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REVIEW

Severe Asthma: Challenges and Precision Approaches to Therapy

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ABSTRACT

Current therapies are inadequate for patients with severe asthma. The development of biomarkers and novel targeted therapies should allow for the introduction of precision medicine for patients with severe asthma and the T2 high endotype. However, there remains a pressing need to better understand the underlying pathophysiology of T2 low asthma to help develop better biomarkers and better treatments for this group of patients. The emergence of biomarkers may serve value in characterizing airway disease and in devising precision approaches to address specific disease mechanisms. To date, biomarkers remain somewhat exploratory until further research can characterize the validity and reliability of these approaches in improving asthma care. Partnerships among providers, payers, and industry will enhance our ability to discover new approaches that target specific mechanisms and improve disease outcomes. Ultimately, our goals are to align phenotypes with endotypes to direct therapies that will provide the right intervention at the right time for the right person with the right diagnosis.

Keywords: Asthma; Asthma-COPD overlap; Biomarkers; COPD; Severe asthma

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INTRODUCTION

Most patients with asthma can be controlled with currently available therapies. However, an estimated 3–5%, remain either poorly controlled or require high doses of corticosteroids [1]. These patients manifest a

significant morbidity and decreased quality of life from the disease and as a consequence of oral corticosteroids [1]. Patients with severe asthma may also be at a higher risk of death [2]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Definition of Severe Asthma

Asthma describes a syndrome for which there are many causes. This is certainly true of severe asthma that is not simply a 'worst form' of asthma. Severe asthma can present in different ways; the 2013 European Respiratory Society/ American Thoracic Society definition of severe asthma recognizes this and encompasses both medication burden and level of asthma control [3]. Severe asthma is defined as asthma that requires treatment with guideline-suggested medications for Global Initiative for Asthma (GINA) steps 4–5 asthma for the previous year or systemic corticosteroids for at least 50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy. Severe asthma is defined as at least one of the following points:

- Poor symptom control
  - Asthma Control Questionnaire (ACQ) consistently >1.5
  - Asthma control test (ACT) <20
  - "Not well-controlled asthma" by NAEP/ GINA guidelines
- Frequent severe exacerbations
  - ≥ 2 bursts of systemic corticosteroids (>3 days each) in the previous year
- Serious exacerbations
  - ≥ 1 hospitalization, ICU stay or mechanical ventilation in the previous year
- Airflow limitation

- After appropriate bronchodilatation withhold, FEV_1 <80% of predicted value (with reduced FEV_1/FVC ratio).

The term 'difficult asthma' encompasses patients who do not respond to prescribed maximum conventional asthma treatment. This may be due to misdiagnosis (i.e., asthma is not the primary cause of their symptoms) or the presence of comorbidities, which are accountable for a significant proportion of the symptoms. Alternatively, patients may have inadequate adherence to therapy. Only after a full systematic assessment can the diagnosis of severe asthma be confirmed [4]. The use of the term 'brittle asthma' is unhelpful and should no longer be used.

Current Treatment Options

For many years there have been limited therapeutic options for patients with severe asthma, which has led to an over-reliance on systemic corticosteroids. The cornerstone of management should be ensuring that every patient is on the optimal inhaled corticosteroid/long-acting beta-agonist combination inhaler for them taking into account patient preference for delivery device and dosing frequency. More recently, the addition of the long-acting muscarinic antagonist, tiotropium, has been shown to improve trough FEV_1 and increase the time to first exacerbation by 56 days in patients with severe asthma [5]. Tiotropium, however, did not produce a clinically significant improvement in either ACQ-7 or AQLQ and did not decrease rescue medication use. At present, tiotropium remains an add-on therapy with incremental benefit and is currently the most logical option at step 4.

Omalizumab, anti-IgE, was the first monoclonal antibody to be licensed for severe

asthma. IgE is a logical target given that the majority of asthmatics are atopic and the selective blockade of IgE appears to have a minimal effect on the immune system [6]. We now have over a decade of experience with omalizumab and real-world studies have demonstrated that in carefully selected patient populations, it is able to decrease exacerbations and decrease reliance on systemic corticosteroids [7]. Despite omalizumab's obvious benefits, there are several limitations to its use. The drug is dosed according to body weight and total serum IgE and is only licensed for patients allergic to a perennial aeroallergen. In practice, this means that only roughly 20% of patients with severe asthma are eligible to trial the drug. Finally, there is currently no biomarker to assess response or to determine length of treatment.

