Guest Review

ADVANCES IN THE LABORATORY DIAGNOSIS OF FOOD ALLERGY

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SUMMARY
A great number of advances have been made in the diagnostic tools and testing methods available for food-allergy diagnosis. Improved and new methodologies have become available not only to identify the presence of a food allergy, but also to aid in determining the severity of an allergy, the likelihood of its resolution and potential cross-reactivity with other allergens. Cross-activity may include that between biologically related and unrelated foods or even between inhalant allergens. These testing methods may also improve patient outcomes by helping clinicians to provide accurate dietary advice and reduce the need for food challenges.

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INTRODUCTION

Suspected food allergy is a common problem in primary care and its diagnosis and subsequent management may often be challenging. This may have an impact on a patient's quality of life and nutritional state, owing to the unnecessary avoidance of certain foods. It may also lead to severe or even life-threatening allergic reactions if certain allergens are not identified and avoided.

Before discussing advances in the diagnosis of food allergy, it is essential to acknowledge that a good patient history by an astute clinician will always remain the cornerstone of allergy diagnosis. The history, aided by a physical examination, should indicate which allergy tests are ordered. Although there have been many advances in laboratory testing for food allergy, these tests should be used only after careful consideration of the patient history and by using a step-wise diagnostic approach. Clinicians should try to answer the following questions before ordering allergy tests:

- Is the patient allergic?
- Does allergy contribute to the patient's symptoms?
- What are the most likely clinically relevant allergens?
- What is the suspected mechanism of allergy (IgE- or non-IgE-mediated)?

Initial testing may include skin-prick or ImmunoCap® IgE tests for one or more specific allergens or an appropriate screening test for food allergens. If a food-screening test is positive, individual foods contained in the mix should be requested.

Additional testing should be considered when more specific information may improve patient management or when the clinician suspects an allergy but the test results are not confirmatory. Advanced diagnostic testing for food allergy may therefore be able to assist clinicians in the optimal management of patients with more complicated allergic reactions.

ADVANCED DIAGNOSTIC TESTS FOR FOOD ALLERGY

COMPONENT-RESOLVED DIAGNOSTICS

With the advent of component allergy testing, it has now become possible to predict allergen cross-reactivity, help predict the severity of reactions, help to offer dietary advice (some allergic patients may tolerate heated or processed foods or even peeled fruit) and reduce the need for food challenges. Component allergy testing may also predict the likelihood that a patient may outgrow a food allergy.[1–3]

WHAT ARE ALLERGEN COMPONENTS?

- Natural allergen sources may contain many different proteins (components), only a few of which are allergenic.[2,3]

TABLE I: SUMMARY OF RELEVANT INFORMATION GAINED BY TESTING FOR CROSS-REACTIVE POLLEN AND FOOD COMPONENTS

	CCD	PROFILIN	PR-10	LTP
Severity of reaction	±	+	++	+++
Localisation of cross-reactive allergen	N/A	Throughout	Pulp of fruit	Peel of fruit
Stability to heat and digestion	N/A	Labile	Labile	Stable

