The Benefits of Specific Immunoglobulin E Testing in the Primary Care Setting

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Abstract

A common link among allergic diseases remains the many allergens that can provoke symptoms. The National Institutes of Health *Guidelines for the Diagnosis and Management of Asthma* and *Guidelines for the Diagnosis and Management of Food Allergy* support the use of in vivo (skin prick) or in vitro (blood) specific immunoglobulin E (IgE) testing, along with a detailed clinical history and physical examination, to document an allergy diagnosis. The initial responsibility of diagnosing allergic diseases falls principally on primary care providers, for whom skin prick testing is impractical. Access to in vitro testing provides a valuable diagnostic tool, in conjunction with patient history, for comprehensive allergy and asthma management, which can result in significant clinical and economic benefits and improved patient outcomes. Identification of specific allergens in patients enhances management through education, targeted allergen avoidance, pharmacotherapy, and immunotherapy. The utilization of specific IgE in vitro allergy testing may also drive efficient and effective utilization of healthcare resources. Testing can facilitate a close collaboration between the primary care provider and the allergy specialist, who is experienced in interpreting allergy tests and correlating them with clinical history, conducting food and drug challenges, educating about environmental controls, and managing chronic or recurrent conditions where allergy is not easily recognized. As healthcare reimbursement moves from fee-for-service to fee-for-outcomes, cooperative, comprehensive, and outcome-based patient management will gain in importance.

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Allergic diseases affect as many as 40 to 50 million Americans,[1] imposing a multibillion dollar economic burden on the healthcare delivery system. In the United States, the initial responsibility of diagnosing and treating allergic diseases falls principally on primary care providers. Approximately 80% of patients with allergy-like symptoms are treated in primary care settings,[2] and the Centers for Disease Control estimates that 76% of patients with asthma are managed by primary care providers.[3] Authoritative new guidelines from the National Institutes of Health (NIH) for the diagnosis and management of asthma[4] and food allergy,[5] provide direction for the proper diagnosis and management of allergic disease, which may subsequently drive the appropriate and cost-effective utilization of healthcare resources. These guidelines recommend diagnostic testing to identify specific immunoglobulin E (IgE) to allergens, in conjunction with the use of a detailed clinical history and physical examination, to document an allergy diagnosis. Allergy specialists have traditionally used skin prick testing (SPT) for this purpose. The technique is not practical in most primary care settings, as it requires access to high-quality, standardized extracts, and personnel who are trained in test administration and interpretation and capable of dealing with life-threatening anaphylaxis. However, the use of specific IgE in vitro allergy testing of blood is recognized and supported by 2 sets of NIH guidelines,[4,5] and the Joint Task Force of the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI). These recommendations allow healthcare providers to identify specific allergic triggers accurately, better manage patients suffering from allergic disease, and make timely and appropriate referrals to an allergy specialist.

This supplement defines the clinical and economic benefits of specific IgE testing for those who deliver healthcare (eg, clinician, office manager, payer, and insurer) and patients. A common link among allergic diseases remains the many allergens that can provoke symptoms. Published guidelines recommend skin (in vivo) or blood (in vitro) testing to identify triggers when symptoms persist and/or have a significant impact on the quality of life, and to guide treatment, including allergen avoidance, pharmacotherapy, and immunotherapy.[6] There are numerous challenges to the diagnosis and management of allergic diseases in the primary

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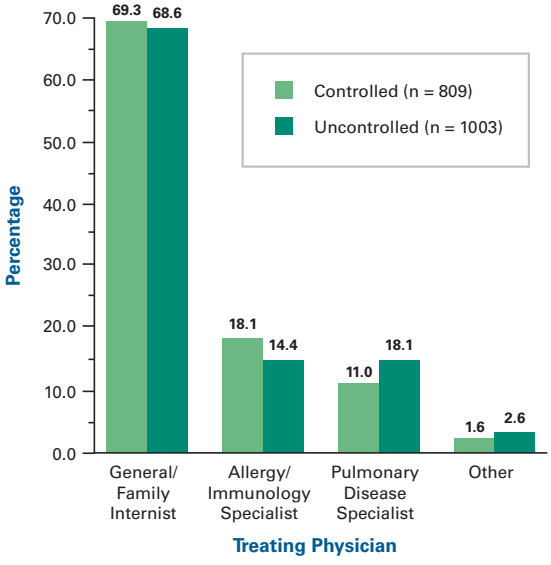
■ **Figure 1.** Physicians Managing Patients With Controlled or Uncontrolled Asthma[8]



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care setting. Access to specific IgE testing provides a valuable diagnostic tool, in conjunction with patient history, for comprehensive allergy and asthma management, which can result in significant clinical and economic benefits and improved patient outcomes.

Challenges to the Accurate Diagnosis and Management of Allergic Diseases in the Primary Care Setting

Primary care clinicians commonly encounter patients presenting with allergy-like symptoms, yet distinguishing allergic from nonallergic disease is difficult based on symptoms alone. As many as two-thirds of patients suffering from upper respiratory, allergy-like symptoms may be misdiagnosed, according to 2 well-designed studies conducted in managed care populations.[7,8] This fact calls into question the appropriate expenditure of at least some of the $7.3 billion spent annually in the United States for the treatment of allergic rhinitis,[9] as well as the $37.2 billion[10] spent to treat approximately 24.6 million Americans who have asthma.[11] The majority of patients with asthma are managed by primary care providers, regardless of asthma severity or control (**Figure 1**),[8] and NIH guidelines recommend allergy testing for perennial indoor allergens for all patients with persistent asthma.[1] Therefore, primary care providers stand on the frontlines of management for millions of patients who may or may not have allergic diseases. The availability of specific IgE in vitro testing in the primary care setting provides an important and accurate tool, in conjunction with patient history and physical examination, to make a diagnosis, and can facilitate allergy testing recommendations by the NIH.[4]

Focusing on asthma and rhinitis overlooks the large number of patients suffering from other allergy-like symptoms, such as eczema, which can have an allergic component. There is strong evidence that identification and exposure reduction of allergic triggers help relieve symptoms and improve control in asthma, rhinitis, and other allergic diseases such as eczema.[1,12,13] Specific IgE testing allows healthcare providers to properly diagnose and manage in accordance with guideline-based recommendations to improve patient care. In addition, specific IgE testing in the primary care setting allows more timely and appropriate referral for patients who could benefit from the expertise of an allergy specialist. The growing prevalence of allergies and asthma supports the wise use of the specialists' knowledge in managing complicated cases and in