Airways hyperreactivity, a cardinal feature of asthma, is thought to be due to hyperplasia and hypertrophy of the airways smooth muscle. This component of asthma has historically been treated with both short- and long-acting bronchodilators. The rationale for bronchial thermoplasty is predicated on its ability to selectively decrease airways smooth muscle without affecting airway epithelium. The well-designed AIR2 study was negative for its primary endpoint of AQLQ, but does significantly decrease healthcare utilization [8]. The primary concern with bronchial thermoplasty is that, at present, it is not possible to predict which patients will respond to this invasive procedure that requires three bronchoscopies.

From Phenotypes to Endotypes to Precision Medicine with Logical Targeted Therapies

Asthma is a syndrome that comprises the symptoms of asthma and variable airflow obstruction, for which there are several different causes. In an attempt to characterize the different causes of the syndrome, asthma was initially categorized into phenotypes depending on observable characteristics with no direct relationship to the underlying disease process, e.g., early versus late-onset or atopic versus non-atopic. More recently, asthma endotypes have been described, which acknowledges that distinct disease entities may be present in clusters of phenotypes, but each is defined by a specific biological mechanism, e.g., severe late-onset hyper-eosinophilic asthma [9]. The actual benefit of endotypes to the patient and clinician lies in accurately identifying the underlying biology, which allows for the generation of biomarkers and targeted therapy for an individual patient, what has more recently been described as precision medicine.

The only useful endotype at present is the T2 high endotype, which is associated with increased levels of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 [10]. The T2 high endotype has been derived from the seminal finding that the expression of IL-13-induced genes in airway epithelial cells can be divided by hierarchical clustering into individuals that express high levels of periostin, CLCA1, and SerpinB2 (Th2 high) and those with low levels of expression (Th2 low) [11]. Markers of allergy, eosinophilic inflammation, and airways remodeling are increased in Th2 high asthma and only Th2 high asthmatics demonstrated an improvement in FEV_1 in response to a trial of inhaled corticosteroids [11]. This endotype has been further refined from Th2 high to type 2 high by the discovery of innate lymphoid cells type 2 (ILC2), which although are present in relatively low numbers produce a large amount of Th2 cytokines [12].

Multiple targeted therapies against the T2 high endotype are being produced, the first of

which are now licensed for use in severe asthma. Multiple selective anti-eosinophilic therapies have been produced. The eosinophil appears to play a major role as an effector cell in T2 high asthma and is a logical target for novel severe asthma therapies. Two humanized monoclonals against IL-5 have been produced, mepolizumab and reslizumab, and following successful phase III programs are licensed for use in severe eosinophilic asthma. Mepolizumab decreases asthma exacerbations when compared with placebo [13] and has demonstrated efficacy in oral corticosteroid sparing following four weekly subcutaneous injections [14]. The magnitude of the benefit from mepolizumab appears to correlate with the blood eosinophil level [15]. Reslizumab has demonstrated a significant improvement in FEV_1 and decrease in asthma exacerbations following 4 weekly intravenous infusions [16].

Benralizumab has a different mechanism of action in that it binds to the IL-5Rα and depletes eosinophils via antibody-dependent cell-mediated cytotoxicity. Published evidence suggests that this mechanism of action may be more effective than IL-5 blockade, as benralizumab produced a 95.8% reduction in airway eosinophils [17] compared with 55% seen with mepolizumab [18]. Two replicate studies of benralizumab have demonstrated a significant decrease in asthma exacerbations with a concomitant improvement in FEV_1 produced by 8 weekly subcutaneous dosing [19, 20].

IL-13 has multiple effects on the asthmatic airway including increased mucus production, airways hyperresponsiveness, and airway inflammation [21], making it a logical target to pursue in clinical trials. The results of IL-13 blockade have been mixed with the two phase III pivotal trials for lebrikizumab, producing underwhelming results [22], compared with

positive results from the phase IIb studies of Dupilumab (combined IL-4 and IL-13 blockade) [23] and tralokinumab, which has the potential benefit of a companion biomarker, Dipeptidyl peptidase-4 [24].

