

Advances in pediatric asthma in 2007

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This year's summary focuses on recent advances in pediatric asthma as reported in 2007 publications in the Journal. This past year, new National Asthma Education and Prevention Program asthma guidelines were released with a special emphasis on new information in pediatric asthma. Journal theme issues in 2007 included the revised National Asthma Education and Prevention Program asthma guidelines, the accomplishments of the National Institutes of Health asthma networks, and focused discussions on environmental allergens, neutrophils, eosinophils, T cells, and epithelial cells, all of which affect pediatric asthma. The new asthma guidelines emphasize several key terms including severity, control, impairment, risk, and responsiveness that are relevant for advancing the care of children with asthma. This review highlights Journal articles that relate to these guideline topics. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, asthma control, asthma impairment, asthma risk, asthma severity, early intervention in asthma, biomarkers, therapeutics

Because pediatric asthma is an area of rapid growth, the Advances series last year included a focused summary on pediatric asthma.¹ This year's summary directs attention to the recently revised National Asthma Education and Prevention Program (NAEPP) asthma guidelines, especially in the area of childhood asthma. The asthma guidelines now emphasize the importance of asthma control, a stepwise approach to asthma management, and the importance of early diagnosis and intervention.^{2,3} This review highlights 2007 Journal publications and several other studies that affect our current understanding of childhood asthma.

KEY COMPONENTS OF THE REVISED ASTHMA GUIDELINES

In 2006, the Global Initiative for Asthma released a revised set of asthma guidelines.² An update to the NAEPP asthma

Abbreviations used

ACRN: Asthma Clinical Research Network
CAMP: Childhood Asthma Management Program
CARE: Childhood Asthma Research and Education Network
ICS: Inhaled corticosteroid
LABA: Long-acting β -adrenergic agonist
LTRA: Leukotriene receptor antagonist
NAEPP: National Asthma Education and Prevention Program
NHLBI: National Heart, Lung, and Blood Institute
PACT: Pediatric Asthma Controller Trial

guidelines followed shortly thereafter. Both sets of guidelines provide an update on current literature and shift the focus to asthma control. Although some of the terminology differs, the intent is the same: move toward control of asthma and minimize the effect of the disease. The NAEPP introduced several new terms to consider in following the course of asthma management. A full resource document and Executive Summary are available.³ The Executive Summary along with a number of commentaries are published in the November 2007 issue of the Journal.⁴⁻⁷

In the guidelines theme issue, Busse and Lemanske⁵ summarize the key areas addressed in the revised NAEPP guidelines and also point out several areas that were not addressed because of the limits of available evidence to support their application. The latter areas include the application of biomarkers, such as exhaled nitric oxide, to define asthma phenotypes that facilitate individualized treatment recommendations; the use of adjustable treatment with combination inhaled corticosteroid (ICS) and long-acting β -adrenergic agonist (LABA) therapy; and the use of intermittent treatment to manage mild persistent asthma. All of these will be topics for future guidelines updates.

Stoloff⁷ reviewed the implications of the asthma guidelines for clinicians. He said the ultimate goal of treatment is to enable patients to live with few, if any, symptoms; no functional limitations; and no impairment in quality of life associated with asthma. Furthermore, there should be few, if any, adverse events from either therapy or the disease.³ Several key terms were introduced with the new guidelines, including *severity*, *control*, *responsiveness*, *impairment*, and *risk*. *Severity* is defined as the intrinsic intensity of the disease process and can be measured most readily and directly in patients who are not receiving long-term controller therapy. *Control* is the degree to which the manifestations of asthma (symptoms, functional impairment, and risks of untoward events) are minimized and the goals of therapy are achieved. *Responsiveness* is the ease with which control is achieved by therapy.