■ **Table 1.** Control of Environmental Factors and Comorbid Conditions That Affect Asthma: Recommendations From *Guidelines for the Diagnosis and Management of Asthma*[4]

Exposure of patients who have asthma to allergens (Evidence A) or irritants to which they are sensitive has been shown to increase asthma symptoms and precipitate asthma exacerbations.
For at least those patients who have persistent asthma, the clinician should evaluate the potential role of allergens, particularly indoor inhalant allergens (Evidence A): • Use the patient's medical history to identify allergen exposures that may worsen the patient's asthma. • Use skin testing or in vitro testing to reliably determine sensitivity to perennial indoor inhalant allergens to which the patient is exposed. • Assess the significance of positive tests in the context of the patient's medical history. • Use the patient's history to assess sensitivity to seasonal allergens.
Patients who have asthma at any level of severity should: • Reduce, if possible, exposure to allergens to which the patient is sensitized and exposed. • Know that effective allergen avoidance requires a multifaceted, comprehensive approach; individual steps alone are generally ineffective (Evidence A).

Adapted from NIH National Heart and Lung Institute. *Guidelines for the Diagnosis and Management of Asthma—National Asthma Educational and Prevention Program Expert Panel 3 Report*. 2007.

Table 2. Comparison of Skin Tests With In Vitro Tests[4]

Advantages of Skin Tests	Advantages of In Vitro Tests
• Results available within 1 hour • Equally as sensitive as in vitro tests • Can be less expensive than in vitro tests • Results are visible to patients, which may encourage compliance with environmental control measures	• Do not require knowledge of testing technique • Do not require availability of allergen extracts • Can be performed in patients who are taking medications that suppress the immediate skin test (antihistamines, antidepressants) • No risk of systemic reactions • Can be done in patients who have extensive eczema • Quantitative results with established 95% cutoff values

Adapted from NIH National Heart and Lung Institute. *Guidelines for the Diagnosis and Management of Asthma—National Asthma Educational and Prevention Program Expert Panel 3 Report.* 2007.

coordinating care between the primary care provider and the specialist.

Specific IgE In Vitro Testing Technology

There are several in vitro IgE testing technologies available, with ImmunoCAP being the most extensively studied[14] and considered the reference standard for specific IgE measurement.[15] ImmunoCAP specific IgE testing is an immunofluorescent assay that detects a specific antigen when it binds with allergen-specific IgE antibodies in the sensitized patient. Many laboratories provide respiratory allergy profiles customized for a geographic region, which include the common aeroallergens.

The recently published NIH *Guidelines for the Diagnosis and Management of Food Allergy* state that immunofluorescent in vitro IgE assays are superior in both sensitivity and specificity to IgE tests using the old technology, the radioallergosorbent test (RAST).[5] The guidelines also clearly state that the predictive values associated with clinical evidence of allergy for ImmunoCAP may not apply equally to other test methods.[5,16] In addition, the ACAAI/AAAAI Joint Task Force on Allergy Diagnostic Testing asserts that it is no longer accurate to use the term "RAST" as a generic descriptor for in vitro allergy tests.[17] Furthermore, allergy test results (whether from blood or skin testing) should always be interpreted in the context of the patient's clinical presentation, age, relevant allergen exposures, and the sensitivity, specificity, and reproducibility of the allergy test in question. Interpretation of test results in the context of clinical history is crucial, as specific IgE tests provide information on sensitization, which is not always equivalent to clinical allergy. According to the ACAAI/AAAAI Joint Task Force[17]:

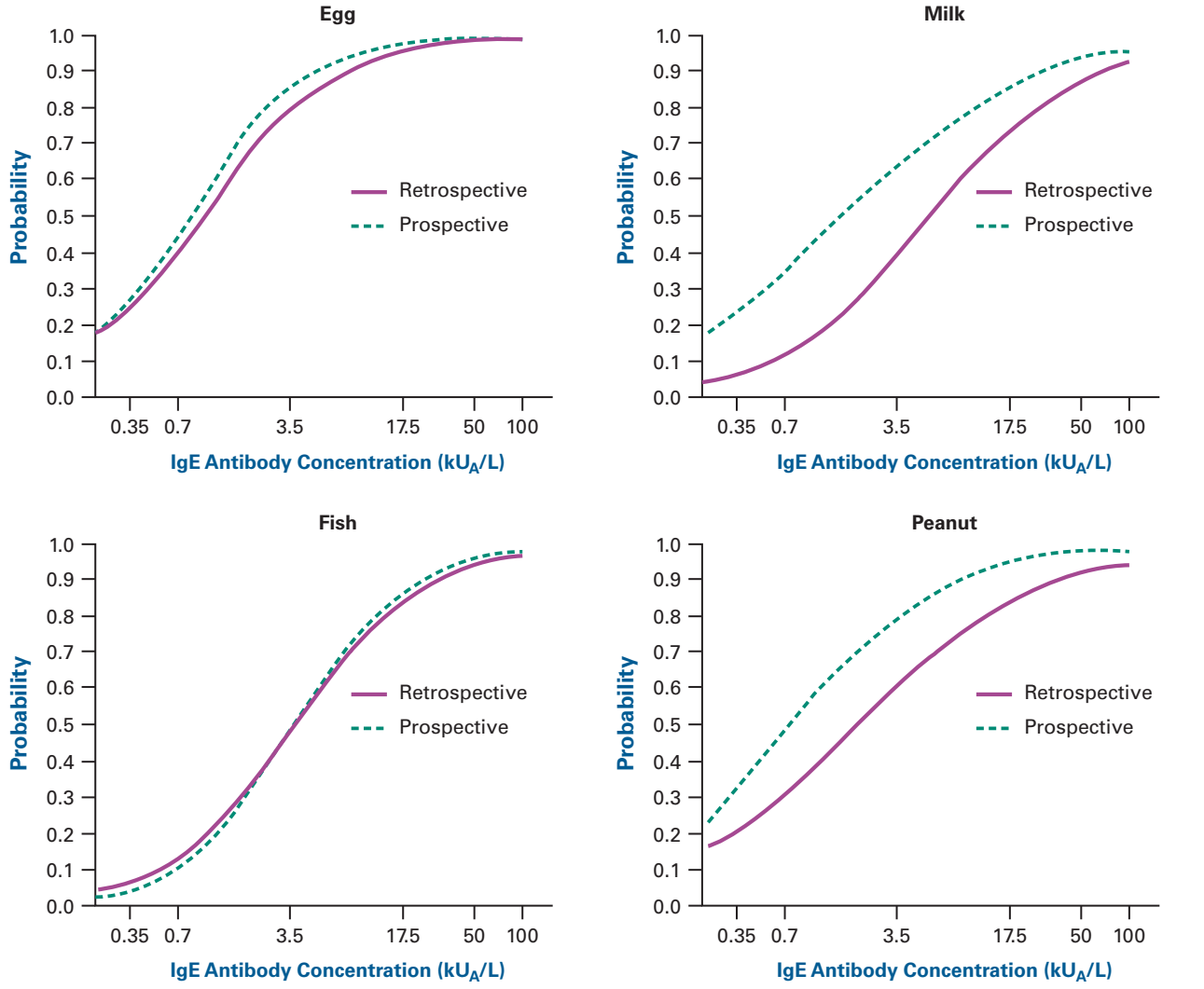
> It is important for this reason that the allergy evaluation be based on the patient's history and directed by a health care professional with sufficient understanding of allergy diagnostic testing to use the information obtained from his/her evaluation of the patient to determine (1) what allergy diagnostic tests to order, (2) how to interpret the allergy diagnostic test results, and (3) how to use the information obtained from the allergy evaluation to develop an appropriate therapeutic treatment plan. The practical value of allergy skin or blood tests rests in their ability to give accurate and consistent results when used as a confirmatory tool.