BIOMARKERS PREDICTING RESPONSES IN SEVERE ASTHMA

The management of chronic disease requires metrics to assess therapeutic responses and prognosis. The heterogeneity of disease pathogenesis and response to treatment poses challenges when considering "one treatment fits all" approaches [25]. Optimally, the health provider seeks predictive attributes of a patient that enhance the likelihood of treatment success while decreasing adverse effects. Unfortunately, current disease management algorithms embrace a trial-and-error mandate that decreases patient adherence and increases adverse effects and health care costs.

What are Biomarkers?

Generally, health care professions group patients according to clinical characteristics, termed phenotypes. Contemporary thought however strives to stratify clinical responses to treatment by underlying mechanisms, i.e., endotypes, to define heterogeneity of disease. Such mechanisms may also define biomarkers that describe genetic, pharmacologic, biologic, or immunologic attributes. In this manner, clarity, fidelity, and prediction of treatment response can be attained [26, 27].

Regulatory agencies have established criteria to assess approval of biomarkers defined as characteristics that objectively measure and evaluate an indicator of a normal biological process, or pharmacologic response to a

therapeutic intervention [27, 28]. The characteristics of an ideal biomarker should confirm a diagnosis, change with disease activity, identify clinical or treatment responses, be non-invasive, inexpensive, and easy to collect and measure [29].

The value of biomarkers has shifted the focus of asthma research from a broad perspective that studies symptom expression, lung function, and medication response to the use of cellular profiles, protein analyses, and genetic markers alone or in combination [29]. Currently, there exist emerging biomarker approaches using sputum (cell counts), exhaled air (FeNO, pH, proteins), saliva (genotypes), urine (leukotrienes), and peripheral blood (cell counts, periostin, IgE, ECP) [30]. Arguably, a single biomarker will be inadequate to completely profile a specific endotype and thus a multidimensional approach will enhance the predictive strength for diagnosis and treatment of asthma. Further, the development of biological therapies in severe asthma, which are substantially more costly than small molecule approaches, has necessitated the development of new metrics that predict therapeutic responses to these agents.

Current Use

The identification, development, and utilization of biomarkers may overcome barriers that hinder the clinical management of severe asthma. The National Institutes of Health in conjunction with other federal agencies convened an expert panel to evaluate the utility of biomarkers and to standardize asthma outcomes in clinical research studies [31]. The goal of this committee was to critically evaluate biomarkers relevant to the underlying disease process, progression, and response to

therapy for severe persistent asthma. Biomarkers were characterized according to three categories that included: *Core*, required for clinical trials based on large observational trials; *Supplemental*, demonstrated validity but optional for trials; or *Emerging*, potential to expand or improve disease monitoring but not yet standardized and require further development. The following discussion will review the validity and reliability of selected biomarkers in severe persistent asthma.

Multiallergen Screen (IgE)

Evidence suggests that asthma pathogenesis can be broadly characterized as atopic or non-atopic and that these categories predict therapeutic responses and prognosis [27, 28]. Subjects with Th2-driven disease often manifest high allergen-specific IgE and elevated levels of IL-4, IL-5, and IL-13 [27]. An expert panel suggested that multiallergen screen (IgE) can serve as a core biomarker for atopic asthma [31]. The IgE level defines the individual as atopic but does not specify the allergen(s) to which the patient is sensitive [31]. Since geographic and demographic diversity is allergen-specific, IgE and/or skin testing for allergens were considered supplemental biomarkers [31].

Fractional Exhaled Nitric Oxide (FeNO)

The levels of nitric oxide (NO) in the airways and in exhaled gas correlates with airway inflammation and NO levels are diminished by anti-inflammatory medications [27, 28]. Although most cells can generate NO, the airway epithelium contributes predominately to exhaled NO levels as measured by current approaches [27]. Collectively, quantitative measurement of airway NO is considered an indirect marker of airway inflammation [31]. Although considered a valuable tool in assessing asthma control and atopy especially in pediatric

patients, there exists inconsistency in characterizing severe asthma and in asthma patients who smoke [31]. Evidence also suggests that FeNO levels are high in atopic subjects without asthma. The measurements require sophisticated instrumentation, and the correlation of FeNO levels with specific asthma phenotypes and airway remodeling remain unclear [32]. Collectively, these limitations suggest that FeNO should be a supplemental biomarker in severe asthma [31].