Asthma severity and asthma control are both divided into 2 domains: impairment and risk. *Impairment* is the assessment of the frequency and intensity of symptoms, as well as the functional limitations the patient is experiencing now or in the past because of asthma. *Risk* is the estimate of the likelihood of an

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TABLE I. Key advances in pediatric asthma in 2007

1. Revised NAEPP asthma guidelines were released in 2007 and now emphasize the importance of asthma control, a stepwise approach to asthma management, and the importance of early diagnosis and intervention.
2. Several key terms were introduced with the new guidelines, including *severity*, *control*, *responsiveness*, *impairment*, and *risk*.
3. Available studies now indicate that high-resolution computed tomography scans might be useful in children as a noninvasive technique for airway inflammation and airway remodeling.
4. The Childhood Asthma Control Test can be a valuable tool in clinical practice and research on the basis of its validation, ease of use, input from the child and caregiver, and alignment with asthma guidelines.
5. Abnormal airway remodeling and persistent dysregulation of airway tone might be the final common pathway for different disease mechanisms, and this might explain the heterogeneity of clinical phenotypic syndromes that go under the common label *asthma*.
6. Many children, including those in the inner-city population, can achieve asthma control with regular visit intervals and guideline-based care; however, long-term control can be highly variable among patients in all severity categories.

asthma exacerbation, progressive loss of pulmonary function over time caused by asthma, or an adverse event from medication or even death. The assessment of severity and control provide guidance on the direction to take in stepping up or stepping down medications. In the same issue, Kelly⁶ discussed some of the key areas in the treatment decisions profiled in the guidelines updates, such as the placement of combination therapy in the stepwise treatment plan.

This review uses the key terms from the guidelines as a template for discussion of recently published articles related to pediatric asthma.

SEVERITY

Although asthma severity is easily measured through clinical and pulmonary function parameters, little is known regarding the relationship of these measures to other indicators of airway structure, such as those determined by imaging techniques. De Blic and Scheinmann⁸ provided a review on using imaging techniques for assessing severe childhood asthma. Available studies now indicate that high-resolution computed tomography scans might be useful as a noninvasive technique for airway inflammation and airway remodeling. Several issues remain to be resolved including the validity of algorithm reconstruction, the imaging parameters to be used, and the application of this technique to young children. Furthermore, because of its cost and irradiation involved, this examination will likely be restricted to patients with severe asthma.

CONTROL

The aspects of asthma control is discussed in relation to the 2 domains described, impairment and risk.

Impairment

One of the new features recommended in the asthma guidelines is the inclusion of a validated questionnaire for following asthma control besides the assessment of symptoms and pulmonary function. However, limited information is available on the validation of such a questionnaire in children. Liu et al⁹ report on the results of validating the Asthma Control Test for assessing inadequately controlled asthma in children 4 to 14 years of age. They concluded, after evaluating 343 children, that the Childhood Asthma Control Test can be a valuable tool in clinical practice and research on the basis of its validation, ease of use, input from the child and caregiver, and alignment with asthma guidelines.

In regard to following the features of asthma impairment over time, one of the longest, most carefully analyzed cohorts is the National Heart, Lung, and Blood Institute (NHLBI) Childhood Asthma Management Program (CAMP). In the January 2007 theme issue on National Institutes of Health asthma networks, Strunk¹⁰ summarizes the experience from CAMP and the lessons learned. A key lesson was absence of a continued effect of ICS on lung growth during long-term follow-up even as symptoms and airway responsiveness remained improved. The importance of following lung function over time was also demonstrated in the CAMP Continuation Study, which included data for 5 years after the CAMP treatment period ended. Comparison of lung growth in participants with patients without asthma from 5 to 18 years has demonstrated that percentages of CAMP participants with abnormal FEV₁/forced vital capacity ratios have increased significantly with age in both sexes.¹¹ Therefore, it is important to follow lung function over time in children.

Because asthma and excessive body weight often coexist, it is important to recognize that the interaction between asthma and excessive body weight is associated with an additional decrease in quality of life in children with asthma.¹² Children with both asthma and excessive body weight had lower scores than children with either asthma alone or excessive body weight alone.

Cazzoletti et al¹³ conducted an epidemiologic study of asthma control in several European centers. To their surprise, they found 6 out of 7 adults with asthma using ICS did not achieve good asthma control, likely because of undertreatment.

Risk

In the updated asthma guidelines, there is increased attention paid to the assessment of risk in the form of previous asthma exacerbations, loss of lung function, and potential risk for adverse effects to medications. Federico et al¹⁴ indicated that it is unclear whether asthma severity measured with previous consensus guidelines is better than a history of a serious asthma exacerbation in predicting current disease activity and future clinical course. They sought to examine this question in a cohort study and reported that although asthma severity and a history of a serious asthma exacerbation both predict pulmonary function abnormalities and current disease activity, bronchial hyperreactivity was associated only with exacerbation history. Exacerbation history improved the ability of severity to predict key asthma measures. This feature is now addressed in the updated asthma guidelines with a more comprehensive assessment of risk features. This will be helpful in assessing not only current disease activity but also future clinical course.

