

Diagnosing Peanut Allergy

Molecular allergy testing provides a more complete picture

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➔ **BETWEEN 1997 AND 2007**, the prevalence of food allergy increased 18% among American children younger than 18.¹ This increase is associated with a significant economic burden.²

Peanuts are the most common cause of fatal food anaphylaxis.³ The National Institute of Allergy and Infectious Diseases (NIAID) estimates the prevalence of peanut allergy in the United States to be 0.6%.⁴ Symptoms of peanut allergy range from a mild reaction to life-threatening anaphylaxis. Most patients who are diagnosed with peanut allergy live in fear of the worst possible outcome. However a well-designed study conducted in the United Kingdom showed that 80% of children with positive skin prick test (SPT) results and/or specific IgE (s-IgE) blood test results and suggestive histories did not experience a systemic response to an oral food challenge to peanuts.⁵

How should a primary care provider evaluate a patient with suspected peanut allergy? An expert panel assembled by the NIAID recommends a detailed medical history and a focused physical examination as the first steps.⁴ Because

Food allergy in children is on the rise, and it presents a significant economic burden.

the history and physical examination alone cannot lead to a diagnosis of food allergy, published guidelines recommend SPT or s-IgE blood testing.^{4,6} These are considered objective diagnostic tools that can demonstrate sensitization to peanuts. Available methods of s-IgE blood testing include ImmunoCAP, Immulite and TurboRAST.^{7,8} When a positive s-IgE test result confirms sensitization to peanuts in a patient with an unremarkable peanut exposure history, the clinician is faced with a diagnostic dilemma: Is the patient at risk for an anaphylactic reaction or only mild symptoms?

Diagnostic Dilemmas

Several difficulties arise when formulating a treatment plan for a patient with suspected peanut allergy. First, the peanut

extracts used for testing are not standardized. An extract is a mixture of all the allergens available in the source material. The peanut extracts used for SPT may contain varying concentrations of different peanut proteins.⁷ Consequently, the allergic content of an extract used by one clinician may vary from the extract used by another. In addition, results from commercially available peanut extracts and test platforms are not interchangeable.⁹ Relevant allergens might be underrepresented or even missing in some extracts,¹⁰ and testing methods and equipment differ. An analysis of 12,708 test results demonstrated that ImmunoCAP performed closest to an ideal immunoassay.⁹

Second, sensitization and allergy are not synonymous. *Sensitization* indicates that the body produces measurable IgE antibodies to peanuts. But not all patients who test positive to peanuts have clinical symptoms. *Allergy* implies the presence of measurable IgE and the manifestation of clinical symptoms. Both SPT and s-IgE results must be interpreted in the context of the clinical history and physical examination, since sensitization to an allergen does not necessarily imply clinical symptoms.¹¹

National guidelines note that diagnosis of food allergy on the basis of sensitization alone can lead to a “gross overdiagnosis of clinical allergic reactivity.”⁴ Such diagnoses often result in unnecessary dietary restrictions.

Third, SPT and s-IgE testing cannot differentiate between primary sensitiza-

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Characteristics and Risk Stratification of Peanut-Specific Components

	Protein Family	Sensitivity to Heat/Proteases	Risk of Severe Reaction	Treatment
Ara h 1	Storage protein	Stable	High	Avoidance
Ara h 2	Storage protein	Stable	High*	Avoidance
Ara h 3	Storage protein	Stable	High	Avoidance
Ara h 8	PR-10 protein	Labile	Low**	Suggest further investigation to find primary sensitizer
Ara h 9	nsLTP	Stable	Low to high	Avoidance
CCD	CCD	Labile	Low	Suggest further investigation to find primary sensitizer

*Positivity to Ara h 2 is the most important predictor of clinical allergy to peanuts.⁵
**Bet v 1 homologues in hazelnuts, celery, peanuts and soybeans are partially heat stable and can cause systemic reactions.

tion and immunologic cross-reactivity. Peanut extracts contain many different IgE antibody-binding proteins. Some proteins are cross-reactive with pollen proteins and not specifically associated with peanut allergy. Pollen sensitization alone may elicit a positive peanut s-IgE test in a subset of patients.¹²⁻¹⁴

These factors cause difficulties in the interpretation of allergy test results.¹⁵ Typically, a primary care clinician completes the first-line workup and then refers to an allergyspecialist, who may perform an oral food challenge. The gold standard for diagnosing peanut allergy is the double-blind, placebo-controlled food challenge.⁴ But it is not feasible to perform a double-blind challenge on every patient with suspected food allergy.⁷ Food challenges are time-consuming, poorly reimbursed and, most importantly, may pose great risk to the patient.^{16,17} Understandably, few allergy specialists perform food challenges and there is a clear need for a simpler and safer diagnostic procedure.¹⁸

Molecular Allergy Testing

Almost anything containing proteins can be an allergen.¹⁹ Every allergen source contains allergenic protein molecules, also called components. A component is recognized and bound by IgE antibody that is specific to that component. Peanut extract contains a mixture of peanut components, each with a corresponding specific IgE antibody. The nomenclature of components is based on the Latin name of the species, followed by a number. For example, Ara h 2 is allergen 2 from peanuts, *Arachis hypogaea*.