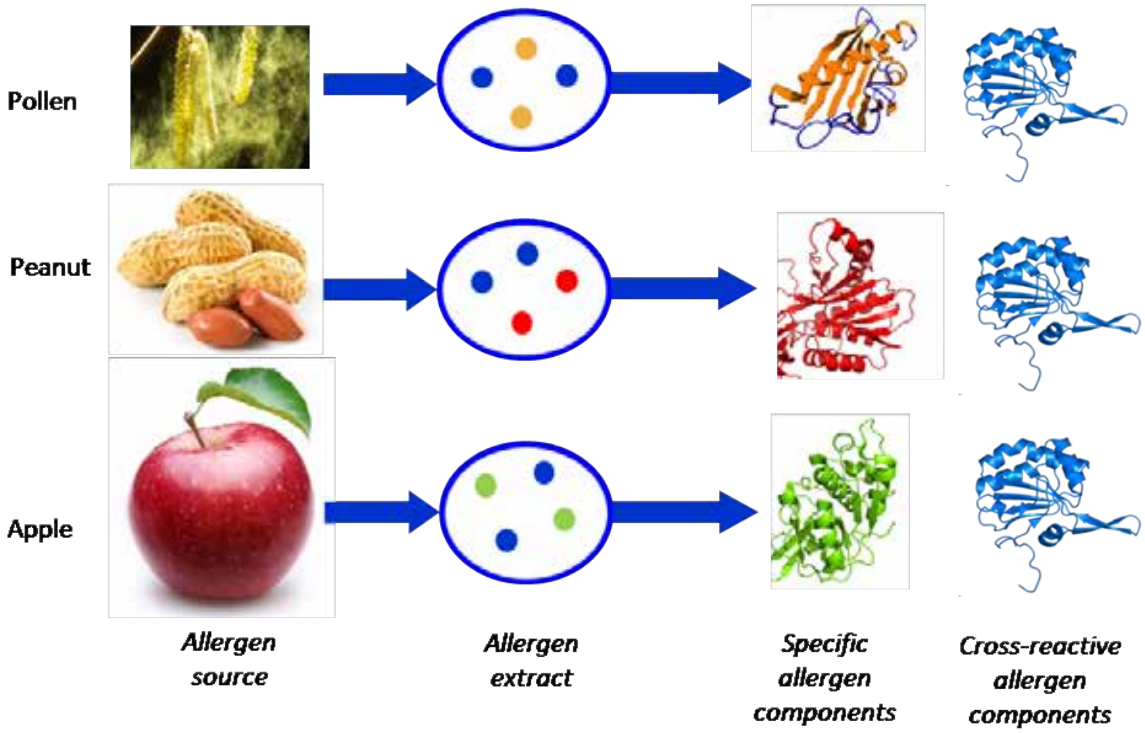

Figure 1: Some allergen components are species-specific and some are cross-reactive

- Some of these protein components are species-specific, but some occur in multiple allergen sources (cross-reactive components).[2,3]
- The allergen component names include their scientific acronym and number (e.g. *Ara h 2* means the second allergen from *Arachishypogaea* or the peanut).[2,4]

APPLICATIONS WHERE COMPONENTS MAY ADD CLINICAL VALUE TO FOOD-ALLERGY DIAGNOSIS

1. POLLEN-FOOD SYNDROME

- Patients have positive food-allergy tests when sensitised to cross-reactive components that occur in pollens as well as in foods of plant origin.[5,6]
- Food–pollen sensitisation may or may not be clinically relevant. The clinical relevance may be predicted by knowledge of the allergenicity of certain protein groups, for example, cross-reactive carbohydrate determinant (CCD)(least allergenic) < Profilin < pathogenesis-related protein group 10 (PR-10) < lipid transfer protein (LTP). Patients with CCD sensitisation should not be advised to avoid those cross-reactive foods to which they tested positive, because CCD sensitisation does not usually cause symptoms.[1]
- Sensitisation to some food–pollen cross-reactive components, most notably profilin and PR-10, are the cause of oral allergy syndrome (OAS) symptoms. Symptoms are usually confined to itching or swelling of the oropharynx, but in rare circumstances systemic reactions may occur.[5,6]
- Some of these food–pollen cross-reactive component proteins are heat labile (profilin, PR-10) and some are heat stable (LTP), which is important in helping to advise whether a patient should try cooking their food.
- Some proteins are localised to certain areas in fruits, for example PR-10 in the pulp of fruit and LTP in the peel of fruit. Patients with LTP allergy can be advised to try to eat peeled fruit (see Table I).
- Sensitisation to cross-reactive pollen components should be suspected when allergy tests to several foods of plant origin are positive.[2] The typical sensitisation pattern to alert to the presence of cross-reactive components is when allergy tests to soy, wheat and peanut are positive in combination. This should prompt testing to CCD, profilin, PR-10 and LTP. Please see laboratory data in Table II to illustrate this.