Tantisira et al,¹⁵ using CAMP study data, reported that genetic variation in FCER₂, a low-affinity IgE receptor gene, may be useful in predicting increased risk for severe asthma exacerbations.

RESPONSIVENESS

The term *responsiveness* refers to the ease with which control is achieved with treatment. This is best measured during the course of symptom presentation with selection of treatment and then follow-up. The CAMP study solidified the position of ICSs as the preferred long-term controller in children with mild to moderate persistent asthma compared with as-needed bronchodilator therapy and in relation to nedocromil, a medication similar to cromolyn, over a 5-year treatment period. However, new medications, such as LABAs and leukotriene receptor antagonists (LTRAs), became available before the CAMP study was complete.

The NHLBI Childhood Asthma Research and Education (CARE) Network Pediatric Asthma Controller Trial (PACT) compared an ICS (low-dose fluticasone propionate), a LTRA (montelukast), and PACT combination therapy (once-daily fluticasone and twice-daily LABA [salmeterol]). Sorkness et al¹⁶ reported that both fluticasone monotherapy and the PACT combination achieved greater improvements in asthma control days than montelukast. However, fluticasone monotherapy was superior to the PACT combination in achieving other dimensions of asthma control. This is consistent with current guidelines recommendations.

One of the missions of the CARE Network and the Asthma Clinical Research Network (ACRN) is to fill gaps in information in the asthma guidelines. The networks have been successful doing this and also recognizing variability of treatment response, factors that modify response to treatment, and potential predictors of treatment response, such as biomarkers and genetics. The accomplishments of ACRN and the CARE Network over the past 15 years were summarized in a review by Denlinger et al.¹⁷ One of the recent ACRN trials attempted to identify asthma characteristics and biomarkers associated with ICS response in adults.¹⁸ This study found that the only strong predictors of ICS response were albuterol reversibility and FEV₁/forced vital capacity. Of greater importance is that this study reported the short-term response to ICS with regard to FEV₁ improvement predicts long-term asthma control. Previous reports by the CARE network indicated ICS pulmonary response could be predicted by biomarkers, such as exhaled nitric oxide.¹⁹ These 2 sets of observations suggest that children and adults may differ in the role of inflammation in predicting response to treatment.

In regard to combination ICS/LABA therapy, Gibson et al²⁰ conducted an evaluation of Cochrane systematic reviews, primarily studies in adults, and concluded that maintenance asthma therapy with ICS/LABA has differential effects on asthma control and asthma exacerbations. The greatest benefit and least harm of LABAs come when they are added to a similar ICS dose in adults with symptomatic asthma.

Another interesting study on ICS/LABA combination in adults comes from an additional evaluation of the Gaining Optimal Asthma control (GOAL) study conducted in 3416 patients with uncontrolled asthma randomized to either ICS monotherapy or ICS/LABA combination therapy for 1 year. Pedersen et al²¹ reported that an additional evaluation of the previously reported outcome data shows for good control, it is imperative patients with asthma stop smoking. The clinical effects of combination

therapy are significantly greater than the effects of ICS monotherapy in patients with asthma who smoke. Most patients who failed to achieve well controlled asthma status still demonstrated clinical improvements in several individual asthma outcomes. The clinical effects of combination therapy are significantly greater than the effects of ICS monotherapy in patients with asthma who smoke.

Similar studies must be conducted in children to define the beneficial effects of LABA; however, the number of studies on ICS/LABA is small in children 5 to 12 years of age, with none in children less than 5 years of age. The NHLBI CARE Network is conducting a study in children to assess the benefits of ICS/LABA compared with ICS/LTRA and doubling dose of ICS.

