

Immunoglobulin E as a Biomarker in Asthma



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KEYWORDS

• IgE • Asthma • Biomarker • Biotherapy

KEY POINTS

- Asthma is a chronic lung disease that has a significant economic impact, as well as an effect, on quality of life.
- The relationships of total and specific immunoglobulin (Ig) E to asthma are complex; however, studies show an association between IgE and the severity of asthma.
- Specific IgE, in particular, has a complex relationship with asthma because patients can be sensitized without a clinical reaction to the allergen.
- Total IgE elevations are seen in patients with atopic disease and pharmacotherapy can affect these levels.
- IgE as a biomarker provides a target for biologic therapy, which is critical for management of this disease.

INTRODUCTION

Asthma, a chronic inflammatory lung disorder marked with reversible airflow obstruction, is a multifactorial disease affected by both genetic and environmental factors. It is estimated to affect 7.8% of the United States population.¹ The annual economic burden of asthma in the United States is \$56 billion. Overall, asthma mortality and health care utilization rates are decreasing; however, the societal and economic burden remains significant. It is classified as a public health concern, leading to approximately 14.4 million lost school days for children and 14.2 million lost work days for adults in 2008. Poorly controlled asthma has been shown to increase health care cost across a lifetime and to decrease productivity.²

Phenotypes of asthma involve the idea of atopy, with the definition of atopy being a genetic susceptibility to produce immunoglobulin (Ig) E against nonpathogenic environmental allergens. IgE is the major immunoglobulin involved in an allergic response

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and parasitic infection.^{3,4} A diagnosis of asthma and wheezing in childhood has been associated with elevated total IgE, and a high level of total IgE at 1 year of age predisposes a child to persistent wheezing and early sensitization to aeroallergens.⁵ Inflammation in asthma can be triggered by both allergic and nonallergic mechanisms, which interact and result in the phenomenon of bronchoconstriction and bronchospasm.⁶ The relationship of specific IgE and asthma is complicated because allergic sensitization can involve multiple allergens, which can have a different clinical effect on the patient.⁷ Also, nonallergic factors, such as genetic makeup and environmental exposure, can influence the patient's symptoms. Sustained inflammation with continued IgE response, as in occupational exposure to an irritant, can also affect an asthmatic patient independent of allergic or atopic history.⁷ All of these factors can affect how IgE is produced and interpreted, as well as its use as a marker for therapy in the individual patient.

Biologic therapies have improved outcomes of asthma. An aspect of therapy is identifying biomarkers that would characterize the disease and associate it with the most effective therapies. Biomarkers for all asthma phenotypes have not been identified. Multiple biomarkers have been studied in relation to disease progression and therapy, specifically blood eosinophils, exhaled nitric oxide, sputum eosinophils, and total and specific IgE.⁸⁻¹⁰ The role of IgE as a biomarker is critical in understanding the progression of asthma, as well as in monitoring the effect of therapy.

PHENOTYPES OF ASTHMA

Identification of the phenotype of asthma is important to identify targets for innovative therapy, as well as for discovering methods for management and outcome prediction. Eosinophilic asthma and allergic asthma are the phenotypes most commonly associated with elevated IgE. Eosinophilic asthma is sometimes associated with nasal polyposis and peripheral eosinophilia, although the cutoff for eosinophilia is not well-defined and varies between clinical studies. Interleukin (IL)-5 recruits eosinophils and is pivotal in eosinophil differentiation, maturation, and survival. It has, therefore, emerged as a target for biotherapeutics. This phenotype of asthma has been shown to have a relationship to particular types of IgE but not necessarily total IgE levels in all aspects of this disease.¹¹ Allergic asthma, however, has a proven association with both total and specific IgE. Allergy and asthma are linked but only a subset of allergic patients develops asthma. An association between elevated total IgE and allergic asthma has been shown, and asthma prevalence was higher in children who have 2 parents with high total IgE.¹¹ Nonallergic asthma, in contrast to allergic asthma, has a lower family history association, which suggests more of an environmental role in its development. Nonallergic asthma can also be associated with elevated total IgE independent of atopy. There is a lack, however, of specific IgE, which is identified in allergic asthma.⁷

