Specific IgE Testing: Objective Evidence of Sensitization Aids Diagnosis and Treatment Decisions

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Before the introduction of radioallergosorbent (RAST) blood tests in the early 1970s, skin prick testing performed by allergy specialists was the only method for confirming IgE-mediated disease. The advent of in vitro blood testing technology moved specific IgE testing into the medical laboratory and greatly enhanced the utility of allergy diagnostics in primary care, where most patients with allergy-like symptoms are managed. Diseases with an allergic component represent a major public health problem in the United States. Allergic rhinitis, for example, is the fifth most common chronic disease, afflicting 40 million people annually and costing more than $18 billion each year. Epidemiologic studies document the increasing prevalence of allergic rhinitis in developed countries, although the reasons for this increase are not entirely clear. Furthermore, approximately 80% of patients with allergy-like symptoms are treated by primary care physicians. A reliable assay for measuring specific IgE can help primary care clinicians diagnose and manage allergy-like symptoms appropriately and cost effectively.

**Clinical Relevance of a Reliable Specific IgE Assay**

Specific IgE testing is still not understood by many primary care physicians. The conventional medical management paradigm—for diabetes or hypercholesterolemia, for example—includes a history and physical examination, appropriate diagnostic testing, and a treatment plan that includes nonpharmacologic and pharmacologic approaches. By contrast, the paradigm for allergy-like symptoms has usually been a brief history and physical exam followed by pharmacotherapy, including over-the-counter (OTC) and prescription medications. Diagnostic testing, typically referral to an allergy specialist for skin testing, is only undertaken when empiric therapy fails. This approach has been reinforced by the perceived lack of a reliable diagnostic test available in the primary care setting.

Unfortunately, even a compelling history and physical examination often leave room for subjective interpretation by the physician or the patient, who may create a bias in favor of a particular diagnosis. Yet history and physical examination, when used alone without confirmatory testing, yield a correct diagnosis of allergic diseases only 50% of the time. Because allergy-like symptoms have a host of allergic and nonallergic etiologies, objective evidence has become increasingly important in primary care. With specific IgE blood test results, primary care clinicians can make an assured differential diagnosis for patients with allergy-like symptoms. A reliable assay for measuring specific IgE supports the clinical diagnosis of allergy and helps guide the management of allergic diseases. Positive identification of allergens is essential before instituting environmental controls and helpful in selecting medication. Equally important, negative results avoid unnecessary, ineffective, and costly treatment. As Hugh Sampson, a pediatric allergist, points out, “[a] simple test that would allow primary care physicians to distinguish allergic from nonallergic children early in life and enable them to initiate appropriate therapy in mild cases or refer the children to an allergy specialist in more severe cases would be extremely useful.”

In fact, such a test exists, and laboratory professionals can help primary care clinicians to order specific IgE assays, aid in results interpretation, and provide reference information useful in making a diagnosis, such as the role of genetic predisposition to allergy or the role of allergen cross-reactivity. Sampson has reported on specific IgE cutoff values that predict clinical reactivity for foods (egg, peanut, milk, and fish) with >95% certainty. Such quantitative results aid materially in the diagnosis and management of allergic disease. The continuing challenge is to educate primary care clinicians regarding the nuances and clinical utility of specific IgE testing.

**Superior Specific IgE Assay Technology Is Now Available in Primary Care**

**Technological Evolution**

The first commercially available specific IgE blood test was the radioallergosorbent test, commonly known as RAST. First-generation RAST tests yielded a high number of false-negative results and were considered unreliable by allergists and primary care physicians alike. This first-generation qualitative assay measured bound specific IgE antibodies using allergens attached to paper discs and radiolabeled antihuman antibodies. Various tests using the RAST name proliferated, although they employed different solid phases, standards, and methods. This may account for the persistence of the term RAST, despite the fact that most contemporary assays use completely different technologies.

Assay technologies evolved in the late 1980s and early 1990s to include a liquid-phase enzyme technique and a new solid-phase method, both using monoclonal antibodies; notably, the solid phase improved upon earlier paper disc methods, with enhanced protein binding capacity to allergens. The solid-phase cellular structure possesses a large surface area and high binding capacity, which ensures the capture of a maximum amount of allergen material. Excess allergen is a prerequisite for generating serum dilution curves that parallel the calibrator curve. The new solid-phase technology provided greater sensitivity and true quantitative reporting of results in mass units of concentration. These refinements were coupled with sophisticated laboratory equipment to increase output and decrease turnaround time.

Today’s specific IgE assays feature similar convenience, and most offer quantitative results (Table 1). However, their respective accuracy, precision, sensitivity, and specificity can vary widely, as can the consistency of raw materials in allergens, the stability of reagents, and the quality of instrumentation. Notably, technology based on the solid-phase method has proven to be the current standard for specific IgE testing in several comparative studies. Global quality assessment programs for specific IgE show that approximately 80% of laboratories processing these tests have chosen assays based on this technology.