The allergen components from a source

can be separated and purified or produced by recombinant technology. Sensitization to the components can then be measured individually in a process called molecular allergy (MA) testing.¹⁵ Peanut MA testing quantifies specific IgE for five peanut-specific components. This process is cleared by the Food and Drug Administration and available to clinicians today. Using peanut component testing, the likelihood of a mild or severe clinical response to peanut can be predicted. To understand the clinical applications of MA testing, it is necessary to understand three basic facts about allergenic proteins and antibody recognition.

1. Some components are species specific. Each allergen source contains one or more species-specific allergen components. Sensitization to these indicates that the allergen source is the primary cause of the clinical symptoms. Species-specific peanut components are Ara h 1, 2 and 3.

2. Some components are cross-reactive. Cross-reactivity occurs when an IgE antibody binds with its specific component and with a structurally homologous component from another source.²⁰ Cross-reactive components are conserved across the plant kingdom. A well-known example of cross-reactivity is birch pollen-related food allergy, a syndrome that affects many patients who are allergic to birch pollen (*Betula verrucosa*). Most of these patients have IgE antibodies to Bet v 1, a birch component. Bet v 1 has structural similarities to related proteins in peanut (and many other foods). IgE antibodies to Bet v 1 can bind or cross-react with the structurally similar peanut component. Cross-reactivity is simply a case

of mistaken identity. The cross-reactive peanut components are Ara h 8, 9 and cross-reactive carbohydrate determinants (CCD).

3. Some components are more stable than others. Components that are stable to heat and digestion are more likely to cause a severe clinical reaction. Heat and digestion-labile components are more likely to be tolerated or cause milder symptoms.¹¹ Differences in stability explain why some food allergens may be tolerated when raw, while others can be tolerated after cooking.

Allergen components are grouped into protein families based on their function and structure. For example, the storage protein family plays a role in plant defense against fungi and bacteria. Storage proteins are found in the seed and are vital for propagation of the plant, and they have evolved to be quite stable. These proteins are not degraded by heat or digestive enzymes. Sensitization to storage proteins is linked to severe systemic symptoms.⁵ Thus, patients sensitized to peanut-specific Ara h 1, 2, and 3 (storage proteins), are at high risk for systemic and severe reactions to peanut. Patients sensitized to peanut-specific Ara h 8, a PR-10 protein, and Ara h 9 (lipid transfer protein), face less risk.

Risk Assessment

Component-specific MA testing complements extract-based s-IgE testing.¹⁵ Whereas s-IgE testing answers whether the patient is sensitized to a particular allergenic source, component testing provides additional information about the likelihood of risk.

Allergy & Immunology

How does MA testing change the food allergy diagnosis? It allows for more focused diagnostic and prognostic abilities than current assays for specific IgE,⁷ and it provides significant insights into the process of sensitization by defining the primary sensitizers, cross-reactivity patterns and potential markers of systemic reactions in plant food allergy.²¹ The clinician can better assess risk for clinical reaction and explain symptoms due to cross-reactivity. Treatment plans can then be individualized based on the results of MA testing.

Risk stratification is an obvious benefit of MA testing and can help guide treatment (see table). Avoidance is the obvious strategy if the risk of severe reaction is high. However, if the risk is low, further investigation into the primary sensitizer could help explain symptoms and allay patient fears.

Case Studies

Case examples illustrate the clinical utility of MA. Consider peanut component testing for two patients. "AB" is a toddler who developed flushing and rhinorrhea after biting a peanut butter sandwich. His MA testing shows high sensitivity to Ara h 1, Ara h 2 and Ara h 3, mild/moderate sensitivity to Ara h 8 and CCD, and undetectable sensitization to Ara h 9 (<0.1 KU_A/L). Because AB has a positive response to Ara h 1, 2 and 3, the seed storage proteins, he is at high risk for a severe allergic reaction to peanuts. He would not likely be a candidate for an oral food challenge. Avoiding peanut-containing foods would be wise, and the clinician may consider prescribing an epinephrine autoinjector.

"CD" is a teenager who has a history of nausea and stomach cramps if she eats "too many" peanuts. She can tolerate a few peanut M&Ms. CD shows undetectable sensitization to Ara h 1, 2 and 3 and mild/moderate sensitization to Ara h 8 and 9 and CCD. She is not at high risk for a severe reaction, although she faces some risk and would be a good candidate for an OFC. An individualized management plan could follow.²²

Both patients are sensitized to peanut extracts (>100 and 19 KU_A/L, respectively) and have suggestive histories, so their risks from ingestion might at first appear similar. However, MA testing clarifies that the toddler faces greater risk than the teen. His positive results occur with the storage proteins Ara h 1, 2 and 3, placing him in a high-risk group. Her positive results to PR-10 (Ara h 8) and lipid transfer protein (Ara h 9) proteins put her in a lower risk group. Thus, two patients with confirmed s-IgE sensitization to peanut extract would be managed differently on the basis of MA testing.

Identifying Actual Risk

Molecular allergy testing complements and refines s-IgE testing by identifying species-specific or cross-reactive allergenic components. Results of specific component analyses can

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help distinguish cross-sensitivity from true allergy and stratify the risk for a clinical reaction. This information can be useful to primary care providers who see patients who have positive s-IgE test results but equivocal histories and unknown risk. Clinicians may want to work with allergy specialists in cases of life-threatening reaction to peanuts. ■

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