ASTHMA AND ALLERGEN INVOLVEMENT

There is a complex causal relationship between asthma and allergen sensitization. Allergens are environmental antigens that can induce specific IgE antibody production. Specific IgE is also known as allergen-specific IgE because it is specific for the allergens to which a patient is sensitized. IgE is a marker of atopy and, in epidemiologic studies, sensitization via positive skin test or IgE antibodies are a risk factor for asthma. This shows the interaction of total IgE, specific allergen IgE, and asthma because they create an atopic picture. Therefore, IgE mediates the reaction of allergens with asthma.¹¹ Allergens and asthma are linked; however, clinical symptoms

produced as a result of sensitization rely on multiple factors.⁵ Some of those factors include the dose of allergen, the route, and the patient's airway reactivity. For example, house dust mite IgE affects 25% to 30% of the world's population and is a major risk factor for asthma. In contrast, specific IgE to pollen is not a clear risk factor for asthma, although it is for allergic rhinitis.⁷

IMMUNOGLOBULIN E IN VIVO

Despite its low concentration and short half-life, IgE is biologically very active. It binds to high-affinity receptors on the surface of mast cells and produces a very specific and selective response to antigens. IgE-producing B cells have a long life, which results in a consistent allergic response over time. The IgE produced by allergic patients is specific for foreign antigens. The consistency of allergic response over time is related to this long lifespan of IgE-producing B cells and stability of mast cells in the skin. Allergens cross-link IgE bound to effector cells, such as mast cells and basophils, resulting in preformed mediator release and the production of new mediators that are responsible for both immediate and late responses.¹¹ This mediator release also involves eosinophil recruitment, although eosinophils can also be upregulated by effector T cells and group 2 innate lymphoid cells (ILC2s).^{3,12}

Immunoglobulin E Synthesis

IgE-mediated immunoregulatory effects on dendritic cells drive a T helper cell type 2 (Th2) or type 2 inflammatory response that is a part of asthma characterization.¹² This inflammatory process is triggered on exposure to certain inhaled allergens that activate dendritic cells and airway epithelium, leading to the synthesis of specific IgE antibodies.⁷ Synthesis of IgE can occur by the Th2-driven process of class switching, either by direct class switch recombination from IgM in germinal center B cells or potentially through sequential switch from IgM to IgG1, then from IgG1 to IgE; this can occur in B cells outside of germinal centers. Antigen presenting cells (APCs), such as dendritic cells, take up an inhaled allergen, process it, and present it via major histocompatibility class II to Th2 cells. This presentation leads to expression of IL-4 and IL-13. Signals provided by IL-4 or IL-13 activate transcription at the IgE isotype-specific switch region, leading to the process of class switching of B cells. A second signal is provided by the CD40 ligand, which activates DNA switch recombination. Class switching and, therefore, IgE synthesis generally occurs in the germinal center of lymphoid organs but also occurs in the respiratory and gastrointestinal mucosa of atopic patients.⁷ Newly synthesized IgE can bind to basophils and mast cells via IgE receptors. After activation, these cells play a role in amplification of IgE production and Th2 cell differentiation.

Immunoglobulin E Receptors

There are 2 receptors for IgE, a low and a high-affinity receptor. The low-affinity receptor is FcεRII, expressed on the surface of B cells and hematopoietic cells, and the high-affinity receptor is FcεRI, which is expressed on mast cells, basophils, and APCs. The high-affinity receptor is expressed as a tetramer on mast cells and basophils, and as a trimer on APCs. Notably, respiratory viruses induce high-affinity receptor expression and signaling, which has a significant IgE response in turn.³

Laboratory Evaluation of Immunoglobulin E

Total and specific IgE are measured by immunoassay. Specific IgE can also be measured by skin prick and intradermal skin test methods; however, there is no

quantitative number associated with it and there is a lack of full standardization. This, therefore, affects the value of clinical research associated with the testing. There are different versions of the immunoassays available, especially for specific IgE to aeroallergens that can trigger asthma. Total IgE is measured with a 2-site noncompetitive immunometric assay, through which anti-IgE antibody directed at the Fc region of IgE is fixed to a solid surface and captures IgE from the serum. After washing, a different anti-IgE antibody linked to an identifiable entity is added to detect captured IgE.⁴ Specific IgE assays detect IgE that will bind to allergen fixed on a solid surface. There is a variability of levels of specific IgE detected by different techniques and reagents because the assay differs depending on which technique or reagent is used.