TABLE II: LABORATORY DATA (2013) INDICATING THE HIGHEST LEVELS (%) OF SOY, WHEAT AND PEANUT SENSITISATION IN AREAS WITH THE HIGHEST POLLEN SENSITISATION

SENSITISATION	KZN	WESTERN CAPE	EASTERN CAPE	FREE STATE	GAUTENG	LIMPOPO	MPUMALANGA	NORTH WEST
Grass pollen	27	61	38	80	56	53	41	77
Wheat	20	44	40	62	49	44	54	56
Soya	18	31	27	51	40	35	43	44
Peanut	32	47	41	58	51	49	45	57

TABLE III: SUMMARY OF THE MAIN EGG-ALLERGEN COMPONENTS

EGG WHITE				EGG YOLK
Ovomucoid Gal d 1	Ovalbumin Gal d 2	Conalbumin Gal d 3	Lyzozyme Gal d 4	Egg serum albumin Gal d 5
• Highly allergenic • Heat stable • Associated with more persistent egg allergy	• Heat labile • If positive, may still tolerate baked egg			• Occurs in egg yolk, chicken meat and feathers • Associated with bird-egg syndrome

TABLE IV: SUMMARY OF MAIN MILK ALLERGEN COMPONENTS

MILK				
CASEIN Bos d 8	ALACTALBUMIN Bos d 4	B-LACTOGLOBIN Bos d 5	BOVINE SERUM ALBUMIN Bos d 6	LACTOFERRIN Bos d LACTOFERRIN
• Heat stable • Most important allergen • Associated with more severe and persistent allergy • Cross-reacts between mammals (e.g. goat's milk, sheep's milk, cow's milk)	• Main whey proteins • Heat labile • Patients with an allergy to whey protein react more severely to fresh milk. May tolerate boiled/baked milk, long-life milk, hard cheese and yoghurt		• Occurs in milk and beef/red meat • Heat labile; patient may tolerate well-cooked milk and dairy • Cross-reaction with other mammals	• Heat labile • May be used as a preservative in beef and nasal sprays

2. EGG ALLERGY:

- The main and most important egg allergen component is ovomucoid, an egg-white protein.[1,2,7]
- Ovomucoid is highly allergenic, heat stable and predicts more persistent allergy.[1,2]
- *Clinical implication*: Patients who have a clinically confirmed (by history or challenge) egg allergy and test positive to ovomucoid are more likely allergic to all forms of egg, including baked egg, and may have a more prolonged allergy. Patients with egg allergy who do not test positive to ovomucoid may be able to tolerate extensively heated egg, for example egg used in cakes and biscuits (see Table III).

3. MILK ALLERGY

- The main and most important milk allergen component is casein.[1–3]
- Casein is highly allergenic, heat stable and predicts persistent allergy.[1–3]
- Casein cross-reacts between mammals, for example cow, sheep and goat's milk.
- *Clinical implication:* Patients who have a clinically confirmed milk allergy and test positive to casein may need to avoid all dairy products (including the baked form). They may have more severe clinical reactions to milk. Patients with milk allergy who do not have a casein allergy may be able to tolerate boiled or long-life milk, hard cheeses, coffee creamer or goat's milk (see Table IV).

4. FISH ALLERGY

- The main and most important fish allergen component is parvalbumin.[1–3]
- Parvalbumin is highly allergenic, heat stable and predicts more severe and persistent allergy.[1–3]
- Parvalbumin is broadly cross-reactive and is a marker for general fish sensitisation.[1–3]
- *Clinical implication*: Patients who have a clinically confirmed fish allergy (by history or challenge) and test positive to parvalbumin usually need to avoid all fish species. However, the parvalbumin content of different fish species may vary, for example lower levels in tuna. Patients not allergic to parvalbumin should consider allergy tests to unrelated fish species to identify possible safe alternatives (see Table V).[2,8]