Clinical Benefits of In Vitro Allergy Testing

Common symptoms of allergic diseases are nasal congestion, cough, wheeze, itchy/watery eyes, and skin rash. These symptoms also occur frequently in nonallergic diseases, which make diagnostic testing so useful in confirming a diagnosis. In one study, approximately 50% of patients with rhinitis symptoms had IgE-mediated allergic rhinitis.[18] Certain symptoms and diseases, however, should raise the suspicion of more serious underlying allergic etiology. For example, as many as 60% of adult asthmatics and 90% of asthmatic children have allergic triggers.[19-21] As many as 30% to 40% of patients with eczema have underlying allergic disease,[22] and allergies to foods often cause recurrent gastrointestinal symptoms, such as abdominal pain and diarrhea in gastrointestinal anaphylaxis, which can range from mild to severe.[5]

Information on specific IgE sensitization can be used to help diagnose and educate patients about the role of allergens in their symptoms, to provide exposure-reduction counsel and target medications, and to recommend immunotherapy when indicated. The value of identification and reduction of exposure to offending allergens is well supported (Table 1).[4] Platts-Mills et al[23] noted that allergy testing to identify offending allergens can be accomplished by either SPT or in vitro IgE assay (Table 2), and cited a number of benefits for patients. In some cases, exposure to the aggravating allergen is obvious. However, most allergic patients are polysensitized (sensitized to more than 1 allergen). Frequently, allergen exposure is perennial and patients may be unaware of their specific triggers. Diagnostic testing can help determine which specific allergens are associated with symptoms because the level of specific IgE is related to the likelihood of clinical allergy. For

Figure 2. A Model for Probability of Symptoms in Relation to Allergen Specific-IgE Antibody Levels[26]



Quantitative results of specific IgE testing with ImmunoCAP have been used to correlate IgE measurements with clinical symptoms. For food sensitization, clinical decision points have been set for egg, milk, fish, and peanut, and can be used to predict the probability that a child will react to these common food allergens.[24-27] With aeroallergens, specific IgE antibody levels at age 3 years can be used to predict the persistence of wheeze at age 5 years.[14,28]
IgE indicates immunoglobulin E; kU_A/L, kilounits of allergen per liter.
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food allergens, the greater the level of specific IgE, the greater the likelihood of clinical reaction upon exposure (Figure 2).[24,25] Expert opinion differs on the number of allergens that should be used for testing. However, testing with 25 to 30 inhalant allergens, preselected on the basis of clinical allergy patterns, is appropriate for diagnostic testing in patients with allergy-like symptoms, and can detect allergy reliably.[9]

Finally, the results of allergy testing have significant clinical implications to enhance patient management and outcomes. Identification of a patient's specific allergic triggers guides allergen exposure reduction interventions, as well as referral for immunotherapy. The early use of diagnostic testing leads to a more specific diagnosis, which enables appropriate referrals, comprehensive evaluation, and implementation of effective treatment plans. Testing can facilitate a close and beneficial collaboration between the primary care provider and the allergy specialist, who is experienced in interpreting allergy tests and correlating them with clinical history, conducting food and drug challenges, educating about environmental controls, and managing chronic or recurrent conditions where allergy is not always identified (rhinosinusitis, conjunctivitis, asthma, cough, urticaria/angioedema, eczema). The following 3 clinical scenarios illustrate how IgE test results can influence therapy.

The Utility of Specific IgE Testing in Clinical Cases

The results of specific IgE testing have management implications, as illustrated by these 3 typical cases. Patients often try numerous over-the-counter (OTC) medications before resorting to an urgent care visit or making an appointment with their primary care physician. They may experience some symptom relief, but in many cases their symptoms recur and never resolve. These patients are often not allergic, and when they are, case management may be further complicated by fragmented care and lack of follow-up. Without an accurate and specific diagnosis, the cycle of symptoms→treatment→recurrence is unlikely to be broken. Accurate specific diagnosis leads to more specific treatment (through more specific environmental control or avoidance AND therapy that specifically targets the immune system). This leads to a change in the immune system (through allergy shots, for example) and hence the disease is modified (and in some cases cured) and the symptoms resolve.