TYPE 2 IMMUNITY

With any discussion of asthma, the cells and cytokines that regulate the airway type 2 inflammation are a critical aspect. The type 2 immune response is characterized by production of interleukins, leading to critical responses to helminthic infections, as well as by a pathophysiological role in allergic diseases such as asthma. Th2 cells and ILC2s are the cells involved in airway inflammation and cytokines regulate this overall process.^{12,13} Hence, controlling the type 2 inflammation of the lower airways would be a therapeutic target for control of asthma. IL-4 and IL-5 act in a sequential fashion to cause airway changes and IL-4 is important for primary sensitization.¹³ IL-13 is theorized to be more important with secondary exposure to allergens.¹³ Decreased expression of immunoregulatory cytokines, such as IL-12, IL-18, and interferon gamma, as well as increases in proinflammatory cytokines, such as tumor necrosis factor alpha, play a role in the inflammatory process.¹³ Specific cytokines that work with the Th2 response are IL-4, IL-5, IL-9, and IL-13. Thymic stromal lymphoprotein (TSLP) is part of the IL-7 family and has increased expression via mast cells and airway epithelium in patients with asthma. It interacts with proinflammatory cytokines and recruits Th2 cells to the airway.¹⁴ IL-25 and IL-33 are other cytokines that have a regulatory effect on airway inflammation. IL-33 is among the earliest signaling molecules to be released following epithelial damage. Its activation of Th2 cells results in promotion of the asthma phenotype.¹⁵ Identifying cytokines is important to the recognition of targets for biologic therapy.

Type 2 ILC2s are a major part of this type 2 immunity. They are present in eosinophilic airway inflammation and have been identified in asthmatic patients. In addition to being key regulators and effectors in type 2 immune response, ILC2s have a role in tissue homeostasis and repair. They regulate eosinophils through production of IL-5 and response to helminthic parasites, as would be expected in a type 2 immune response.¹⁶ ILC2s interact with both innate and adaptive immune systems, and dysregulation of this system leads to allergic manifestations such as asthma. Emerging research has shown that targeting the function of ILC2s can control the type 2 immune response. Subjects with allergic rhinosinusitis were noted to have elevated numbers of ILC2s in nasal polyps compared with controls, which was the first evidence that ILC2s have a role in allergic disease.¹⁶ ILC2s induce Th2 responses by affecting T cells, which in turn leads to a B-cell effect. Because Th2 cells work with B cells to promote IgE production, they are central in allergic asthma and lung inflammation. With these noted effects, there is a pivotal role for ILC2 to drive an allergic response, which would indicate that modifying the ILC2 function can help prevent type 2 inflammation affecting the lung. Therefore, IgE is a marker of type 2 immune response and interference of this ILC2 response can affect IgE.¹⁶ A study by Liu and colleagues¹⁷ showed increased ILC2 in eosinophilic asthma subjects compared with controls of

noneosinophilic asthmatics and subjects without asthma. Of note, there was also a statistically significant increase in levels of sputum eosinophils, exhaled nitric oxide, blood eosinophil counts, and IgE in the asthmatic subjects. This study's analysis did note that the biomarker best related to airway eosinophilic inflammation was ILC2, which was even more closely related than IgE. This introduces a new aspect into biomarker research because ILC2 had not previously been considered to have a large biomarker role.

ROLE OF IMMUNOGLOBULIN E

Specific IgE and total IgE are biomarkers for asthma of multiple phenotypes. Mechanisms regulating the production are still being studied. Specific IgE identifies sensitization to a suspected allergen. Increased total IgE levels are seen in patients with atopic diseases. The highest levels are seen in those with atopic dermatitis, followed by allergic asthma and allergic rhinitis.⁴ Elevated total IgE can also be associated with parasitic infections, inflammatory disorders, hematologic disorders, and primary immunodeficiency disorders.⁴ Both total and specific IgE levels are important from clinical and research perspectives because this can denote a certain asthma phenotype and provide a direction in management strategy.¹⁰

