Refactory Asthma

Importance of Bronchoscopy to Identify Phenotypes and Direct Therapy

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Background: The pathophysiology of refractory asthma is not well understood; thus, treatment modalities are not targeted to specific phenotypes but rather to a broad-based treatment approach. The objective of this study was to develop refractory asthma phenotypes based on bronchoscopic evaluation and to develop from this information specific, directed, personalized therapy.

Methods: Fifty-eight patients with difficult-to-treat (refractory) asthma were characterized by the use of fiber-optic bronchoscopy with visual scoring systems of the upper and lower airways as well as with BAL, endobronchial biopsy, and brush. Response to changes in therapy was evaluated by changes in the Asthma Control Test and pulmonary function.

Results: Five mutually exclusive phenotypes were formulated based on bronchoscopic evaluation: gastroesophageal reflux, subacute bacterial infection, tissue eosinophilia, combination, and nonspecific. Specific directed therapy yielded a significant improvement in the Asthma Control Test and pulmonary function for the entire group as well as for each defined subgroup except for the nonspecific group. Of interest, visual scoring of the supraglottic abnormalities identified 34 of 35 patients with gastroesophageal reflux and may give a better insight into asthmatic problems associated with chronic proximal reflux than standard testing.

Conclusions: Bronchoscopic evaluation of the upper and lower airways can provide important information toward characterizing refractory asthma so as to better individualize therapeutic options and improve asthma control and lung function in patients with difficult-to-treat asthma.

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Abbreviations: ACT = Asthma Control Test; BI = bronchitis index; GER = gastroesophageal reflux; hpf = high power field; PCR = polymerase chain reaction; SBI = subacute bacterial infection; SGI = supraglottic index; VCD = vocal cord dysfunction

Even with guideline-based asthma therapy, up to 50% of patients are not well controlled or are refractory to treatment. Poor asthma control is associated with substantial morbidity and mortality and increased health-care resource utilization, with the greatest proportion of costs in the more-severe or refractory asthma group.

Patients with refractory asthma represent different phenotypes than those who respond to standard controller therapy. Wenzel described three asthma phenotypes: (1) clinical or physiologic, (2) trigger and allergen, and (3) inflammatory. Because the patient with refractory asthma may have any of the above phenotypes, directed therapy may be more effective than broad-based therapy.

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these phenotypes, characterization of the airway pathology could potentially lead to more-specific phenotypic identification. Additionally, Moore and colleagues defined five cluster-analysis groups, but patients with refractory asthma were present in each cluster. These classifications highlight the difficulty of individualizing treatment programs for patients with asthma. In the present study, we questioned whether fiber-optic bronchoscopy with upper and lower airway evaluation and results of analysis from bronchoscopy for phenotypes could lead to personalized therapy.

**Materials and Methods**

**Patient Population**

National Jewish Institutional Review Board approval (HS2477) was obtained to use these prospective clinical data for publication. Patients aged ≥ 18 years were assessed by history, physical examination, routine laboratory studies, Asthma Control Test (ACT), and spirometry. Prospective inclusion criteria were a 12% improvement in FEV₁, postbronchodilator or positive provocative concentration of methacholine to produce a 20% fall in FEV₁ of ≤ 6 mg/mL. Refractory asthma was defined by American Thoracic Society guidelines. One of two major criteria (high-dose inhaled corticosteroid or systemic steroid use) and two or more minor criteria were needed for inclusion. Exclusion criteria were a smoking history of ≥ 5 pack-years and evidence of vocal cord dysfunction (VCD) by history or flow-volume loops compatible with VCD prior to bronchoscopy. Initially, 20 consecutive patients with refractory asthma referred to one author (J. T. G.) were evaluated and treated without bronchoscopic phenotyping on the basis of ensuring the diagnosis of asthma, potential contributing factors, and guideline therapeutic steps. An additional intensified program for 4 months was undertaken that produced no further improvement in the patients’ asthma control or lung function. These patients served as their own comparison. The next 38 patients with refractory asthma referred who met the inclusion criteria also were evaluated with bronchoscopy. Follow-up postbronchoscopy outcomes were measured between 12 and 60 weeks postprocedure.