5. SHELLFISH ALLERGY

- True shellfish allergy is best indicated by the shrimp allergen component Pen m 2, an arginine kinase.[3,9,10]
- The main and most important cross-reactive allergen component in shellfish is tropomyosin, a muscle protein.[1,3,9,10]
- Pen a 1 is a tropomyosin and a major allergen in shrimp. This protein is very heat stable and cross-reacts with other tropomyosins found in crustaceans (prawns, crayfish, crab), arachnids (house dust mite), insects (cockroach) and molluscs (squid).[3,9,10]
- *Clinical implication*: Patients who have a clinically confirmed shellfish allergy (by history or challenge) and test positive to tropomyosin usually need to avoid all crustaceans. They may also react to tropomyosin in molluscs such as squid and in anasakis, a fish parasite. Clinical reactivity to tropomyosin from aero-allergens such as house dust mite and cockroach may also be seen. Primary sensitisation to tropomyosin

TABLE V: SUMMARY OF MAIN CROSS-REACTIVE FISH ANS SHELLFISH ALLERGEN COMPONENTS

FISH		SHELLFISH
Cod parvalbumin Cyp c 1	Carp parvalbumin Gad c 1	Tropomyosin Pen a 1
• Heat stable • Broad cross-reactivity; marker for general fish sensitisation • Parvalbumin content of different fish species may vary, for example lower levels in tuna		• Heat-stable muscle protein • Found in crustaceans, molluscs, insects and mites with clinical cross-reactivity

TABLE VI: STORAGE PROTEINS PRESENT IN VARIOUS NUTS AND SEEDS

FOOD ALLERGEN	2S ALBUMIN	7/8S GLOBULIN	11S GLOBULIN
Hazelnut	Y	Y	Y
Almond	Y	N	Y
Brazil nut	Y	N	Y
Cashew nut	Y	Y	Y
Pistachio nut	Y	Y	Y
Chickpea	Y	N	Y
Garden pea	N	Y	N
Lentil	N	Y	N
Peanut	Y	Y	Y
Soyabean	Y	Y	Y
Sesame seed	Y	Y	Y
Sunflower seed	Y	N	N
Pecan nut	Y	N	N
Walnut	Y	Y	Y
Buckwheat	Y	Y	Y

may originate from foods or aero-allergens containing tropomyosin (see Table V).[4]

6. MEAT ALLERGY

- Patients with red meat allergy may be sensitised to α-Gal, a sugar structure found on the glycoproteins of non-primate mammals.[3,4,11,12]
- IgE antibodies to α-Gal may be associated with severe allergic symptoms and with delayed-type anaphylaxis.[3,11]
- Sensitisation to α-Gal may be induced by tick bites.[3,4,11]
- Bovine serum albumin (BSA) is a heat-labile allergen present both in milk and beef which may cause cross-reactivity between different mammalian meats.[3]

7. NUT AND SEED ALLERGY

- Storage proteins are the dominant allergens in nuts, seeds, fruit stones and kernels.[1,13]
- The main storage proteins are designated according to molecular weight and are grouped in 7/8S and 11S globulins and 2S albumins.[1]
- These proteins are very stable to heat and digestion, therefore sensitised patients may also react to cooked and processed nuts/seeds.[1,13]
- Sensitisation to storage proteins is regarded as an important risk factor for severe systemic reactions, particularly if sensitisation to more than one storage protein in a particular allergenic source is identified.[1,13]
- The 2S albumin seems to be the dominant allergen with the highest risk for severe systemic reactions in tree nut, seed and peanut allergies.[1,14–16]

7.1 PEANUT ALLERGY

- The main and most important peanut allergen components are Ara h 1, Ara h 2, Ara h 3 and Ara h 6 storage proteins.[1,2]
- These storage proteins are heat stable and may predict severe and persistent allergy.[1,2]
- Storage proteins may cross-react with other nuts, seeds and legumes.[1,2]
- Sensitisation to peanut storage proteins, particularly Ara h 2, is most frequently associated with peanut anaphylaxis.[1,2]
- *Clinical implication*: Patients who have a clinically proven peanut allergy (by history or challenge) and who test positive to Ara h 2 need to avoid all peanuts and cross-reactive nuts and seeds. Patients not allergic to Ara h 2 who do not have a clinical history of anaphylaxis do not need to implement such strict avoidance measures, for example avoidance of foods produced in a factory that uses nuts or requesting products produced in a nut-free environment. Sensitisation to pollen cross-reactive components can lead to the over-diagnosis of peanut allergy and unnecessary avoidance. Many individuals sensitised to the peanut may be tolerant to it, therefore food challenges are recommended if the clinical history is unclear.