Specific Immunoglobulin E

Specific IgE is particularly useful in asthmatics for trigger avoidance with identification of certain allergens. High levels of specific IgE to allergen triggers are related to wheeze and decreased lung function.¹⁸ These specific IgE levels mediate asthmatic responses in allergic individuals; however, the clinical expression of asthma is more complex because specific IgE denotes sensitization. Sensitization should be correlated to symptoms because an asymptomatic patient can have elevated levels of specific IgE that are irrelevant to the clinical picture.¹⁹ Inflammatory and immunologic responses arising in bronchial mucosa following exposure to an allergen have been shown to modulate the developing reaction in an asthmatic subject.¹⁸ Studies also show that elevated allergen-specific IgE levels are associated with more severe asthma.¹⁸ Higher specific IgE levels can indicate more exposure and sensitization, which can result in worsened asthma. In particular, higher cockroach, dust mite, mouse, and cat-specific IgE levels are associated with poorer lung function.¹⁸ Cat, dust mite, and mouse IgE are related to increased risk of exacerbation or hospitalization in asthmatics.¹⁸ Again, levels must be correlated to symptoms that occur with exposure but, overall, the trend shows that severe asthmatics with high specific IgE are triggered by those particular allergens. In general, the presence of specific IgE to environmental allergens is more strongly associated with allergic asthma.

Total Immunoglobulin E

Total serum IgE levels are age-dependent, with atopic infants having earlier and steeper increases in their levels than nonatopic infants. Total IgE also varies by exogenous factors, including genetics, environment, and immune system status.⁵ In particular, location should be taken into account when analyzing laboratory results owing to geographic variation in levels. In the absence of disease, IgE expression is tightly regulated. There is no transplacental transfer, as evidenced by low cord blood levels. The levels increase throughout childhood, with a peak in early puberty, and decrease throughout the adult years.⁵ Total IgE levels are affected by multiple factors, including genetic, environmental, and immune system status. The pattern of IgE variation can differ significantly but, generally, total IgE levels greater than 333 IU/mL are strongly

associated with atopy in children older than 14 years of age.⁵ Corticosteroids can induce IgE production but decrease total IgE levels, especially in allergic bronchopulmonary aspergillosis (ABPA). IgE can be relatively resistant to steroid effects, therefore these changes can be less significant.²⁰ Other biomarkers, such as exhaled nitric oxide and sputum eosinophils, have been implicated in corticosteroid response in asthmatic subjects. These biomarkers did decrease with corticosteroid treatment; however, the significance of these findings is debatable and further study is needed.²⁰

Increased total IgE can negatively correlate with lung function in patients with a history of asthma.²¹ There is a noted relationship between IgE and eosinophils. High IgE concentrations can draw eosinophils to the site of an allergen patch test, and nonatopic controls who receive an atopic transfer of serum or intradermal purified antibody can also have noted eosinophil recruitment.¹¹ It has been theorized that total IgE changes in asthmatic patients are indirect measures of airway inflammation, as are eosinophils; however, this association is not fully studied. Thus, blocking IgE is a strategy to prevent or attenuate an allergic response.

Immunoglobulin E in Other Atopic Diseases

IgE has been identified in other atopic diseases and its role as a biomarker in these diseases continues to be studied. Elevated IgE has been noted in patients with atopic dermatitis; however, its specific role as a biomarker in this disease has not been clearly identified. In chronic urticaria, elevated IgE has been recognized as a potential biomarker based on studies showing an association between total IgE level and severity of the subject's chronic urticaria.²² Regarding food allergy, specific IgE has been studied as a potential biomarker of clinical reactivity to the allergen. Baseline specific IgE in discussions of hen eggs and cow milk are important predictors of tolerance. With food allergy, however, component testing, such as with peanut, wheat, and eggs, has been identified as preferential for diagnostic marking.²³ Atopic disease does have a relationship to IgE, and elevated levels of IgE can be associated with disease severity and effect in certain cases.

BIOTHERAPEUTICS

Current targeted therapy in asthma includes anti-IgE therapy or anti-IL-5 agents. None of these biologic targeted treatments has been proven superior to others; however, their mechanisms of action are separate, although the end goal and result is improvement of severe asthma. As noted in [Table 1](#), there are many biologic treatments that are currently available or under investigation.