EARLY ASTHMA

Onset

The NAEPP asthma guidelines have been instrumental in pointing out the huge gaps in information regarding the management of asthma in young children.³⁻⁵ Available studies show that this is a critical period, because the disease is emerging and its early features may be related to long-term outcomes in the level of severity and progression to irreversible loss in lung function. This aspect of the disease was highlighted in an editorial by Martinez,²² who reflected on recent epidemiologic, long-term, and intervention studies. He makes the point that abnormal airway remodeling and persistent dysregulation of airway tone might be the final common pathway for different disease mechanisms, and this might explain the heterogeneity of clinical phenotypic syndromes that go under the common label *asthma*. A publication from the Tucson Children's Respiratory Study indicated that poor airway function shortly after birth should be recognized as a risk factor for airflow obstruction in young adults.²³ Therefore, prevention of chronic obstructive pulmonary disease might need to start earlier.

Along these lines, Bisgaard et al²⁴ reported on the evaluation of microbial cultures from hypopharyngeal aspirates in 1-month-old newborns from a birth cohort. They concluded that neonates colonized in the hypopharyngeal region with *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*, or with a combination of these organisms, are at increased risk for recurrent wheeze and asthma early in life. However, it is not clear whether the bacteria are a cause of asthma or perhaps a marker of an imbalanced immune system that predisposes to asthma.

Scirica et al²⁵ also examined early predictors of asthma and atopic disease by evaluating cord blood IgE in a birth cohort of 874 infants. Maternal age, Hispanic ethnicity, residence in low-income communities, and maternal total serum IgE levels were associated with levels of IgE in cord blood of infants at increased risk of asthma and allergies.

Treatment

Inhaled corticosteroids are recognized as the preferred long-term controller in children 5 years of age and older on the basis of strong evidence from comparison studies. Szeffler et al²⁶ reported on a 1-year study comparing oral montelukast and nebulized budesonide suspension in children 2 to 8 years old with mild asthma or recurrent wheezing. They found that both treatments provided acceptable asthma control; however, overall efficacy measures favored budesonide inhalation suspension over montelukast.

Prevention

Arshad et al²⁷ evaluated the effect of reduction in food and house dust mite allergen exposure in infancy in preventing allergy and asthma for infants at high risk based on family predisposition. They found that allergic diseases could be reduced for at least the first 8 years of life and recommended this for consideration in high-risk infants. Mandhane et al²⁸ examined asthma and atopy outcomes by sex, reported specific parenteral history of atopy, and breast-feeding in a birth cohort. They concluded that the influence of breast-feeding on development of atopy and asthma differs by sex and by maternal and paternal atopy and is most significant among subjects at lower baseline risk.

Chan-Yeung et al²⁹ reported on their experience of a primary prevention program for asthma in a high-risk cohort. Intervention measures, initiated shortly before birth and applied only during the first year of life, included avoidance of house dust mites, pets, and environmental tobacco smoke, encouragement of breast-feeding and delayed introduction of solids. The study showed that the intervention measures were effective in preventing asthma in children who did not develop atopy by age 1 year, but the specific measure could not be identified. Linehan et al³⁰ examined the influence of neonatal BCG vaccination on the prevalence of wheeze in a large historical cohort of a community population of children in Manchester, United Kingdom. Their results demonstrated an association between asthma symptom prevalence and neonatal BCG vaccination relating to a possible 27% reduction in prevalence, warranting further investigation.

An interesting observation was reported by Lehtinen et al³¹ regarding risk factors for recurrent wheezing and determining the *post hoc* efficacy of prednisolone in risk groups. They concluded that rhinovirus-induced early wheezing is a major viral risk factor for recurrent wheezing. In addition, prednisolone may prevent recurrent wheezing in rhinovirus-affected first-time wheezers, warranting a prospective trial to test this observation.^{31,32}

SPECIAL POPULATIONS OF INTEREST IN CHILDHOOD ASTHMA

Inner-city asthma

For children living in the inner city, asthma tends to be more frequent and severe. Programs have been established by the National Institute of Allergy and Infectious Diseases to focus on this issue, and attention is now being directed towards immunomodulation as a course of management. The contributions of the National Institute of Allergy and Infectious Diseases program to our understanding of inner-city asthma are summarized in a review by Busse and Mitchell.³³ Jones et al³⁴ reported that many children, including those in the inner-city population, can achieve asthma control with regular visit intervals and guideline-based care; however, long-term control can be highly variable among patients in all severity categories. A tracking system is necessary to identify variability in response and to individualize treatment.