8. WHEAT ALLERGY:

- The most important wheat allergen component is Omega-5-gliadin.[1,2,17,18]
- Omega-5-gliadin predicts true wheat allergy in children and is associated with wheat-dependent, exercise-induced anaphylaxis (WDEIA).[1,2,17,18]
- Alpha Amylase/TI or Tri-a aA TI sensitisation may be associated with respiratory allergy symptoms after exposure to inhaled wheat flour (Baker's asthma).[1]
- *Clinical implication:* Patients who have clinically confirmed wheat allergy with a positive component test to omega-5-gliadin need to avoid all wheat products. Patients who are sensitised to pollen cross-reactive components are often wheat tolerant and do not necessarily need to avoid wheat. LTP allergy may also be associated with WDEIA, therefore sensitisation to food-pollen cross-reactive components should be

TABLE VII: SUMMARY OF MAIN PEANUT ALLERGEN COMPONENTS

PEANUT				
Storage proteins	Profilin	PR-10	LTP	CCD
Ara h 1 Ara h 2 Ara h 3 Ara h 6	Ara h 5	Ara h 8	Ara h 9	CCD
• Stable to heat and digestion • Associated with a risk of anaphylaxis • Cross-reactivity with other nuts and seeds	OAS	OAS	Risk of anaphylaxis, mainly in Mediterranean countries	Pollen cross-reactivity Avoidance not necessary

TABLE VIII: SUMMARY OF MAIN WHEAT ALLERGEN COMPONENTS

WHEAT						
Ω 5 Gliadin	αβɣω Gliadins	Alpha amylase/TI	Profilin	PR-10	LTP	CCD
Tri-a 19		Tri-a aA TI			Tri a 14	
Risk marker for systemic reactions Wheat allergy persistence Wheat-dependent, exercise-induced anaphylaxis	Marker of severe reactions Marker of wheat allergy persistence	Baker's asthma to inhaled wheat flour	OAS	OAS	Associated with wheat-dependent, exercise-induced anaphylaxis	Pollen cross-reactivity Avoidance not necessary

identified in these patients.

9. SOY ALLERGY

- The most important soy allergens are Gly m 5 and Gly m 6 seed-storage proteins.[1,2,14]
- These allergens indicate primary sensitisation to soy and are also high-risk markers for more severe allergic reactions to soy.
- Pollen-sensitised individuals may also react to Gly m 4, the PR-10 in soy. These patients may experience severe OAS or even systemic reactions.[1,2,14,19]
- *Clinical implication:* Patients who have a clinically confirmed soy allergy (by history or challenge) and test positive for Gly m 5 and Gly m 6 should avoid all soy products. Asymptomatic sensitisation to Gly m 5 and Gly m 6 may occur, therefore food challenges are recommended if the clinical history is unclear. Patients who are sensitised only to pollen cross-reactive components are usually soya tolerant. Most commercial allergy tests for soy extracts contain low levels of Gly m 4, therefore pollen-sensitised patients with a suspicion of soy allergy should be tested separately to Gly m 4.

SPECIFIC IGE TESTING TO ALLERGEN COMPONENTS

Testing for IgE-mediated components can be requested individually (ImmunoCap® IgE to specific allergen components) or to multiple allergen components simultaneously (immuno solid-phase allergen chip (ISAC) allergen microarray testing).[2,3,8] The choice of test will depend on the availability of allergens, the patient history and financial considerations.