Case 1: Chronic Sinusitis

A 38-year-old mother of 3 finally finds time in her schedule for an appointment with her primary care provider to investigate a sinus condition that has lingered for months. When her symptoms first surfaced, she took phenylephrine, which made her feel shaky, hyper alert, and also raised her (already elevated) blood pressure. She switched to diphenhydramine, which just made her drowsy. By mid-afternoon she was struggling to get through her workday. The OTC medications relieved her nasal symptoms somewhat but never completely. She visited an urgent care center, where she was diagnosed with a sinus infection and received a prescription for antibiotics and instructions on using a saline nasal rinse. During a spring break vacation, her symptoms worsened dramatically, so she visited another urgent care center and received another course of antibiotics. Back home again, she's still feeling miserable and realizes that she is spending a good portion of her weekly discretionary cash on products from the allergy/hay fever aisle at the drugstore. Still, nothing seems to provide more than temporary relief and her quality of life has deteriorated markedly.

Her doctor recognizes the pattern. Patients often try OTC medications, repeatedly visit urgent care centers, and take multiple courses of antibiotics, all without finding relief. Careful questioning reveals that the symptoms have lasted for more than 5 months, not just during the spring pollen season. From the history and physical examination, the physician suspects that allergy plays a significant role in this patient's sinus symptoms. He orders specific IgE testing. The results indicate significant levels of IgE to dust mites, dog, and grasses. The first step in management is to institute environmental controls, including encasing bedding in impermeable covers and moving the dog out of the bedroom at night. He also refers the patient to an allergist who begins immunotherapy, a long-term desensitization process that can resolve allergic symptoms rather than just mask them. More importantly, her sinus symptoms resolve.

Case 2: Asthma

A college student has been taking oral corticosteroids to control his asthma. He visits an emergency department (ED) one late summer weekend with an acute asthma attack. There, he is prescribed a rescue inhaler, instructed not to use more than 4 puffs per week, and given a prescription with 3 refills. The rescue medication works well, but he notices that he needs it more frequently than prescribed to control symptoms, using 1 inhaler a month. Two more acute attacks result in 2 more ED visits and still more prescriptions for rescue medication. No follow-up care is scheduled, but continuing symptoms have restricted his extracurricular activities at school. His parents, concerned about the cost of ED visits and frequent asthma attacks, make an appointment with their family physician while their son is on break. The physician elicits a history of poor asthma control and overuse of rescue medications (all of the inhaler prescriptions have been refilled by mail). No pulmonary function testing has been done since the patient was first diagnosed with asthma. Allergy testing performed many years ago showed allergies to soy, beef, and grass pollens, as well as high total IgE levels. These results seemed unreliable because the student never experienced symptoms after eating soy or beef.

The doctor orders specific IgE testing, suspecting that the acute asthma attack may have been related to heavy pollen exposure. He also replaces the frequent course of oral corticosteroids with a maintenance dose of inhaled steroid medication. Results of the testing indicate high levels of IgE to seasonal grasses, dust mites, and ragweed. The student is referred to an allergist to monitor his asthma with pulmonary function testing, and for possible immunotherapy in the city where he attends school. The doctor also schedules a follow-up visit during the student's next vacation.

Case 3: Food Allergy

First-time parents with a history of atopic disease worry that their daughter will inevitably have allergies. Despite breastfeeding exclusively for 6 months and carefully introducing new solid foods, the toddler develops eczema. Allergy testing reveals allergies to foods their daughter has never encountered, which leads them to impose an even more restrictive diet. Purchasing and preparing special foods becomes increasingly expensive and cumbersome. Their daughter also fusses over not being able to eat the same foods as her cousins, who frequently visit. Now, the parents are concerned that she will have an anaphylactic reaction and think they should ask for an EpiPen prescription. The family doctor orders specific IgE testing for milk, egg, peanut, tree nuts, soy, wheat, and fish, the foods that account for the majority of identified childhood food allergies. Quantitative clinical food cutoff values of IgE have been established for egg, milk, fish, and peanut, and are widely accepted and utilized by specialists (Figure 2).[26] Test results reveal high IgE concentrations for egg and milk, and the patient is referred to an allergist for further evaluation. After seeing the allergist, she is started on soy and wheat products (now knowing that she is not allergic to these), which widens her diet considerably. Her parents are also educated about the probability of outgrowing milk and/or egg allergy, and the possibility of reintroducing these foods by school age.

Food allergy management illustrates how primary care providers and allergy specialists can work together for clinical improvement (**Table 3**). The initial diagnosis, or suspected diagnosis, is often made by the primary care provider through a careful history, physical examination, and blood testing. The definitive diagnosis may include skin testing (most helpful for foods when negative) and/or challenge testing of the incriminated food under direct supervision. Based on the results, a diet that excludes only the truly allergenic foods could be implemented. The allergist, familiar with the natural history and prognosis of allergic diseases, can follow up and guide therapy. Prevention of anaphylaxis to foods is a shared responsibility.

Table 3. Primary Care Provider/Allergy Specialist Partnership to Diagnose and Manage Food Allergy[29]

Function	Primary Care	Allergy Specialist
Initial diagnosis	✔	
Definitive diagnosis		✔
Single-food elimination diet	✔	✔
Multi-food elimination diet		✔
Natural history		✔

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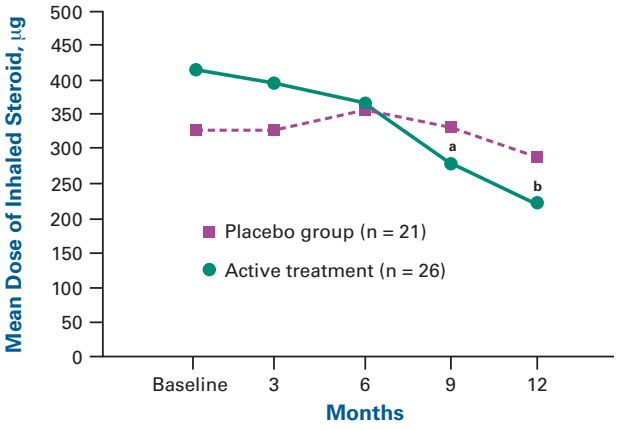
Figure 3. Effectiveness of Targeted Exposure Reduction[30]



[a]P <.05 vs placebo.
[b]P <.01 vs placebo.