**Sensitivity and Specificity**

The poor sensitivity of first-generation RAST tests reinforced the commonly held view that skin testing represented a gold standard for detecting specific IgE. Current technology has much improved sensitivity, and improved reproducibility due to automation and use of monoclonal antibodies. Tests using calibrators directly tied to the World Health Organization Reference Preparation for IgE (75/502) also delivered truly quantitative measurements of IgE.
The relative sensitivity, specificity, positive and negative predictive values, and efficiency (a combined measure of sensitivity and specificity) of skin prick and blood testing for specific IgE were compared by Wood and colleagues. Results from skin prick and blood tests were comparable. After reviewing the scientific literature, Poon and colleagues came to the same conclusion. They noted that results from the 2 tests cannot be directly compared, because there is no independent standard for detecting inhalant allergens. They also found more standardization in blood testing than in skin testing, a finding corroborated in a recent editorial published in the Annals of Allergy, Asthma & Immunology.

Clinicians should know that assay cutoff values can differ significantly between diagnostic tests. Assay cutoffs should be determined by the lowest level from which a signal can be differentiated from background noise. Laboratories that report low allergen levels should verify each allergen cutoff point. Determining low-level specific IgE results may allow the early detection of allergy sensitization—a predictive indicator that patients (especially children) are at risk for developing additional, or more severe, allergic sensitivities. Current research is addressing the true clinical significance of extremely low-level sensitization in these young patients.

**Laboratory Proficiency**

Most primary care clinicians assume that diagnostic test results will be consistent from laboratory to laboratory. Although there are currently no industry wide formats, chemistries, reagent development, and result presentations for specific IgE assays, some manufacturers are working to improve standardization of their own assays to ensure consistent, reproducible results. One well-controlled study compared the accuracy and precision of specific IgE blood tests on 26 masked serum samples sent to 6 laboratories using 5 testing procedures for 17 allergens. Analysis of 12,708 test results demonstrated that 1 assay used in 2 laboratories was consistently superior to other commercially available assays, measuring specific IgE antibodies over a wide range with precision and accuracy.

Laboratory proficiency can be evaluated with the Diagnostic Allergy Proficiency Survey administered by the American College of Pathologists. The Clinical Laboratory Standards Institute, CLSI, (formerly the National Committee for Clinical Laboratory Standards or NCCLS) also publishes standards for quality control and minimal performance targets, including recovery of antibodies, precision, linearity, and parallelism over the measuring range.

**Reporting and Interpreting Results**

Many laboratories report specific IgE results using a simplified class system with reactions ranging from class 0 (no reaction) to class VI (very high specific IgE levels). On the surface, this method provides an easily understood way to categorize allergic sensitivity. However, assays may not employ the same class system—and even those that do may not report the same results in the same classes, due to varying calibration between tests. The class system obscures the true picture of patient sensitivity to allergens. The American Academy of Allergy, Asthma & Immunology has long recommended reporting quantitative results in units proportional to antibody content instead. True quantitation of results demonstrates a link between specific IgE levels and allergy-related reactions.

A better way of assessing results from various tests is to consider their coefficients of variation (CV) rather than comparing arbitrary class designations. NCCLS (CLSI) has set a minimum performance target of 15% CV for IgE antibody assays. Assays with a low CV provide a quantitative, clinically useful gauge to measure the probability of patient sensitivity to allergens, and thus to the probability of symptomatic response. As noted earlier, participating in or reviewing data from intralaboratory proficiency testing provides a critical evaluation of a prospective assay’s performance.

Although no universally accepted standard calibration system for specific IgE exists, specific IgE assays should report quantitative results calibrated to the World Health Organization 75/502 IgE standard, using a multipoint calibration curve; this ensures reproducibility over time and across allergens. In October 2004, the NCCLS (CLSI) established a new protocol for defining the limit of quantitation and the limit of detection of specific IgE assays. Technology is available that reports results from 0.1 kU/L to 100 kU/L for unmatched sensitivity and meets NCCLS (CLSI) requirements. At present, 0.1 kU/L is the lowest limit of quantitation available among specific IgE assays.

Equipping primary care clinicians with accurate and sensitive specific IgE test results helps differentiate patients who can be managed in primary care from those requiring referral to specialists. Objective diagnostic testing completes the medical management paradigm and serves as the basis for effective control of allergy-like symptoms.

**Conclusions**

During the past 3 decades, specific IgE assays have evolved, as has the understanding of their clinical utility. Quantitative results for specific IgE that are statistically robust and consistently

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**Table 1_Specific IgE Assays**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Technology</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified RAST CLA</td>
<td>Hitachi Chemical Diagnostics</td>
<td>Solid phase (paper disc)</td>
<td>Enzyme immunoassay</td>
</tr>
<tr>
<td>Allergen-Specific IgE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified RAST Turbo-MP</td>
<td>Hycor Biomedical</td>
<td>Activated cellulose solid phase</td>
<td>Radioimmune assay</td>
</tr>
<tr>
<td>HYTEC Enzyme</td>
<td>Hycor Biomedical</td>
<td>Activated cellulose solid phase (cellulose matrix in test tube)</td>
<td>Enzyme immunoassay</td>
</tr>
<tr>
<td>ImmunoCAP Specific IgE</td>
<td>Diagnostic Products Corp.</td>
<td>Liquid phase</td>
<td>Chemiluminescence</td>
</tr>
<tr>
<td>Test</td>
<td>Phadia AB</td>
<td>Activated cellulose solid phase (sponge in reaction vessel, CAP)</td>
<td>Fluoroenzyme immunoassay</td>
</tr>
</tbody>
</table>

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**Feature**

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reliable now provide objective evidence of allergic sensitization, which can optimize care and improve patient outcomes. LM

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