**Airway Visual Evaluation**

**Supraglottic and Bronchitis Indexes:** Supraglottic evaluation at the time of bronchoscopy used a modified scoring system (e-Table 1) to calculate the supraglottic index (SGI). A modified bronchitis index (BI) (e-Table 2) was used to score visualization of the airways.

**Bronchoscopy With BAL, Endobronchial Biopsies, and Brushing**

All patients had fiber-optic bronchoscopy. Six lower-lobe biopsy specimens were obtained, followed by ipsilateral BAL in the right middle lobe or lingula. Biopsies were evaluated for histology and polymerase chain reaction (PCR) for Mycoplasma pneumoniae and Chlamydia pneumoniae. (Two patients did not have biopsies because of technical reasons.) Two 60-mL aliquots were used for the BAL and evaluated for cell count and differential, PCR studies for mycoplasma and chlamydia, and bacterial and fungal cultures. Nineteen patients had ≥ 50 mL lavage return; thus, one-third 60-mL aliquot was used. Three patients did not have BAL differential counts performed (for technical reasons different from those patients missing biopsy samples). Thirty-four patients had endobronchial brushings, which were taken from the ipsilateral upper lobe for PCR analysis. The histologic and bronchoscope sterility methods are found in e-Appendix 1.

**Gastroesophageal Reflux**

Gastroesophageal reflux (GER) was determined by one of the following: esophageal pH probe, esophageal pH/impedance probe, or 48-h Bravo esophageal pH study (e-Table 3) based on availability. If the patient refused testing, then barium swallow was used. Six patients refused all tests.

**Statistical Analysis**

Statistical analysis was performed using Microsoft Excel (Microsoft Corporation). General analysis was done using t test for continuous variables and χ² test for categorical variables. The standard P < .05 significance level was used for these tests. Bland-Altman paired t tests were used for pretest and posttest analysis.

**Results**

Demographic characteristics are shown in Table 1. Forty-five patients (78%) met the FEV₁ reversibility criterion of > 12%, with the remaining 13 meeting the provocative concentration of methacholine to produce a 20% fall in FEV₁ criteria of < 6 mg/mL. Prior to bronchoscopy and phenotyping, the 20 initial patients treated with intensified asthma therapy showed no improvement in ACT or lung function (Fig 1).

**Gastroesophageal Reflux and Supraglottic Index**

Forty-four patients (76%) had a moderate to severe SGI score (≥ 10) (e-Table 3). Forty-three of these patients had GER testing, and 34 had documented GER. Fourteen patients had an SGI of < 10, with nine having GER testing, eight of whom had negative results. The SGI was significantly higher in patients with GER (15.8 ± 3.6) than in those without GER (8.9 ± 5.5, P < .0001).

**Bronchitis Index**

There was a significant correlation between the severity of the SGI and the BI (r = 0.53, P < .001). However, of the 35 documented cases of GER, there was a wide distribution of the BI from normal to severe. For other correlations between the BI and BAL cells, see e-Appendix 2.

**BAL and Endobronchial Biopsy Specimens**

Table 2 shows for the entire group the BAL cell count and differential (55 patients) as well as the biopsy specimen characteristics (56 patients).

**Subacute Bacterial Infection and Associated Neutrophilia:** A total of 25 patients (43%) had evidence
of subacute bacterial infection (SBI) based on a positive culture or PCR analysis (Table 3). BAL neutrophil counts >20% always were associated with culture (eight positive) or PCR (one positive) bacterial findings. Five patients had culture-positive SBI with <20% BAL neutrophils. Thirteen patients had positive PCR findings for mycoplasma (10 patients) or chlamyphila (three patients) using a combination of BAL (nine positive), endobronchial biopsy (three positive), and endobronchial brush (two positive), with one having positive BAL and brush results. Excluding the one patient with a positive PCR finding with BAL neutrophils >20%, the remaining 12 patients with positive PCR results averaged 4.25% neutrophils (range, 0%-14%). There was not a significant correlation between SBI neutrophils in BAL and the biopsy specimens ($r = 0.13, P > .05$).