Asthma

The clinical utility of allergy testing for patients with asthma includes evidence from a number of randomized controlled clinical trials. Halken et al[30] investigated whether mattress and pillow encasings resulted in effective long-term control of dust mite allergen levels, thereby reducing the need for asthma medication in children diagnosed with asthma and allergic to household dust mites. The prospective, double-blind, placebo-controlled study included 60 children aged 6 to 15 years. They were randomly assigned to active (mattress and pillow casings) or control (placebo mattress and pillow casings) groups, and followed every 3 months for 1 year. After 1 year, the active treatment group showed a significant decrease in the mean dose of inhaled steroids (408 to 227 µg; P <.001). In addition, the dose of inhaled steroids was reduced by at least 50% in significantly more children in the active treatment group than in the placebo group (73% vs 24%, respectively; P <.01) (**Figure 3**).

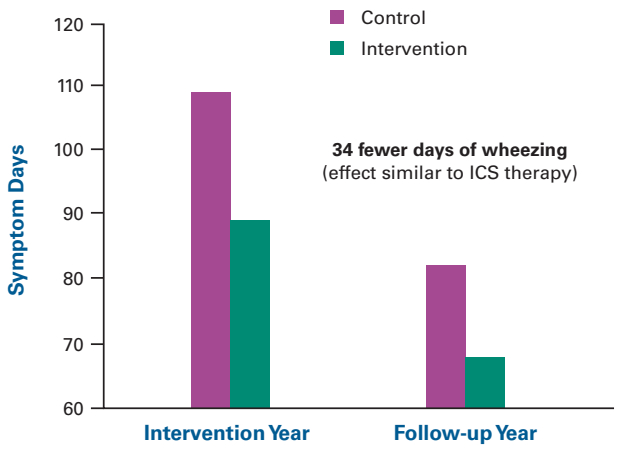
Morgan et al[12] explored whether environmental intervention tailored to each patient's allergic sensitization could improve asthma-related outcomes in 937 inner city children aged 5 to 11 years with allergic asthma. The families in the intervention arm received allergen-avoidance instruction specific to those allergens to which the child was sensitized, which took place during 5 to 7 home visits throughout the 2-year study. Families in the control arm received home visits at 6-month intervals but no instruction about avoidance strategies. There were no significant differences in the baseline allergen sensitization or exposures between the groups, and 87% of the children completed the 2-year study. The intervention group experienced 21.3 fewer days per year with asthma symptoms than the control group, a statistically significant reduction of 19.5%. Targeted allergen reduction resulted in 34 fewer days of wheezing over 2 years (**Figure 4**). Patients in the intervention group also had a 13.6% reduction in unscheduled office visits, and a trend toward decreased ED visits compared with the control group. The gain of fewer days with asthma symptoms persisted throughout the study.

Janson et al[13] performed a randomized controlled trial that evaluated 84 adult patients with moderately severe asthma who were managed with an individualized action plan, including environmental control based on the results of allergy testing. The control group participated in peak flow monitoring but did not have an individualized action plan. The study demonstrated that individualized management resulted in consistently higher inhaled corticosteroid adherence and improved asthma control. Treatment decreased nighttime awakenings (**Figure 5**), and resulted in more symptom-free days (SFDs) and less use of beta agonist rescue therapy. These studies are representative of growing evidence demonstrating that identification of allergic triggers and subsequent environmental controls can result in improved disease control and medication reduction in asthma patients.

Rhinitis

Allergic and nonallergic rhinitis symptoms are similar and often difficult to distinguish on the basis of history and physical examination alone (**Table 4**). As management of these forms of rhinitis differs, an accurate diagnosis is essential to target effective treatment. In several studies, as many as 65% of patients diagnosed as having allergic rhinitis and prescribed nonsedating antihistamines (NSAs) or leukotriene receptor antagonists (LTRAs) did not have IgE-mediated allergies.[31,32] Neither NSAs nor LTRAs are effective in treating most forms of nonallergic rhinitis.[32,33] In a study of a retrospective cohort of 693 patients seen at a military medical

Figure 4. Comparison of Symptom-Free Days[12]



Targeted allergen reduction resulted in 34 fewer days of wheezing over 2 years in a randomized, controlled trial of environmental intervention that enrolled 937 children with atopic asthma. The effect of targeted allergen reduction was similar to therapy with inhaled corticosteroids (ICS).

center in 2005 and tested with ImmunoCAP, 414 (59.7%) were IgE negative.[32] In this group with rhinitis that was not IgE mediated (nonallergic), 275 patients (66.4%) received 861 prescriptions, including refills. These largely ineffective medications cost $46,490, which is approximately $255 per patient spent unnecessarily. The authors concluded that a proper and timely diagnosis of nonallergic rhinitis would have prevented inappropriate medication usage, avoided potential side effects, and averted unnecessary costs.[32]

Food Allergy

The National Institute of Allergy and Infectious Diseases published guidelines for the diagnosis and management of food allergy; they acknowledge that food allergies are a growing and serious health problem.[5] The prevalence of food allergy is increasing, and an estimated 5% of children under the age of 5 years[34] and as many as 4% of teens and adults have food allergy. Food allergy can cause numerous symptoms (eg, gastrointestinal, cutaneous, and respiratory), which can range from mild to severe. The guidelines stress the importance of early testing, specific allergen identification, and follow-up, and warn that basing a diagnosis of food allergy on either history or physical examination alone may lead to an erroneous diagnosis of food allergy. The NIH Expert Panel states that further evaluation, including laboratory studies or oral food challenges, is required to confirm a diagnosis of food allergy. IgE testing is valuable in identifying foods that are potentially responsible for allergy and may be eliminated from a child's diet based upon additional investigation of the patient's history and/or food challenges.