CELLULAR ALLERGY TESTS

The most prominent cellular allergy tests for the diagnosis of food allergy measure basophil reactivity to allergens. Basophils have IgE receptors on their cell surfaces, therefore they may be activated via cross-linking specific IgE in the patient's serum or directly in an IgE-independent manner.[20,21] Whereas protein allergens are usually required for IgE binding, basophils may also be activated directly by small molecular-weight allergens.[22] Certain foods, colourants, preservatives and food additives may induce non-IgE-mediated basophil activation. Basophil-mediated allergy may include either an immediate or a delayed allergic response. Symptoms of basophil-mediated allergy may include sino-pulmonary respiratory symptoms, gastrointestinal symptoms and urticaria.

Basophil-mediated allergy can be measured by a basophil activation test (BAT) or the commercially equivalent cellular allergen stimulation test (CAST®).[23,24] The first-generation CAST® test was a CAST®-ELISA, where sulfidoleukotrine release from activated basophils was measured by ELISA technology. This assay was very time-consuming and had to be performed within four hours of venepuncture, making it impractical for routine laboratory diagnostics. The next-generation assays use flow-cytometry (flow-CAST® or other in-house flow-cytometry based BATs) to identify particular basophilic activation markers after stimulation by a particular allergen.[15,16] These assays are more suited to routine use, as specimens can be processed for up to 24 hours after collection. A wide range of commercial allergens are available, which include foods, food-allergen components, colourants, preservatives and food additives. A commercial food allergen screen containing milk, egg white, wheat, soy, peanut, hazelnut, codfish and shrimp is also available.[24]

Studies of the sensitivity and specificity of BAT in patients with food allergy have yielded varied results, due to the diversity of available food allergens.[25] In individual patients, BAT has confirmed the diagnosis of primary food allergy to multiple different food allergens.[15] In two specific studies of patients with apple allergy and carrot, celery and hazelnut allergy, the sensitivity of BAT was shown to be 85–90% and the specificity 80–90%. However, these are research studies that do not necessarily translate into clinical practice.[16]

TABLE IX: SUMMARY OF THE MAIN SOY ALLERGEN COMPONENTS

SOY					
Storage proteins		Profilin	PR-10	LTP	CCD
Gly m 5	Gly m 6		Gly m 4		
• Associated with more severe reactions • Heat stable		OAS	May cause severe reactions	May cause severe reactions	Pollen cross-reactivity Avoidance usually not necessary

IgE testing to food allergens by skin-prick testing or specific IgE testing (e.g. ImmunoCap®) is still the gold standard for detecting IgE-mediated allergy to foods. There is no indication to use a BAT for detecting allergen-specific IgE in lieu of current testing methods. The usefulness of BAT for the diagnosis of food allergy lies in its capabilities of detecting non-IgE-mediated basophil activation to foods and food additives such as colourants and preservatives. Recently, BAT has also been found to be useful in differentiating true peanut allergy from false positives and predicting a more severe peanut allergy.[26] The clinical implication is that BAT should be considered when the clinician suspects an allergy, but the results of IgE-mediated tests do not confirm this or when the patient history is suggestive of an allergy to a food additive. Where available, BAT can be used as an adjunctive *in vitro* test in the diagnostic workup of patients with food allergy.[8] As with all test results, these results should be correlated with the clinical history. Food challenges should be performed to confirm the clinical significance if the patient history is unclear.

CONCLUSION

The clinical history should always be the first starting point in allergy diagnosis. The likelihood of allergy, the pathogenic mechanism as well as the most appropriate allergen selection should be considered when allergy tests are requested. Screening or allergen-specific tests should be used to make the initial diagnosis and identify the offending allergens. More specialised tests should be used to predict the severity of allergy, identify the primary sensitiser and relevant cross-reactivity, and predict the likelihood of allergy resolution. Clinicians should be aware of the different testing modalities available and their uses and limitations. As the field of allergy diagnostics is rapidly expanding and becoming more technologically advanced, clinicians may need to rely more on advice about testing and interpretation from specialists in the field.

DECLARATION OF CONFLICT OF INTERESTS

The authors are employed by AMPATH Pathologists, a private provider of diagnostic testing for allergy.

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