Asthma phenotypes

The key to answering some of the questions related to asthma heterogeneity and to the relationship of genetics to disease expression lies in the careful definition of asthma phenotypes. Several unique populations have been described and set the stage for genetic and biomarker evaluation for individualizing management. Oryszczyn et al³⁵ studied the interrelationships of allergy markers and FEV₁ in relation to asthma and sex in children and

adults. They found that each allergy-related phenotype showed a distinct relation with asthma, with the role of eosinophils different than that for IgE levels and allergen skin test positive responses.

Bacharier et al³⁶ sought to characterize a cohort of children age 12 to 59 months from a NHLBI CARE Network study with recurrent severe wheezing. They found that among these preschool children, a subgroup was identified with severe intermittent wheezing characterized by atopic features and substantial illness-related symptom burden despite prolonged periods of wellness. Management strategies are needed to reduce the illness burden.

Another understudied population is children with severe or difficult-to-treat asthma. Chipps et al³⁷ analyzed children and adolescents in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study and reported high rates of health care use and loss of lung function, despite multiple long-term controllers. This study highlights the need for increased targeting of intervention programs and novel strategies to prevent loss of lung function and reduce illness burden.

Exercise-induced bronchospasm

Children with asthma are often compromised by the effect of exercise-induced bronchospasm. Weiler et al³⁸ published the American Academy of Allergy, Asthma & Immunology Work Group Report on exercise-induced asthma, which summarizes issues around epidemiology and pathogenesis, clinical presentation, prevalence, evaluation, differential diagnosis, and treatment, including those in competitive sports.

Viral respiratory infections

Khetsuriani et al³⁹ sought to determine the contribution of respiratory viruses to asthma exacerbations in children. They found that symptomatic rhinovirus infections are an important contributor to asthma exacerbations in children, and there is a need for more effective therapies against rhinovirus to reduce the risk of severe exacerbations.

FUTURE DIRECTIONS: THE PATHWAY TO INDIVIDUALIZED THERAPY

With each Advances review, we can follow the shift in approach to asthma management. In the 2006 Advances review for adult and pediatric asthma, the natural history of asthma emerged as an important component of childhood asthma management.⁴⁰ In the 2007 Advances review focused on pediatric asthma, the concept of individualized management of asthma was addressed that would take into consideration the features of early-onset asthma including risk factors such as patient characteristics, biomarkers, and genetics for management decisions.¹ With this information in place, the asthma guidelines have now included more information on the management of childhood asthma. This time, 3 age groups were described including those 12 and above, 5 to 11 years, and less than 5 years. The major differences include the amount of information related to medication dosages for these age groups as well as comparative clinical trials. As an example, when one compares the stepwise approach for children less than 5 years to that developed for age 12 years and older, there are some remarkable differences. For one, there are many gaps at step 3 in young children compared with multiple