Childhood Allergic Diseases

Eczema or atopic dermatitis (AD) is one of the most common skin conditions of childhood, afflicting more than 10% of children in mild or severe forms.[34] In 90% of affected children, eczema presents before the age of 5. Because of the associated sleep disturbances and school absenteeism, AD can have a significant impact on the daily functioning, and the social and emotional health, of children and their families.[35] In 30% to 40% of young children with eczema, food allergies such as milk, egg, soy, wheat, peanut, and tree nuts play a role in pathogenesis.[5] Multiple clinical studies focusing on the role of food allergy in eczema have shown that elimination of relevant food allergens can lead to improvement in skin symptoms.[36] Consequently, expert opinion stresses the importance of identifying clinically relevant sensitization to

Figure 5. Changes in Self-Management Behavior Due to Personalized Asthma Management[13]

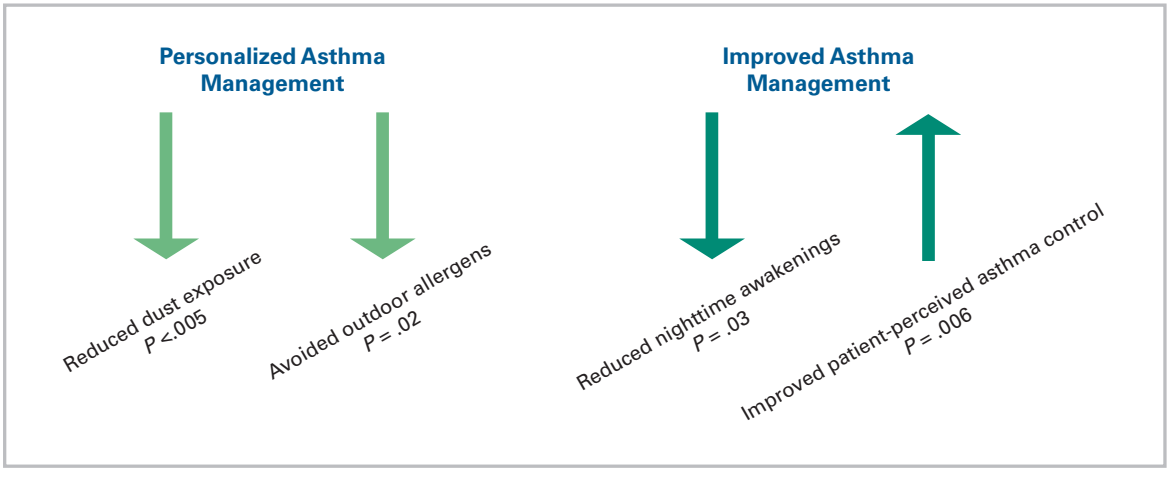


Table 4. Similar Symptoms, Different Causes

Allergic Rhinitis	Nonallergic Rhinitis	Infectious Rhinitis
Nasal congestion	Nasal congestion	Nasal congestion
Nasal discharge	Nasal discharge	Nasal discharge
Sneezing	Sneezing	Sneezing
Nasal pruritis		Headache

food allergens in children with eczema using a detailed history and allergy diagnostic testing, so that appropriate dietary interventions and therapy can be considered.[37]

Considerations for Managed Care

The Costs of Asthma and Allergic Disease

Over the past 40 years, the prevalence of allergic disease has increased, particularly in Western, industrialized countries; most of the allergy-related respiratory morbidity is accounted for by asthma and rhinitis.[38] Allergic conditions impose a heavy burden through both direct and indirect medical expenditures. In the United States, direct asthma-related healthcare costs are estimated to be $37.2 billion. Asthma morbidity and mortality encompass 1.8 million ED visits, 497,000 hospitalizations, and 15 million doctor office visits annually, plus 80,000 absentee workers and 11 deaths per day.[10,39] Costs due to allergic rhinitis, like those associated with asthma, can be direct or indirect. There are also costs associated with the comorbidities of allergic rhinitis, such as sinusitis and asthma, which are classified as "hidden" direct costs.[40] Overall medical spending to treat allergic rhinitis almost doubled between 2000 and 2005, from $6.1 billion (in 2005 US dollars) to $11.2 billion annually. Expenditures for care and treatment of allergic rhinitis in ambulatory care settings increased 73% during the same period, and mean annual expenditures for those with an out-of-pocket expense related to allergic rhinitis increased from $350 per person in 2000 (in 2005 dollars) to $520 per person. During those 5 years, more than half of the total allergic rhinitis expenses were for prescription medications. Among the direct costs for allergic rhinitis is the money spent on OTC allergy medications. Data from Euromonitor and Nicholas Hall estimate that between $1.2 and $1.5 billion (US dollars) was spent on OTC allergy medications in the United States in 2008.[40] The hidden direct costs of allergic rhinitis include the costs to manage associated medical conditions, such as those for antibiotics, radiographs, surgical procedures, asthma, and ocular symptoms.[40]

The hidden indirect costs of allergic diseases dwarf direct expenditures. For example, workers who are not fully functioning because of illness (sometimes called presenteeism) account for a $150 billion drain on productivity in the United States.[40] This decreased productivity may be far more expensive than the direct, health-related costs, and includes absenteeism and long- and short-term disability. Allergic rhinitis ranks fifth among chronic conditions in the United States in terms of overall economic burden, with over 75% of the costs caused by presenteeism (Table 5).[41] Lamb et al found that presenteeism costs associated with allergic rhinitis were higher than for any other condition, including asthma, diabetes, and coronary heart disease.[42] A study conducted by Lockheed Martin in 2002 assessed the impact of 28 medical conditions on worker productivity in their employee population.[40] The largest single category of costs was attributed to "allergies or sinus trouble," with an estimated annual loss of $1.8 million. Many of the additional high-cost categories were related to allergies in the form of comorbidities.

Table 5. Prevalence of Conditions Causing Presenteeism[41]

High Prevalence	Medium Prevalence
Allergy[a]	Arthritis
Depression/mental illness	Asthma
Migraine/headache	Heart disease
Musculoskeletal	Hypertension
Respiratory (except asthma)	

[a]Disease of the ear, nose, or throat, or mastoid process not elsewhere classified.

The largest direct costs for asthma are for prescription medicines and office-based visits—approximately 38% of the total expenditure for childhood asthma and 49% for adult asthma.[39] These expenditures could be reduced with the use of specific IgE testing to aid in the diagnosis of allergy, improve patient outcomes, and guide qualified referrals from primary care to allergy specialists.[43,44] The current healthcare environment requires resources to be used appropriately to improve outcomes. Assessment of the total costs and benefits of various outcomes over time should play an important role in pricing and reimbursement decisions and in the allocation of healthcare resources.