Eosinophils

Eosinophils, bone marrow-derived granulocytes, modulate the function of structural cells and immunocytes and play critical roles in host defense against virus and bacteria, in the homeostasis of innate and adaptive immunity, and in tissue and vascular remodeling. Dysregulated eosinophilia, however, evokes pathology such as asthma, nasal polyps, vasculitis, and atopic dermatitis [33, 34]. Using bronchial biopsies, investigators showed that numbers of inflammatory cells including eosinophils were elevated in subjects with atopic asthma when compared with those who were non-atopic or healthy [35]. Others determined that severe persistent asthma subjects could be divided into those with or without airway tissue eosinophils [36]. Importantly, therapeutic strategies that decreased sputum eosinophil levels, a surrogate of airway eosinophilia, markedly improved pulmonary function and exacerbation rates in comparison to subjects who were treated by guidelines alone. Unfortunately, accessibility to testing sputum or tissue eosinophil levels remains reserved for research purposes and requires substantial expertise. Accordingly, investigators have extensively studied the validity and reliability of blood eosinophil levels as a biomarker of

disease onset and severity [31]. Using monoclonal antibodies, recent studies show that targeting IL-5, an important survival factor for eosinophils, decreased blood eosinophil counts that were associated with markedly improved exacerbation rates, patient reported outcomes and pulmonary function as compared with subjects treated with standard care [27, 32]. Unfortunately, limitations exist in using blood eosinophil counts as severe asthma biomarkers that include: diurnal variations in blood eosinophil levels, sensitivity to systemic glucocorticoids, and lack of concordance between sputum and blood levels [31, 37]. These limitations suggested that blood eosinophil counts should serve as supplemental biomarkers [31].

Emerging Biomarkers

The development of novel therapies including biologic agents provide clinical platforms for discovery of biomarkers that predict therapeutic responses [25]. Essentially, biologics can serve as human *knockouts* of target proteins or cells. In severe persistent asthma, the recognition that monoclonal antibodies targeting IL-5 and IL-13 signaling pathways improved disease outcomes identified eosinophils, periostin, or dipeptidyl peptidase-4 (DPP4) as potential biomarkers, respectively [27]. Serum levels of periostin, an extracellular matrix protein induced by interleukin IL-4 and IL-13 in airway epithelial cells and lung fibroblasts, correlated with Th2-driven airway inflammation and with airway eosinophil numbers [27, 38]. Evidence also suggests serum periostin may predict the response to targeted therapy with biologic agents such as tralokinzamab (anti-IL-13) and omalizumab (anti-IgE) [27, 38]. The protein encoded by the *DPP4* gene, which is induced by IL-13, represents an antigenic enzyme expressed on the surface of most cell types and

modulates immune regulation, signal transduction, and apoptosis. Serum levels of DPP4 correlated with Th2-associated inflammation and serum periostin [38]. Although periostin and DPP4 serve as predictors of Th2-associated airway inflammatory responses, neither are approved biomarkers and both are affected by myriad processes unassociated with asthma [27]. Other emerging biomarkers include imaging techniques such as high-resolution CT scanning or optical coherence tomography (OCT) that can measure lung density (air trapping), airway lumen size, and wall thickness—metrics of airway remodeling. Unfortunately, OCT requires bronchoscopy, and CT scanning necessitates more validation and reproducibility before the risk of exposure to ionizing radiation justifies the repetitive measures of characterizing asthma outcomes [31].

ASTHMA OR COPD?

Throughout the years, attempts have focused on finding specific disease characteristics in order to establish whether a specific patient has asthma or COPD. The definitions of asthma and COPD have similarities which make differential diagnosis difficult. Both asthma and COPD are heterogeneous, chronic, and inflammatory diseases. The same type of inflammatory cells may be active in asthma and COPD and inflammatory features do not always clearly differ between the two diseases. Both diseases are characterized by airflow obstruction, which may be variable and persistent, i.e., not fully reversible. Although the variability of symptoms over time usually is more common in asthma, many COPD patients also experience variability of symptoms. Chronic obstructive pulmonary disease is often

caused by harmful exposure, predominantly smoking, whereas in asthma the cause is not clear and the development of irreversible airway obstruction seems to be related to eosinophilic inflammation [39]. Many subjects with asthma are smokers, which may complicate disease characteristics. It has been reported that around 20% of the asthmatic subjects are smokers [40], which may negatively influence clinical outcomes such as quality of life and need for hospital care due to asthma [41].