**Eosinophils:** Biopsy and BAL eosinophils are listed in Table 4. Thirty of 55 patients had ≥1 eosinophils in BAL fluid (mean, 2.4% ± 4.6%). Thirty-five of 56 patients had ≥1 eosinophil per high power field (hpf) (6.4 ± 13.1) in biopsy specimens. A correlation existed between BAL eosinophils and biopsy eosinophils ($r = 0.44, P = .001$). However, 13 patients had biopsy eosinophils and none had BAL eosinophils, whereas seven patients had BAL eosinophils and none had biopsy eosinophils. Twelve patients had no biopsy or BAL eosinophils. Of the 30 patients with BAL eosinophils, 24 (80%) had positive skin tests. Of the 35 patients with biopsy eosinophils, 31 (89%) had positive skin tests. There was no significant correlation between IgE levels and BAL eosinophils ($r = -0.12, P = .40$) or biopsy eosinophils ($r = -0.06, P = .64$).

**BAL Macrophages and Lymphocytes:** These cells did not add to phenotyping refractory asthma. For correlations between these cells and other outcomes, see e-Appendix 3.

**Squamous Metaplasia in Biopsy Specimens:** Of 23 patients with squamous metaplasia, 18 had documented GER, four had SBI, and one had a nonspecific phenotype. Twenty-one of the patients with squamous metaplasia had an SGI in the moderate to severe range (15.22 ± 4.19), which was significantly greater than those without squamous metaplasia (SGI, 11.86 ± 6.03; $P = .02$).

**Response to Therapy**

**General:** After 12 to 60 weeks of targeted specific therapy for the entire group, there was a significant improvement in the ACT (pretest, 11.6 ± 4.1; posttest, 18.5 ± 4.1; $P < .001$), FEV$_1$ % predicted (pretest, 58.9 ± 17.0%; posttest, 74.3 ± 15.2%; $P < .001$), and FEV$_1$ (pretest, 1.8 ± 0.6 L; posttest, 2.2 ± 0.7 L; $P < .001$).

**Treatment Phenotypes:** Five distinct phenotypes evolved from the bronchoscopic evaluation: GER,
SBI, tissue eosinophilia, combination, and nonspecific (e-Table 4; specific characteristics in Tables 1, 2, and 4; medication changes in e-Tables 5 and 6). The prebronchoscopy characteristics listed in Tables 1 and 4 were not predictive of any phenotype ($P > .05$).

Gastroesophageal Reflux: Twenty-two patients had GER as the single discernible cause for their refractory asthma. Fifteen patients responded to intense medical treatment, and seven patients required Nissen fundoplication for improved asthma control. For the entire group, ACT and lung function improved significantly with therapy (Figs 2A, 2B). In the medically treated group, ACT measured at 6 to 8 months increased from 10.7 ± 3.5 to 15.5 ± 4.3 ($P < .001$), and FEV$_1$ % predicted increased from 62.1% ± 17.5% to 76.7% ± 18.3% ($P < .01$). For the fundoplication group, ACT (measured at 6 months) increased from 8.6 ± 2.9 to 19.6 ± 4.6 ($P = .001$), and FEV$_1$ % predicted increased from 64.3% ± 15.7% to 74.1% ± 10.8% ($P = .08$).

Subacute Bacterial Index: Thirteen patients had SBI as the single finding for refractory asthma. Nine of these patients had mycoplasma or chlamydyphilia. After at least 3 months postinitiation of therapy, both ACT and the lung function test improved significantly (Figs 2A, 2B) with bacteriologic directed therapy (Table 3).

Tissue Eosinophilia: We arbitrarily selected ≥10 eosinophils/hpf as a potential cutoff for the use of omalizumab therapy. Four patients met this criterion as the sole bronchoscopic finding for refractory asthma. All patients receiving omalizumab met the clinical criteria of perennial allergen positivity, IgE levels, and weight level for its use. Standard dosing used IgE and weight levels. At least 6 months of therapy was given before ACT and lung function were remeasured. There were significant improvements in the ACT and lung function (Figs 2A, 2B) with treatment. An additional three patients had ≥10 eosinophils/hpf in the combination group and had similar improvement with omalizumab as one of the directed therapies for this phenotype. Two patients (No. 44 and 49) in the SBI group also had tissue eosinophils >10 eosinophils/hpf. Because infection can cause an elevated IgE (specific) and circulating eosinophil$^{17,21}$ without a typical allergen exposure, these patients were left in the SBI phenotype group and not treated with omalizumab.