Sullivan et al[45] published a prospective study comparing the economic burden of severe or difficult-to-treat asthma in patients with uncontrolled versus controlled disease. Eighty-four percent of the study population had poorly controlled asthma. Medical costs (medications, physician visits, hospitalization) in those with poor asthma control were more than double those of patients with controlled asthma throughout the 2-year study (Table 6). Patients with uncontrolled asth-

Table 6. Mean Total Costs for Controlled and Uncontrolled Severe Asthma Over 2 Years[45]

	Controlled Asthma	Uncontrolled Asthma
Baseline	$2422.20 (n = 216)	$5963.60 (n = 3700)
12 Months	$2410.20 (n = 251)	$4530.00 (n = 2545)
24 Months	$2194.40 (n = 215)	$4046.30 (n = 2063)

ma missed a mean of 7.1 workdays due to asthma, whereas those with controlled asthma missed only 0.4 days. Cisternas et al[46] reported similar findings, with annual asthma-related costs of approximately $4900 per patient, and 35% of that amount attributable to indirect costs related to lost productivity. The same study also reported a correlation between annual direct costs and asthma severity—$2646 for patients with mild disease and $12,813 for those with severe disease.

Reducing Asthma-Related Expenditures

Fortunately, comprehensive management of asthma can reduce healthcare expenditures. Savings have been documented in health plan and vendor-based disease management programs, as well as in community-based initiatives. For example, Liao et al[47] published the outcomes achieved by the Children's Hospital of Orange County Breathmobile program (Table 7). This school-based program included a mobile clinic providing asthma severity assessment, allergy testing, patient/family asthma education, and therapeutic interventions in accordance with the NIH asthma guidelines. The percentage of patients in the program who were hospitalized for asthma fell from 18.5% in the year prior to the program to 3% just 1 year later. This represents an 85% reduction in hospitalizations. ED visits also fell, from 38% of patients before the program to 16% following the program, representing a 57% reduction.

A direct cost-savings analysis by Bollinger et al[48] reviewed data from 255 patients enrolled in the Breathmobile program in Baltimore, to estimate the savings associated with an SFD. Investigators then performed subpopulation analyses on incremental costs and incremental effects based on their observations. All SFDs were calculated, and only direct medical savings attributable to decreased ED visits and hospitalizations were calculated. From these data, investigators calculated incremental cost-effectiveness ratios for each SFD gained (Table 8). They found savings of $79.43 per SFD gained, with greater savings for children aged 5 to 11 years (-$116.84 per SFD) and those with intermittent asthma (-$126.71 per SFD).

In a study utilizing a similar, difficult-to-treat population of inner city patients with low socioeconomic status, Morgan et al[12] found that a home-based (primarily bedroom) intervention (focusing on identification and reduction of exposure to multiple indoor allergens and tobacco smoke) resulted in significantly fewer symptom days (21.3) per year over a 2-year period (P <.001).

Other studies have shown that the costs of medication are more significant than hospitalization for patients with allergy.[49,50] Recently, Zethraeus et al[51] examined the costs of

Table 7. Hospitalizations and ED Visits in Patients Before and After at Least 1 Year of Enrollment in the Breathmobile Program[47]

	Asthma Severity														
	Overall (n = 205)			Mild intermittent (n = 32)			Mild persistent (n = 45)			Moderate persistent[b] (n = 67)			Severe persistent[c] (n = 61)		
Measure	**Pre**	**Post**	***P*[a]**	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***
Total patients hospitalized, %	18.5	2.9	<.001	6.3	0	.157	20.0	4.4	.007	23.8	3.0	.001	18.0	3.2	.012
One hospitalization	8.3	2.4	—	6.3	0	—	6.7	4.4	—	13.4	3.0	—	4.9	1.6	—
One or more hospitalizations	10.2	0.5	—	0	0	—	13.3	0	—	10.4	0	—	13.3	1.6	—
Total patients with ED visits, %	37.5	16.1	<.001	15.7	12.6	.262	33.4	11.1	.001	40.3	20.9	.008	49.2	16.4	<.001
One ED visit	14.6	10.2	—	9.4	6.3	—	6.7	11.1	—	23.9	11.9	—	13.1	9.8	—
One or more ED visits	22.9	5.9	—	6.3	6.3	—	26.7	0	—	16.4	9.0	—	36.1	6.6	—

ED indicates emergency department.
[a]Wilcoxon test of preyear versus postyear distribution differences.
[b]Removed 1 outlier from total calculation (reported >100 hospitalizations and ED visits during preperiod).
[c]Removed 1 outlier from total calculation (reported >100 ED visits during preperiod).
Adapted from Liao O, Morphew T, Amaro S, Galant SP. *J Sch Health.* 2006;76(6):313-319.

Table 8. Incremental Cost-Effectiveness Ratios for Each Symptom-Free Day Gained[48]

	ICER/SFD Gained	Mean Incremental Cost (SD), $	Mean Incremental Effect/ SFD (SD)
Overall	–79.43	–3494.99 (817)	44 (9)
Baseline severity			
Intermittent	–126.71	–3674.69 (1388)	29 (14)
Mild	–35.09	–1719.40 (1149)	49 (17)
Moderate-severe	–84.54	–4565.61 (1511)	54 (15)
Age (baseline), years			
<5	–16.87	–1282.30 (884)	76 (21)
5-11	–116.84	–4206.52 (1027)	36 (10)
≥12	–44.87	–2198.50 (3541)	49 (31)
Sex			
Male	–79.17	–3483.51 (1196)	44 (12)
Female	–77.98	–3508.97 (1083)	45 (13)

The incremental cost-effectiveness ratio (ICER) is defined as the ratio of the change in costs associated with a therapeutic intervention compared with no intervention or alternative therapies. In this case, the ICER pertains to the cost-per-day difference between days with symptoms and symptom-free days (SFDs).
Adapted from Bollinger ME, Morphew T, Mullins CD. *Ann Allergy Asthma Immunol.* 2010;105:274-281.

