



In vitro allergy testing Where are we now?



Last month in clinic, I was asked to evaluate an adorable 4-year-old boy who had symptoms of chronic rhinitis, in addition to numerous other clinical conditions, including seizure disorder, chronic lung disease, G tube dependence, and developmental delay. His history and physical examination were not suggestive of an allergic origin, and he was already on medical management for allergies, including an antihistamine and a nasal steroid. We were unable to perform skin prick testing and decided to proceed with in vitro testing. I was certain testing results would be negative and I would be able to reassure his mother, a concerned, nurturing, and proactive advocate for her son. Results came back with a dog specific IgE (sIgE) of 0.47 kIU/L. His mother asked to put her son on allergen immunotherapy for dog, certain that his therapy dog was contributing to his symptoms. I was again reminded how much faith we are often asked to put in imperfect tests.

In a recent article in *Annals of Allergy, Asthma Immunology*, Wojtalewicz et al¹ published a compelling article evaluating the reliability of in vitro testing for the important indoor allergens of house dust mites (HDM) and cat epithelium, with a specific aim to see whether any improvement in interlaboratory agreement has occurred in recent years in response to previous reports that highlighted inconsistencies with in vitro allergy testing.^{2,3} The authors analyzed the data sources from 6 years of allergy external quality schemes on HDM and cat epithelium and compared results of the 4 main suppliers of sIgE tests. They used these data to evaluate interlaboratory comparability as well as to measure internal consistency.

Their work confirmed previous findings that suggested differences between results obtained from different laboratories.^{3–5} However, they found high test reliability within results obtained from each laboratory. These findings are not surprising, because the allergens used by each laboratory are not standardized; rather, standardization is based on potency.⁶ Similar results have previously been reported by their group for other allergens, such as birch.⁷ They did, however, report some positive findings in recent years that may suggest some improvement over the last several years, reporting a “cautious trend.” Higher agreement between laboratories has been seen at lower levels of sensitization. These levels tend to be the most challenging for clinicians trying to understand the clinical significance of each allergen and to offer appropriate guidance, as my earlier case illustrates.

Despite these modest improvements, the results of this analysis continue to show an overall poor agreement between laboratories. Historically, this is a problem that has been very difficult to address. Extract standardization is actually based on bioequivalent allergy

units, which result from erythema size after serial intradermal testing. As a result, some clinical (or at least in vivo) correlation is seen. The authors themselves point out that specific proteins will be present at different concentrations in the allergen extract. Individual patients may be sensitized to a protein that is present at low concentrations, resulting in a misleadingly low IgE level. Furthermore, allergens themselves are very different, with varying degrees of immunogenicity. As we move forward with a more personalized approach to treating patients, accurate diagnosis will be even more essential to the proper patient selection for newer therapies. This study continues to show the need for improved diagnostics.

However, as we continue to work to improve our diagnostic ability, one must understand that in vitro allergy testing (or in vivo allergy testing for that matter), even at its maximal potential, can only identify whether sensitization to an allergen is present. Often, we would like our testing to do the next step, which is to determine whether clinical disease exists as a result of this sensitization. Put another way, the clinician must determine the clinical significance of sensitization; no laboratory value is able to do this.

Despite these limitations, laboratory evaluation is essential in the diagnosis of allergy, because evidence of sensitization can be crucial. We need evidence of sensitization in the diagnosis of allergy. History by itself can be a very poor predictor of allergic disease. We know that in up to half of asthma cases, an allergic trigger can often be unrecognized, and guidelines recommend allergy evaluation for children with persistent asthma.⁸ Allergic rhinitis at its essence is a response to allergic sensitization. In the field of food allergy, history suggestive of an allergic reaction can only be confirmed in 50% of cases.⁹ The world of in vitro allergy testing, first introduced in 1967, made this testing available to a much broader audience.¹⁰ As with many things in medicine, this came with many benefits—particularly improving access to health care—and also, many pitfalls, such as a false security and interpretation of an imperfect test. As this analysis demonstrates, we must know the limitations of the testing we are using and evaluate the whole picture.

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