Combination Phenotype: Thirteen patients had two or three phenotypes and were treated for each abnormality. Nine had the combination of GER and SBI, one had GER and tissue eosinophilia, and three had all three phenotypes. For the group, there were significant improvements in ACT and lung function after at least 6 months of therapy (Figs 2A, 2B).

Nonspecific Phenotype: Six patients did not have any of the described phenotypes. For this group, neither ACT nor lung function had statistically significant improvement with therapy after 4 months (Figs 2A, 2B).

Initial 20 Subjects: For the 20 subjects who received increased standard asthma therapy without improvement in the ACT or FEV$_1$ before specific directed therapy based on bronchoscopy, directed therapy resulted in significant improvement in ACT and FEV$_1$ (Fig 1). These improvements occurred in spite of a marked decrease in other asthma medications (e-Table 5).
DISCUSSION

The purpose of this study was to evaluate the effectiveness of bronchoscopic analysis in managing patients with refractory asthma. In spite of standard asthma therapy, up to 50% of patients are still not well controlled or can be refractory to treatment.  From this evaluation, four different phenotypes were identified that, even with decreased standard asthma therapies, demonstrated improvement in lung function and asthma control using specific directed interventions (Figs 2A, 2B, e-Tables 4-6). The nonspecific phenotype did not improve significantly.

Table 3—Total Patients With SBI Alone and Combination Phenotype (n = 25)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Infection/Positive PCR</th>
<th>Biopsy Neutrophils/hpf</th>
<th>BAL % Neutrophils</th>
<th>Treatment</th>
<th>Treatment, mg</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a-Hemolytic streptocci</td>
<td>0</td>
<td>26</td>
<td>Amox/clav</td>
<td>875/125</td>
<td>q12h x 14 d</td>
</tr>
<tr>
<td>2</td>
<td>Alcaligenes xylosoxidans, a-hemolytic streptocci</td>
<td>1</td>
<td>51</td>
<td>Trimeth/SM</td>
<td>160/800</td>
<td>q12h x 30 d</td>
</tr>
<tr>
<td>3</td>
<td>Mycoplasma pneumoniae</td>
<td>0</td>
<td>7</td>
<td>Azi</td>
<td>250</td>
<td>daily x 6 mo</td>
</tr>
<tr>
<td>4</td>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td>9</td>
<td>Cipro</td>
<td>750</td>
<td>q12h x 21 d</td>
</tr>
<tr>
<td>5</td>
<td>Moraxella catarrhals</td>
<td>10</td>
<td>2</td>
<td>Trimeth/SM</td>
<td>160/800</td>
<td>q12h x 21 d</td>
</tr>
<tr>
<td>6</td>
<td>Haemophilus influenzae</td>
<td>2</td>
<td>4</td>
<td>Azi</td>
<td>250</td>
<td>daily x 10 d</td>
</tr>
<tr>
<td>7</td>
<td>M pneumoniae</td>
<td>0</td>
<td>1</td>
<td>Clari</td>
<td>500</td>
<td>q12h x 6 mo</td>
</tr>
<tr>
<td>8</td>
<td>M pneumoniae</td>
<td>1</td>
<td>6</td>
<td>Azi</td>
<td>250</td>
<td>daily x 6 mo</td>
</tr>
<tr>
<td>9</td>
<td>Chlamydia pneumoniae</td>
<td>0</td>
<td>3</td>
<td>Clari</td>
<td>500</td>
<td>daily x 6 mo</td>
</tr>
<tr>
<td>10</td>
<td>M pneumoniae, H influenzae, P aeruginosa</td>
<td>2</td>
<td>5</td>
<td>Cipro/azi</td>
<td>750/250</td>
<td>daily x 14 d; daily x 6 mo</td>
</tr>
<tr>
<td>11</td>
<td>Acinetobacter</td>
<td>0</td>
<td>57</td>
<td>Clari</td>
<td>500</td>
<td>q12h x 2 mo</td>
</tr>
<tr>
<td>12</td>
<td>Stenotrophomonas maltophilia</td>
<td>1</td>
<td>68</td>
<td>Ceftaz/aztre</td>
<td>2 g/inhaled 75</td>
<td>IV q12 h x 2 mo; qsh x 2 wk (2 wk off/2 wk on x 6 mo)</td>
</tr>
</tbody>
</table>

Discussion

From this evaluation, four different phenotypes were identified that, even with decreased standard asthma therapies, demonstrated improvement in lung function and asthma control using specific directed interventions (Figs 2A, 2B, e-Tables 4-6). The nonspecific phenotype did not improve significantly.