IgE testing versus no testing using a clinical decision model based on a prospective, nonrandomized clinical trial of 721 Italian children with respiratory or skin problems seen in the primary care setting. The expected costs per patient over 2 years decreased by 43% in the specific IgE test group compared with the no test group; costs for physician visits were similar for both groups. The savings were largely due to the reduced need for medications (antihistamines, bronchodilators, and corticosteroids). Specific IgE testing increased the percentage of patients correctly diagnosed with allergies from 54% to 87%. These findings support evidence-based recommendations for allergy testing of children at increased risk for allergy development, and for targeted allergy treatments.[52]

The Cost of Specific IgE Testing

In an effort to maximize efficiency to provide value—not just volume—the healthcare industry is trending increasingly toward a greater role for personalized medicine and looking to the clinical laboratory for answers. While laboratory diagnostics influence roughly 80% of all healthcare decision-making, the clinical laboratory industry receives only 3% to 4% of overall healthcare spending.[53] Asthma and allergies place an economic burden on the healthcare system, and interventions that improve asthma and allergy control decrease healthcare costs. These interventions include those based on the results of allergy testing as recommended in the NIH guidelines.[4,5] Primary care clinicians need to be educated and have access to specific IgE testing to manage patients according to guideline recommendations. Specific IgE testing should be considered in the majority of patients who have persistent asthma. Recall the difference in annual cost between patients with mild asthma ($2646) and those with severe asthma ($12,813),[46] or the difference between controlled ($2194) and uncontrolled ($4046) asthma.[45] With the majority of asthma uncontrolled (55% according to the Real-world Evaluation of Asthma Control and Treatment study[8]), insurers and payers are paying for too many physician office visits, asthma medications, ED encounters, and days of hospitalization in patients with poorly controlled disease. While many factors such as medication compliance, access to medications, and severe intrinsic disease account for a significant proportion of uncontrolled asthma, identification of allergy triggers that results in effective avoidance and immunotherapy can reduce the number of patients with uncontrolled disease.

The cost reductions in healthcare resource utilization with the use of specific IgE testing in primary care are best seen in relation to the alternative, which is to rely solely on case history, physical examination, and nonspecific medication trials, without the support of any diagnostic tools to determine the presence or specific identification of allergens. The value of a correct diagnosis influences not only cost but clinical outcomes. In relation to the total healthcare costs of allergic diseases, IgE testing typically represents a small cost per patient,[26] ranging from $125 to $450, depending on the laboratory provider and the number of allergens tested.

Clinical and Economic Implications of Guideline-Based Care for Allergy and Asthma

In the United States, NIH *Guidelines for the Diagnosis and Management of Asthma* single out allergen identification and exposure reduction as essential components for comprehensive asthma management.[54] Comprehensive allergy and asthma management adds clinical value for the patient and helps ensure the appropriate utilization of healthcare resources. As healthcare reimbursement moves from fee-for-service to fee-for-outcomes, comprehensive and quality outcome-based patient management will gain in importance.

The Patient Protection Affordable Care Act (PPACA) of 2010 introduced many new quality-of-care initiatives and gives us a glimpse of what healthcare reimbursement may look like in the future. The Center for Medicare and Medicaid Services (CMS) began by focusing on participation in the Physician Quality Reporting System (PQRS) with increasing incentive payments to participants made through 2014. After 2014, physicians who choose not to participate will see their payments reduced by 1.5%. Along with increased participation in PQRS, the law also brings an increase in transparency with quality measures being made available to the public through the CMS Physician Compare Web site. The Web site serves as a platform for the public to find physicians and compare them with their peers based on the CMS-collected quality measures starting in 2013. A new asthma measures group was added in 2011, with more to come. Payers will continue to find ways to measure and reward the quality of care provided to patients. With the continued focus on quality, patient management has never been more important. Guideline-based care is necessary to achieve defined quality measures and improve patient outcomes.

One of the main PPACA initiatives was the introduction of Accountable Care Organizations (ACOs). The traditional fee-for-service payment system, which rewards doing more, is changing to a new payment system that rewards the delivery of high-quality care with measurable outcomes. With the increasing cost of healthcare, ACOs are one of many possible solutions. The concept of accountable care involves bringing healthcare providers of many specialties together to ensure and improve appropriate utilization of healthcare resources. To be successful, ACOs must reward hospital and physician collaboration toward the common goal of a renewed focus on primary care, wellness, and accountability for the health of the population served. ACOs support patient-centered comprehensive care that encourages less duplication and the targeted use of healthcare resources to reduce cost. ACOs will reimburse based on a combination of capitation and fee-for-service arrangements. Providing quality care is at the forefront of initiatives like these, and providers will start evaluating their current practices and preparing for the future.

Conclusion

The presence of specific IgE is an indicator of sensitization to allergens. Exposure to specific environmental allergens plays a central role in the development of allergic symptoms. Identification of specific allergens in allergic patients enhances management through education, allergen avoidance, and immunotherapy, each of which can improve clinical outcomes.

Allergy testing is fundamental to the effective management of asthma and is recommended by the NIH guidelines for all patients with persistent asthma.[4] The guidelines state that allergy testing can be performed by SPT or in vitro assays. Specific IgE testing is an essential tool in the primary care setting to manage patients with allergy efficiently and effectively. Use of specific IgE testing and identification of a patient's specific allergic triggers is essential for the development of a targeted exposure reduction plan, and identification of patients who are candidates for referral to allergy specialists. The identification of patients with asthma without specific IgE sensitization also supports appropriate management in the primary care setting, with a qualified referral to a specialist as needed. Experts agree that management according to the NIH guidelines could improve asthma control, with a subsequent decrease in costs.[55]

Comprehensive allergy and asthma management can result in significant economic value to the clinician and the provision of healthcare through the delivery of guideline-based care. This care requires the identification of allergic disease through testing and the subsequent interpretation of results, and management of patients according to evidence-based national guidelines. The NIH guidelines recommend aeroallergen testing for all patients with persistent asthma to assess sensitivity to perennial allergens. However, adherence to this aspect of the guidelines is difficult unless healthcare providers are able to access and order in vitro specific IgE testing and to understand the utility of the test results. The per-patient cost of specific IgE testing is small relative to the clinical and economic consequences of misdiagnosed and poorly managed allergic diseases, such as chronic asthma and rhinitis. Alternatively, comprehensive guideline-based care leads to collaboration between primary care providers and specialists, precisely targeted interventions, including exposure reduction and medications, fewer ED visits and hospitalizations, increased productivity, and improved quality of life.

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