During recent years, the overlap between asthma and COPD has attracted increasing interest and has, in some contexts, been called asthma-COPD overlap syndrome (ACOS). Recently, international guidelines for management of conditions with this overlap have been published [42, 43]. A substantial number of patients classified as having asthma also have features of COPD and many patients classified as having COPD also have features of asthma, and patients with asthma seem to run an increased risk of developing emphysema [44]. As these patients do not fulfill the separate criteria for either asthma or COPD, they have been excluded from randomized clinical asthma and COPD trials. Thus, the knowledge of how to treat patients with features of both asthma and COPD is limited.

Clinical Aspects on Asthma—COPD Overlap

A recent overview reported that the incidence of the asthma/COPD overlap phenotype is approximately 20% in patients with the diagnosis of asthma or COPD [45]. In severe asthma the overlap phenotype was characterized by severe airflow obstruction and almost half of the patients were on maintenance treatment with oral steroids [45]. In studies of adult asthma, the overlap phenotypes had more severe airflow

obstruction and were equally male and female, whereas there was a male predominance for overlap in COPD [45]. COPD patients who also have features of asthma have worse quality of life and experience more severe exacerbations, leading to more hospitalizations than patients with "pure" COPD [45–47]. The occurrence of emphysema does not seem to differ much between patients with COPD and patients with asthma-COPD overlap, indicating that airflow limitation in these patients to a large extent is associated with small airways disease [46].

Lung Function

Bronchodilation, assessed as improvement of FEV_1 following inhalation of bronchodilators, has been claimed to be a useful tool for differentiating between asthma and COPD. Bronchodilator reversibility is, however, not a constant feature, as it varies over time [48] and is therefore not a reliable diagnostic measure. Furthermore, FEV_1 increases more than 12% and 200 ml after bronchodilatation in more than half of the COPD patients [49].

Most asthmatic patients have variable airway obstruction with normal lung function during remission. There are, however, patients with asthma who develop irreversible airflow limitation over time [50, 51]. Asthma patients who develop fixed airflow limitation seem to have lower lung function and bronchodilator response at a younger age and they suffer from more symptoms such as cough and phlegm production [51].

In 1977, Fletcher and Peto showed that smokers with COPD exhibit a faster lung function (FEV_1) decline over time than do non-smokers [52]. The rapid lung function decline is, however, not an exclusive feature of patients with COPD; it has been shown that non-smoking asthma patients have a more rapid lung function decline over time than non-asthmatic subjects [53].

Inflammation in Asthma and COPD

Half of the patients with asthma exhibit a persistent eosinophilic condition [54], which implies that half of asthma patients may have a non-eosinophilic inflammation that may respond poorly to traditional anti-inflammatory treatment such as steroids. Previous studies showed that patients with COPD may have increased the number of eosinophils in the airway and peripheral circulation [55, 56] and eosinophilia may also appear in association with acute exacerbations [57].

In COPD, neutrophils may play an important role in mediating airway inflammation. Asthma may, however, also be associated with neutrophil inflammation, which is primarily associated with severe asthma [36, 58, 59] but may also be found in more mild disease [54] and in smokers with asthma [60].

Systemic inflammation is most often assessed by measurement of circulating inflammatory cells, cytokines, and acute phase proteins. It is associated with poor prognosis and increased all-cause mortality and seems to be present in two of three individuals with COPD, implying that approximately 30% of subjects with COPD do not have signs of systemic inflammation. Systemic inflammation is, however, not a constant feature and only one out of six COPD patients has signs of persistent systemic inflammation, which does not seem to be related to disease severity assessed by lung function measurement [61]. The variation of systemic inflammation in COPD is associated with ongoing infection and is enhanced in the presence of airway pathogens [62]. In asthma,

systemic inflammation has not been studied much. Apart from an increased number of circulating eosinophils in some patients, there is no clear systemic inflammatory pattern in asthma.

Treatment of Patients with Features of Asthma and COPD

The consequences of the strict inclusion and exclusion criteria in asthma and COPD trials have resulted in limited knowledge on how to treat these patients.