Table 4—Airway Eosinophils and Associated IgE and Sinus Score Tests for Entire Group and for Treatment Phenotype Groups

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Biopsy Specimen Eosinophils/hpf</th>
<th>BAL % Eosinophils</th>
<th>IgE</th>
<th>Sinusitis Severity</th>
<th>Positive Skin Tests, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire group (N = 58)</td>
<td>6.4 ± 13.1</td>
<td>2.4 ± 4.6</td>
<td>263 ± 558</td>
<td>1.4 ± 1.1</td>
<td>78</td>
</tr>
<tr>
<td>GER (n = 22)</td>
<td>1.5 ± 2.1</td>
<td>0.8 ± 1.1</td>
<td>198 ± 369</td>
<td>1.1 ± 1.1</td>
<td>64</td>
</tr>
<tr>
<td>SBI (n = 13)</td>
<td>5.6 ± 7.8</td>
<td>1.9 ± 3.5</td>
<td>359 ± 889</td>
<td>1.3 ± 1.2</td>
<td>85</td>
</tr>
<tr>
<td>Tissue eosinophilia (n = 4)</td>
<td>37.3 ± 27.9</td>
<td>9.8 ± 11.2</td>
<td>131 ± 38</td>
<td>2.0 ± 0.8</td>
<td>100</td>
</tr>
<tr>
<td>Combination (n = 13)</td>
<td>8.2 ± 12.4</td>
<td>2.2 ± 2.9</td>
<td>365 ± 629</td>
<td>2.1 ± 1.0</td>
<td>85</td>
</tr>
<tr>
<td>Nonspecific (n = 6)</td>
<td>1.8 ± 2.9</td>
<td>5.5 ± 7.9</td>
<td>154 ± 168</td>
<td>0.8 ± 1.0</td>
<td>83</td>
</tr>
</tbody>
</table>

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

From this evaluation, four different phenotypes were identified that, even with decreased standard asthma therapies, demonstrated improvement in lung function and asthma control using specific directed interventions (Figs 2A, 2B, e-Tables 4-6). The nonspecific phenotype did not improve significantly.
An SGI $\geq 10$ may represent a better picture of chronic trauma in the supraglottic area from proximal reflux than standard GER evaluations, which are limited to a 20- to 48-h period. Additionally, six patients refused the standard GER evaluation, of whom only one had an SGI of 10. Thus, obtaining this index can help to define the process. Although fiberoptic laryngoscopy is easier to perform than bronchoscopy to evaluate the SGI, multiple other patients would not be correctly classified and treated (e-Table 4). To better evaluate SGI benefits, because it is not commonly used by bronchoscopists, a multicenter trial would be indicated.

The American Lung Association\textsuperscript{22} reported no benefit with esomeprazole therapy in patients with poorly controlled asthma with no GER symptoms. In contrast, Kiljander and colleagues\textsuperscript{23} demonstrated improvement in FEV\textsubscript{1} and asthma-related quality of life with GER symptoms and esomeprazole therapy. The present study suggests the need to document GER and to note that not all patients with GER responded to intense medical therapy. Seven patients with GER and five with combination phenotypes needed fundoplication before improved asthma control. In addition, all aspects of the combination phenotype need to be treated.

Forty-three percent of patients had SBI (single criterion or combination phenotype). Neutrophilia of $\geq 20\%$ in BAL fluid indicated SBI with positive bacterial cultures or PCR studies. However, $< 20\%$ neutrophilia does not rule out SBI. All patients were specifically treated and showed improved asthma outcomes. Without bronchoscopic evaluation, it is unlikely that these infectious etiologies would have been established.