Biologic therapy targeting IgE was the first biotherapy to be studied for use in asthma, with subsequent case reports demonstrating a benefit in ABPA.²⁸ Omalizumab is an anti-IgE monoclonal antibody used in asthmatics older than 12 years of age with uncontrolled severe persistent asthma. The range of recommended total IgE for omalizumab use is between 30 and 700 IU/mL; levels higher or lower than this range have an uncertain treatment benefit. High IgE levels greater than 1300 IU/mL can exclude patients from using omalizumab based on studies showing that the free IgE reduction in these cases is inconsequential, therefore resulting in minimal efficacy of treatment.⁷ Also, important considerations before using omalizumab are the patient's weight and presence of a perennial allergen sensitization because certain weights and lack of a perennial allergen sensitization can exclude a patient from use of this drug.²⁹

Omalizumab inhibits IgE interactions for receptors that are high and low affinity, and causes dissociation of high-affinity receptors from IgE. Omalizumab binds to the C3

Table 1
Biotherapeutics in asthma

Drug	Target	Effect
Omalizumab (Xolair)	IgE	Decreases IgE with significant impact on severe persistent asthma
Quilizumab	IgE	Investigational; decreases IgE without significant impact on asthma
Ligelizumab	IgE	Investigational; greater decrease in IgE than omalizumab, and may be more effective in skin and inhalant response
Mepolizumab (Nucala)	IL-5	Improves eosinophilia in patients with moderate-to-severe eosinophilic asthma and improves control in these patients
Reslizumab (Cinqair)	IL-5	Improves eosinophilia in patients with moderate eosinophilic asthma and improves control in these patients
Benralizumab	IL-5R α	Improves eosinophilia in patients with moderate-to-severe eosinophilic asthma and improves control in these patients
Dupilumab	IL-4R α	Investigational in asthma (approved for atopic dermatitis); for uncontrolled persistent asthmatics, reduces exacerbations and increases forced expiratory volume in 1 second (FEV1)
Lebrikizumab	IL-13	Investigational; for uncontrolled asthmatics, no consistent significant change in exacerbations
Tralokinumab	IL-13	Investigational; for severe uncontrolled asthmatics, no significant reduction in exacerbations
REGN 3500	IL-33	Investigational with clinical trials currently underway in moderate asthmatics
AMG 157	TSLP	Investigational; reduces allergen-induced bronchoconstriction and inflammation in mild asthmatics

Data from Refs.^{24–27}

region of the IgE Fc fragment, leading to complexes and, therefore, decreasing free IgE available to bind the IgE receptors.³⁰ Reduction in free IgE correlates with symptom control; however, the IgE levels do return to baseline after cessation of therapy.

The complex of omalizumab and IgE can interfere with detection via assay.³¹ Due to continued accumulation of these complexes, as well as production of IgE, measured total IgE concentration can be increased by 3-fold to 5-fold because it reflects both free and omalizumab-bound IgE. Thus, in the setting of either asthma or ABPA, it is important to be aware of the assay being used and to use the same assay over a period of years because there is significant variability in the accuracy of different methods of total IgE measurement in the presence of omalizumab. Measurement of free IgE is difficult but methods have been developed. Studies have shown that free IgE levels can decrease by up to 95% with omalizumab treatment.⁴ Based on the difficulties that can occur with measurement of IgE with omalizumab use, anti-IgE therapies that have rapid clearance from circulation without concern for interference in the assay are of interest for further study.

In ABPA, in which an IgE level of greater than 1000 ng/mL (or 416 IU/mL) is a major diagnostic criteria. IgE levels are often measured serially to assess response to therapy. In these patients, a decrease in total IgE of at least 35% correlates with improvement both clinically and radiographically. Given the formation of IgE-omalizumab complexes and their effect on total IgE levels, standard practice is not to follow total IgE levels following initiation of omalizumab in ABPA patients. A recent case report, however, suggests that total IgE levels will decrease in some ABPA patients despite

the use of omalizumab and, therefore, total IgE levels could still be followed to evaluate treatment efficacy in select patients.³¹

Overall, omalizumab can reduce asthma exacerbations regardless of the initial IgE level and has shown to also be useful in the treatment of ABPA. IgE as a biomarker specifically for anti-IgE therapy is a complicated science, although it is based on a large amount of research on both disease processes and the relationship between IgE, the allergic disease process, and omalizumab.⁷

Antiinterleukin 5 Relationship

IL-5 is a key cytokine required for development, recruitment, and activation of eosinophils; therefore it plays a role in the phenotype of nonallergic hypereosinophilic asthma. It is an interleukin produced by Th2 cells, ILC2s, and mast cells. Inhibiting IL-5 reduces blood and sputum eosinophils and the current anti-IL-5 therapies on the market have been shown to have this effect. Mepolizumab and reslizumab, both monoclonal antibodies against IL-5, and benralizumab, a recently approved antibody against the IL-5 receptor alpha, have all been shown to reduce asthma exacerbations and peripheral eosinophilia in subjects with eosinophilic asthma.^{32–35} A relationship has been noted between eosinophilic asthma and IgE, although the effect of anti-IL-5 therapy on IgE has not been clearly defined. Although eosinophilic asthma is a phenotype that is generally associated with nonallergic asthma, eosinophilia can also be present in allergic asthma. Therefore, patients with allergic asthma can also respond to anti-IL-5 therapy, in addition to anti-IgE therapy.