The finding that COPD patients with sputum and/or blood eosinophilia respond better to steroids than do COPD patients without eosinophilia [63, 64] supports that patients with features of both asthma and COPD likely will benefit from treatment with inhaled steroids. It has been demonstrated that the response to steroid treatment in asthma is impaired in smokers [60, 65]. To our knowledge, there is no study in which the steroid response has been compared in non-smoking and smoking patients with COPD or asthma-COPD overlap.

Although specific studies are sparse, it is reasonable to assume that patients with features of both asthma and COPD will benefit from maintenance therapy with inhaled long-acting bronchodilators. Studies of other pharmacologic treatment alternatives are lacking, and there are no data on the effect of leukotriene antagonists, PDE_4-inhibitors, and biologic drugs in this particular group of patients.

Asthma/COPD Overlap

To date, there is not one specific entity defined as asthma-COPD overlap syndrome. Patients who manifest asthma and COPD characteristics represent a number of different phenotypes with various clinical pictures, inflammatory profiles, physiological features, and prognoses; asthma-COPD overlap is not a unique syndrome. Expressions of pathologic conditions are defined by the genetic profile and environmental factors. Each individual has unique combinations of genetic and environmental factors, which result in expression of different pathologic conditions (Fig. 1). In many subjects, genetic-environmental combinations include a condition that is recognized as asthma, e.g., young, allergic subjects with typical symptoms which we associate with asthma. A non-allergic, heavy smoker who develops dyspnea and airway obstruction at the age of 50 years is easily recognized as COPD. There are, however, a number of individuals who develop pathologic conditions that are not clearly within our definitions of asthma or COPD. These patients constitute a heterogeneous group and represent a number of different pathologic conditions. Therefore, for two reasons, the expression asthma-overlap syndrome should not be used. First, because it does not constitute one single condition but several conditions, and second, it is not a syndrome. Further efforts must be focused on defining different subgroups of obstructive lung diseases in order to enable tailoring individualized treatment for the different groups of patients.

CONCLUSIONS

Current therapies are inadequate for patients with severe asthma. The development of biomarkers and novel targeted therapies should allow for the introduction of precision medicine for patients with severe asthma and
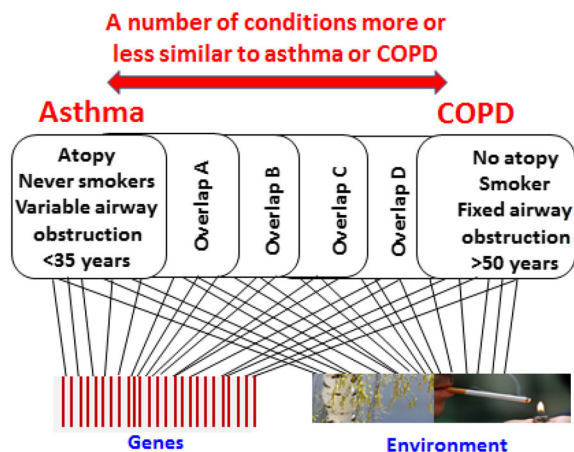
Fig. 1 The genetic profile in combination with exposure may result in a number of different pathological conditions. A young allergic non-smoker who experiences periods of variable airflow limitation with symptom-free intervals in between has typical features of asthma, whereas an older non-atopic long-term smoker who develops non-reversible airflow obstruction and dyspnea at light exercise dyspnea has typical features of COPD. Between those two "extremes", a number of different pathological conditions may occur that more or less resemble asthma or COPD. Efforts have to be made to characterize those patients in order to find clusters of patients with similar profiles and eventually individualized treatment. The process to characterize and find treatment for these patients is seriously hampered by lumping all conditions "between asthma and COPD" together into one single condition called, e.g., asthma-COPD overlap syndrome

the T2 high endotype. However, there remains a pressing need to better understand the underlying pathophysiology of T2 low asthma to help develop better biomarkers and better treatments for this group of patients.

The emergence of biomarkers may serve value in characterizing airway disease and in devising precision approaches to address specific disease mechanisms. To date, biomarkers remain somewhat exploratory until further research can characterize the validity and reliability of these approaches in improving asthma care. Partnerships among providers, payers, and industry will enhance our ability

to discover new approaches that target specific mechanisms and improve disease outcomes. Ultimately, our goals are to align phenotypes with endotypes to direct therapies that will provide the *right* intervention at the *right* time for the *right* person with the *right* diagnosis.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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