The importance of the neutrophil in asthma has been emphasized in multiple studies\textsuperscript{24-26} and is a potential means of targeting therapy.\textsuperscript{27} The present study suggests that an infectious etiology is probably a major contributor to the pathobiology in a subset of patients, which is supported by the findings of endotoxin predominance in neutrophilic asthma.\textsuperscript{26} However, nonmicrobial aspects also need to be investigated in future studies.

Because there are no strong predictors of response to the monoclonal IgE-blocking antibody omalizumab, we arbitrarily selected a very high tissue eosinophilia of $\geq 10$/hpf as a cutoff for consideration for omalizumab therapy. Uller and colleagues\textsuperscript{28} demonstrated that airway tissue eosinophils are eliminated by migration into the airway lumen followed by apoptosis and clearance rather than by undergoing apoptosis. Thus, we believed that selecting a high tissue level would give the best chance for a positive outcome. The eight patients who met this criterion for therapy (four eosinophil, four combination phenotype) had improvement in both asthma control and lung function.

There were two patients in the SBI phenotype that had $< 10$ eosinophils/hpf. Several publications have documented increased IgE-specific antibodies and circulating eosinophils with bacterial infections,\textsuperscript{17-21} and thus, we kept these patients in the single SBI phenotype and only treated with directed antimicrobial therapy, producing marked improvement.

It could be proposed that patients with refractory asthma with eosinophils on initial biopsy would have a lower steroid requirement than those with neutrophils. The results were the reverse (e-Table 7), suggesting that these patients are steroid insensitive and that other therapies as discussed here are indicated. Because asthma is a syndrome and not a specific disease entity, any given patient may have multiple factors leading to poor control rather than to a single cause.

Thirteen patients had more than one phenotype with multiple targeted interventions, which resulted in significant improvement in asthma control and lung function for this combination phenotype. In this study, only three patients were treated with sequen-

![Figure 2](http://chestjournal.chestpubs.org/)

**Figure 2.** Prebronchoscopy on standard therapy and postbronchoscopy with specific directed therapy for each of the five phenotypes. A, ACT. B, FEV\textsubscript{1} % predicted. Eos = eosinophil; GER = gastroesophageal reflux; ns = not significant; SBI = subacute bacterial infection. SD bars are shown. See Figure 1 legend for expansion of other abbreviation. $^*P < 0.0005$, $^\dagger P \leq 0.02$, $^\ddagger P \leq 0.004$, $^\S P \leq 0.003$.\textsuperscript{25}
tial therapy. There was improvement with the initial therapy, but this did not hold until patients with all phenotypes were treated.

The last phenotype—nonspecific—included six patients who did not fit the other categories. There was not a significant improvement in either ACT or FEV$_1$ with further treatments. One patient had VCD diagnosed after bronchoscopy with improvement following speech therapy plus standard asthma therapy. VCD masquerades as asthma but also occurs in asthma. Supraglottic evaluation is thus important even with a negative history and flow-volume loop.

Prior to specific directed therapy in the initial 20 patients who were first treated without bronchoscopic phenotyping, there was no improvement in asthma control or lung function (Fig 1). Following specific directed therapy, ACT and FEV$_1$ both significantly increased in the face of marked reduction in medications (e-Table 5). With any type of a new intervention, there can be a placebo effect; however, all patients were outside referrals, and because the initial nonbronchoscopy interventions did not improve asthma outcomes and the follow-up data were collected between 3 and 12 months postbronchoscopy, it is unlikely that bronchoscopy itself produced the positive results. Furthermore, the nonspecific group, excluding the one patient with VCD, had limited changes in the outcome variables, even with bronchoscopy. Further multicenter studies are needed to confirm the findings of this study.

The present study suggests that fiberoptic bronchoscopy evaluation dictates a more directed diagnostic and therapeutic approach for the treatment of refractory asthma. Furthermore, bronchoscopic evaluation provides a clinical assessment of the dynamic process of airway abnormalities rather than a snapshot of a pathophysiologic process from other types of evaluation. Future studies based on this phenotyping can lead to development of molecular phenotypes and to further refine personalized asthma care.

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Additional information: The e-Appendices and e-Tables can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/141/3/599/suppl/DC1.

REFERENCES