Blood and sputum eosinophilia have been noted in severe asthmatics in eosinophilic asthma, and sputum eosinophilia, in particular, correlates with higher total IgE. Sputum eosinophilia is less clearly associated with poorer control than peripheral eosinophilia. Enterotoxin-producing *Staphylococcus aureus* colonizes the upper airways of patients with eosinophilic asthma and IgE responses to this bacteria have been identified in this phenotype. A relationship was noted between the IgE produced to *Staphylococcus aureus* and severe asthma but this specific IgE can also be identified in the general population with asthma regardless of atopy history.⁷ Because this IgE has been identified regardless of atopy, a relationship between eosinophilia and IgE can be made. IL-5 has a synergistic effect on the IL-4-induced production of IgE but, overall, it has more of a role in eosinophil production.³⁶ Therefore, a role for IgE in this phenotype of nonallergic asthma is supported.

Immunoglobulin E and Biotherapeutics Under Development

Biologic therapy remains an emerging science and many biologic agents remain under study. Therapies targeting additional cytokines and proinflammatory modulators such as TSLP are in development for therapy. AMG 157 is an anti-TSLP monoclonal antibody that attenuates early and late phase asthmatic responses in patients with allergen-induced reactions. In studies of subjects with mild allergic asthma, it was identified to reduce eosinophilia and exhaled nitric oxide.³⁷ This biologic therapy is groundbreaking because it is the first to target the underlying allergic inflammation by blocking the airway epithelium's response to the inhaled allergen. Epithelial cell involvement in asthma has also identified IL-25, IL-33, and interferon beta as potential targets for biotherapeutics.³⁷ Anti IL-13 drugs, such as lebrikizumab and tralokinumab, are also being investigated for use in patients with uncontrolled asthma, with variable results.²⁴ Although these biologics do not target IgE directly, they may still affect IgE levels indirectly.

Dupilumab is a monoclonal antibody to IL-4 receptor alpha, which is a component of both the IL-4 and IL-13 receptors. By blocking IL-4 and IL-13-mediated inflammation,

dupilumab indirectly inhibits IgE production by preventing B cell IgE class switch. Dupilumab is approved for atopic dermatitis and in phase 3 trials for asthma. Dupilumab has been shown to reduce serum IgE levels, as well as other biomarkers such as exhaled nitric oxide.^{32,38} Although it does not directly affect IgE function, it does decrease the production and, therefore, has a role in treatment of allergic asthma.³⁸

Immunoglobulin E as a Biomarker for Response to Allergen Immunotherapy

Patients with asthma and identified specific IgE to environmental allergens can benefit from immunotherapy, which has been implicated in a reduction of total and specific IgE levels.⁵ This has been evident specifically in house dust mite immunotherapy; however, all allergens used for immunotherapy had statistically significant reduction in total and specific IgE.⁵ Immunotherapy has been postulated to alter production of mast cell mediators and specific IgE, which could affect patients with asthma. IL-4 decreased and IL-10 was induced in patients with asthma after immunotherapy, which leads to suppression of IgE production and amelioration of the triggered response to allergens seen in asthma patients^{5,39}

SUMMARY

IgE use as a biomarker can be helpful in a multitude of ways, including diagnosis, treatment, and predicting the outcome of allergic disease. Regarding asthma, this identification is critical for early intervention and prevention of morbidity. As a part of an expanding list of biomarkers, IgE has an established role in defining phenotypes of asthma and its treatment. Elevated levels of specific IgE can be pathognomonic for allergic disease; identification of specific IgE is important for allergens that trigger asthma. Biotherapy targeting IgE has also been shown to improve outcomes in asthma; free IgE decreases significantly with omalizumab use. Overall, these findings suggest that IgE is a reliable biomarker and should be followed for certain phenotypes of asthma to ascertain improvement and appropriate therapeutic interventions.

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