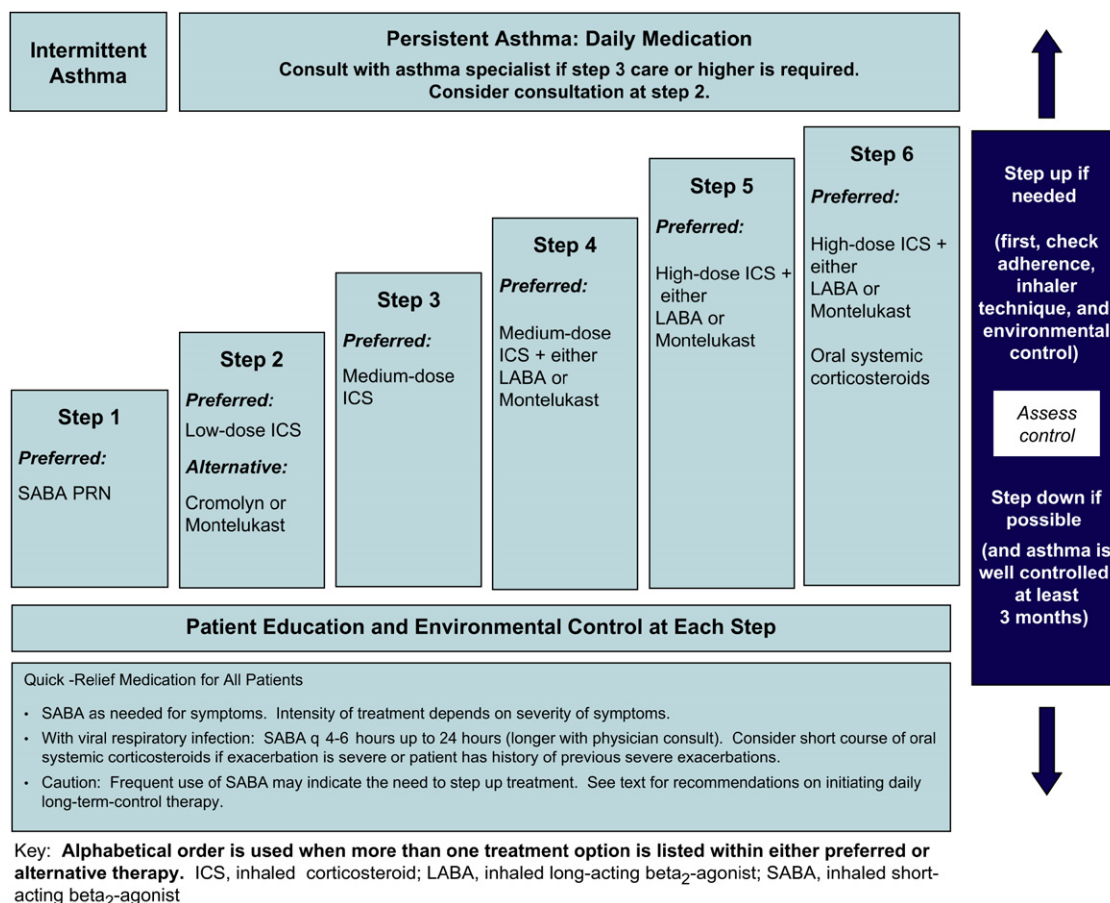


FIG 1. Stepwise approach for managing asthma in children 0 to 4 years of age. National Institutes of Health. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. August 2007. NIH publication no. 07-4051. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/index.htm>.³ Accessed December 30, 2007. PRN, As necessary.

options in older children and adults (Fig 1). This is related to the differences in age-specific product information; for example, LABA and omalizumab are not approved for use in young children, and the availability of evidence-based comparison studies are few in children less than 5 years of age. The National Institutes of Health asthma networks have contributed to filling information for gaps for children 5 years and older and are working to fill the gaps for children less than 5 years of age.⁴¹

The 2007 version of the NAEPP Expert Panel Report-3 asthma guidelines is now available for implementation. As indicated by Dr Craig Jones, a carefully implemented guidelines approach works well to get most patients well controlled; however, there is still significant variability in response that is identified when patients are carefully monitored.³⁴ How do we continue to improve asthma control by reducing impairment and risk domains? It is likely that few new drugs will be introduced in the next several years, so we must take this time to understand the disease better with the careful application of biomarkers and genetics, and to use this information to help direct treatment. For example, if the story unfolds that certain β -adrenergic polymorphisms carry a risk of harmful effects with LABA use, then patients should be directed away from this treatment to other alternatives at step 3 therapy.⁴² Currently, omalizumab is not approved for use

in children less than 12 years of age, and some challenge its cost-effectiveness in adults with well established disease.^{43,44} Perhaps it would be more effective if used earlier in certain patient populations at risk for significant allergic airway inflammation that results in airway remodeling and consequent irreversible loss of pulmonary function. Another alternative might be judicious use of sublingual immunotherapy.⁴⁵

Perhaps the answer is in identifying characteristics of patients in combination with biomarkers and genetics. One asthma characteristic could be atopic dermatitis, but a recent systematic review suggests this risk factor is lower than previously assumed.⁴⁶ Biomarkers and genetics association are still in a discovery stage and wide open for clinical application. Maybe some of these biomarkers and genetics will come from those discussed in our current reviews and molecular mechanisms reviews in understanding severe asthma, noneosinophilic asthma, airway remodeling, innate immunity, the role of cell signaling, eosinophils, neutrophils, T cells, dendritic cells, epithelial cells, and so forth.⁴⁷⁻⁵⁶ Some remain to be discovered, but all must be validated before they are applied clinically. Would breast-feeding be more effective in preventing disease if it were prolonged for a sufficient time?⁵⁷ These are indeed exciting times to advance the care of asthma.

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