mean daily number of

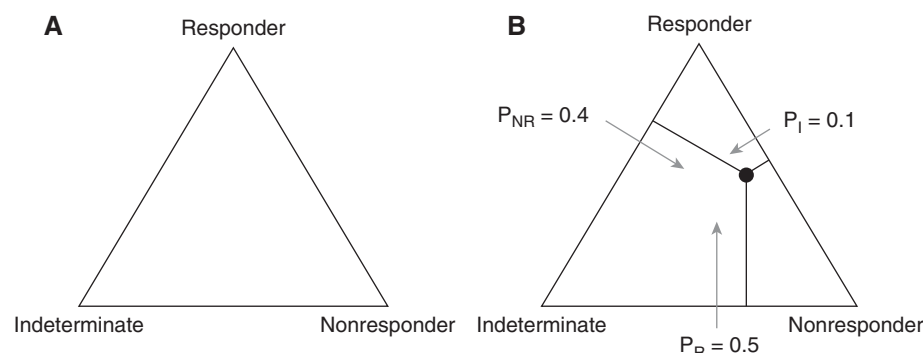


Figure 2. (A) Simplex plot showing the method for representing probabilities of responder, nonresponder, and indeterminate. (B) Illustration of an example patient with probabilities $P_{NR} = 0.4$, $P_I = 0.1$, and $P_R = 0.5$. P_I = probability indeterminate; P_{NR} = probability nonresponder; P_R = probability responder.

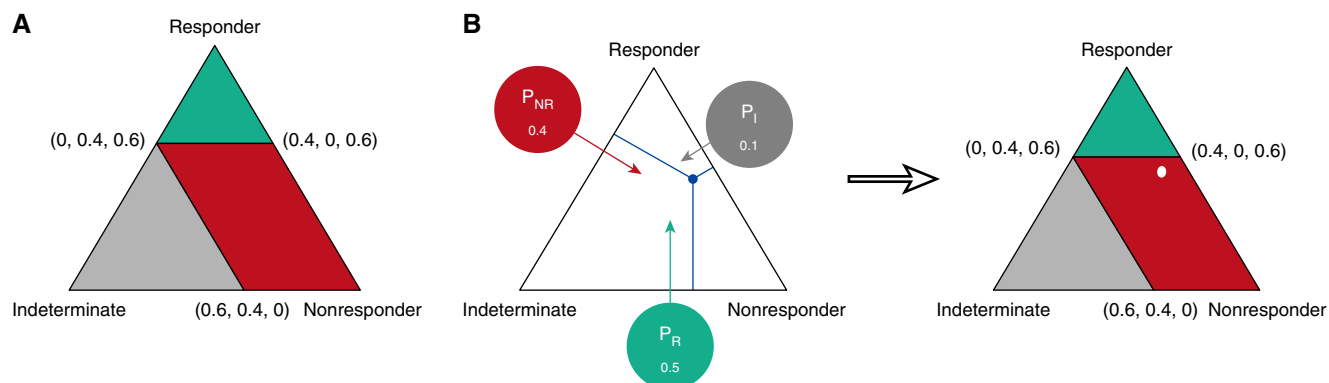


Figure 3. Interpretation of results from single patients using simplex plots. (A) Overall categorization and (B) data from the example patient with probabilities $P_{NR} = 0.4$, $P_I = 0.1$, and $P_R = 0.5$. Values in parentheses represent P_{NR} , P_I , and P_R . P_I = probability indeterminate; P_{NR} = probability nonresponder; P_R = probability responder.

reliever inhalations, post-bronchodilator FEV₁, ACQ-5 score, and body mass index) and used to develop a risk score for exacerbations (22). Similarly, two previous studies examined the ability of Global Initiative for Chronic Obstructive Lung Disease classifications to predict outcomes in patients with chronic obstructive pulmonary disease (COPD). In one study involving 6,628 patients with COPD, the 2011 classifications (based on symptoms, lung function, and history of exacerbations) were found to provide effective prediction of COPD exacerbations over a mean follow-up of 4.3 years (23). The second study, performed in 1,540 individuals with COPD, showed that the older Global Initiative for Chronic Obstructive Lung Disease classifications based only on spirometric evaluation predicted COPD mortality over a 5–7-year period more accurately than the more recent 2011 classifications (24). Similar methods of predicting outcomes have been explored in other disease settings. For example, in rheumatoid arthritis, disease activity

scores have been harnessed to predict radiographic progression (25).

In their report of the European Consensus Meeting for Severe Eosinophilic Asthma, Buhl and colleagues proposed that monitoring should include a combination of relevant clinical measures reflecting symptoms, health status, lung function, and exacerbations to identify patients who have responded to treatment, and they suggested a “traffic light” system at 16 weeks to decide which patients should continue on treatment or stop (14). However, no detail was provided regarding how this assessment should be performed or, significantly, the basis on which a decision to stop treatment might be made. Although progress has been made in developing guidelines for assessing treatment response, there is room for continued refinement of definitions of treatment response and nonresponse and guidance regarding the continuation or otherwise of therapy. The implementation of a standardized method for assessing clinical data early in treatment, which would be less provider

dependent than the current methods of assessment, should result in a higher quality of care across patients.

The earlier report by Gunsoy and colleagues suggested that changes in lung function and ACQ-6 score at 16 weeks are not useful for predicting future reductions in asthma exacerbations in patients being treated with mepolizumab (26). Improvements in CAE rates cannot be clinically assessed before a full year has elapsed. However, we believe that the inclusion of historical and 16-week CAE data in our model, in addition to other clinical inputs at 16 weeks, enhances the predictive ability of our algorithm relative to the individual metrics considered by Gunsoy and colleagues. The findings of our analysis, using a combination of measures reflecting four domains of response, suggest that a positive response to treatment may be predicted with a high degree of certainty. However, the more important prediction, that of long-term nonresponders, remains problematic, suggesting that identifying with precision patients in the consensus meeting “red traffic light” category in whom treatment might be stopped requires further study.

A potential contributing factor to the low prediction accuracy for nonresponders in our study may be the small numbers of nonresponders among the reslizumab-treated population. Use of a training dataset with larger numbers of nonresponders may improve the specificity and negative predictive value of the algorithm. However, a more important need is to review current criteria for a nonresponse. Our algorithm was, by necessity, arbitrary and based on widely used clinical thresholds for these

Table 2. Comparison of Actual Week 52 Responses versus Those Predicted from Week 16 Data

	Predicted			Total
	NR	I	R	
Actual				
NR	13	8	11	32 (10%)
I	8	4	17	29 (9%)
R	5	7	248	260 (81%)
Total	26 (8%)	19 (6%)	276 (86%)	321 (100%)

Definition of abbreviations: I = indeterminate; NR = nonresponder; R = responder.

parameters. For example, our criteria defined a patient with two or more CAEs at 52 weeks as a nonresponder, unless the patient experienced a clinically significant improvement on at least two measures of impairment and/or a 50% reduction in CAEs compared with the historical number of CAEs before treatment. This definition is more conservative than the definition of response used in some clinical studies. Despite this, a majority of patients in our dataset were scored as responders, and we considered our approach to be clinically appropriate. Furthermore, in support of our algorithm, the Lin's correlation coefficient indicated a highly statistically significant result for overall agreement between actual and predicted status at 52 weeks. In addition, the results of both jackknife and cross-study validation indicate that the algorithm is robust. Generally, in cross-validation exercises, 10% is held out, but in this exercise, approximately 50% of the data were held out, indicating robustness of the results.

A strength of our algorithm is the use of data from a large patient population to develop the model and the positive validation outcomes suggesting that the algorithm is robust. A second strength is the inclusion of four parameters of clinical response. However, prevention of asthma exacerbations is typically considered the major goal of treatment with biologics and

might be considered more important than the other components of the algorithm. Our algorithm does not weight the parameters but rather considers all four to be of equivalent importance, which could be considered a limitation of our study. Other limitations included that we did not attempt to assess the value of the algorithm in reducing the risk of asthma exacerbations alone (as the primary objective of treatment). However, as seen with reslizumab, treatment with biologics achieves significant improvements in other clinical endpoints that are important to both patients and payers. Although the definition of a CAE was determined by the studies from which the model derivation data were sourced, the classification of "worsening of lung function or asthma symptoms requiring a doubling of the ICS dose" as a CAE could be questioned. Such events may be considered to have less clinical relevance than those requiring treatment with systemic corticosteroids. However, the number of these former events was small, and removing them from the analysis would likely have further increased the proportion of patients who were classified as responders to treatment and underrepresented the continued burden of asthma. Furthermore, the ACQ and AQLQ instruments are not routinely used in clinical practice. However, because biologics are costly, and because guidelines

propose that patients requiring biologics be under the care of specialists, the added burden of performing these assessments at infrequent intervals may be acceptable, especially if their use at specific time points could provide valuable objective input into treatment continuation decisions. Consideration may, in due course, be given to replacing the AQLQ with an alternative tool that captures the patient's perspective and health status. Finally, the accuracy and utility of our algorithm requires prospective examination in a real-world patient population.

In conclusion, our algorithm enabled the prediction of response to reslizumab treatment at 52 weeks in patients with severe eosinophilic asthma, based on assessment of FEV₁, ACQ-6, AQLQ, and CAE status after 16 weeks of treatment. The algorithm had a sensitivity of 95.4–95.5% and specificity of 40.6–54.1%, indicating that it is successful in predicting responders but suggesting that it should not be the sole criterion used to determine nonresponse. The methods investigated in the present study could potentially be used to help guide treatment decisions after 16 weeks of reslizumab therapy, whereby a positive score at 16 weeks should encourage continued treatment. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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