

# Go molecular!

## A clinical reference guide to molecular allergy

### Part 1: The basics

Second edition | By Neal Bradshaw

For more information on this topic  
[allergyai.com](http://allergyai.com)

# Preface

Molecular allergens have been described in scientific literature for well over a decade now, but it has only been in recent years that they have been used more routinely in the allergy clinic.

New technology can be challenging, and it often requires a period of adjustment and adaptation. There are many allergen components covering many different sources and their clinical relevance is continually emerging year on year. This can make it difficult to remember their relevance. Many physicians have commented to me that they could do with a simplified 'all in one guide' so I have tried to simplify molecular allergology based on the allergen components Thermo Fisher Scientific has in its portfolio.

The intention of part 1 in this guidebook series is to give a basic introduction to molecular allergology focusing on plant food allergy, although other molecular sources such as venoms and

aeroallergens are also discussed. This guide gives an introductory overview of the important themes within molecular allergology, especially protein families, their clinical relevance and nomenclature. If there is one important aspect to learn in molecular allergology it is the scientific relevance of protein families, as they are the key to understanding clinical molecular allergology.

A straightforward summary of the main allergen components, what ImmunoCAP™ products are available and an aid to interpret test results can be found in part 2 of this series – 'The Allergen Components'.

I hope you find this guidebook series useful.

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### Disclaimer:

The content of this book is intended as an aid to the physician to interpret allergen specific IgE antibody test results. It is not intended as medical advice on an individual level. A definitive clinical diagnosis of IgE mediated allergic disorders should only be made by the physician based on the clinical history for the individual patient after all clinical and laboratory findings have been evaluated. It should not be based on the results of any single diagnostic method.

# Contents

Foreword	4
Introduction: Molecular allergens tell us more	5
Protein families	7
Allergen component nomenclature	9
Specific and cross-reactive allergens	10
Other clinical considerations	11
Food allergy	13
Plant components	17
Interpreting results from cross-reactive protein families	19
Summary of plant food components	21
Plant allergen components in some common foods	24
Other allergen components	26
Immunotherapeutics – Aeroallergens and venoms	37
Common questions regarding molecular components	38
Glossary	40
Educational resources	41
Using ImmunoCAP Allergen Component tests	42
ImmunoCAP Allergen Component list	44
ImmunoCAP ISAC 112 Allergen Components	48

# Foreword

With the advent of allergen components, allergy has got much more complicated. However whole allergen diagnostics, with skin prick testing or serum specific IgE, commonly don't allow us to unravel the complexity that some of our allergy patients exhibit. Using allergen components to understand the molecular allergology of these complex patients has a real potential to improve our clinical decision-making. The use of component resolved diagnostics may optimize our investigation plans and improve our diagnoses, management plans and the advice we give to our allergy patients. All this though relies on clinicians acquiring an understanding of molecular diagnostics. This is a rapidly evolving

area with, for example, the whole peanut allergen suddenly been replaced by more than 10 individual components with different clinical impacts. The second edition of this book is very welcome with its updated information about each of the various allergen components. Importantly, their clinical implications are explained allowing us to use information about allergic sensitization to each individual component to improve the management of our patients.

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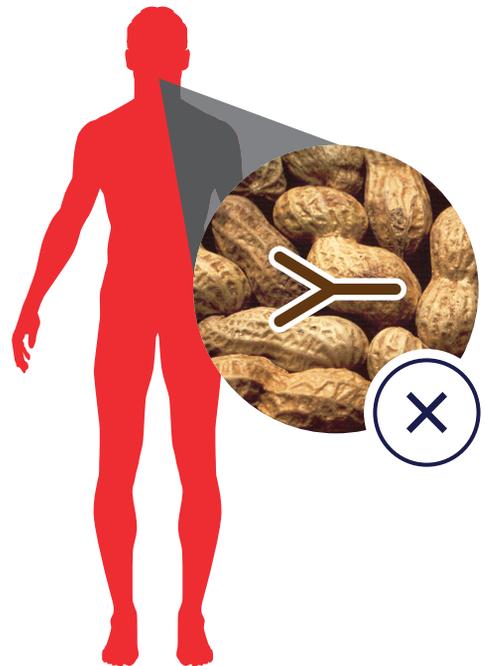
## INTRODUCTION

# Molecular allergology tells us more

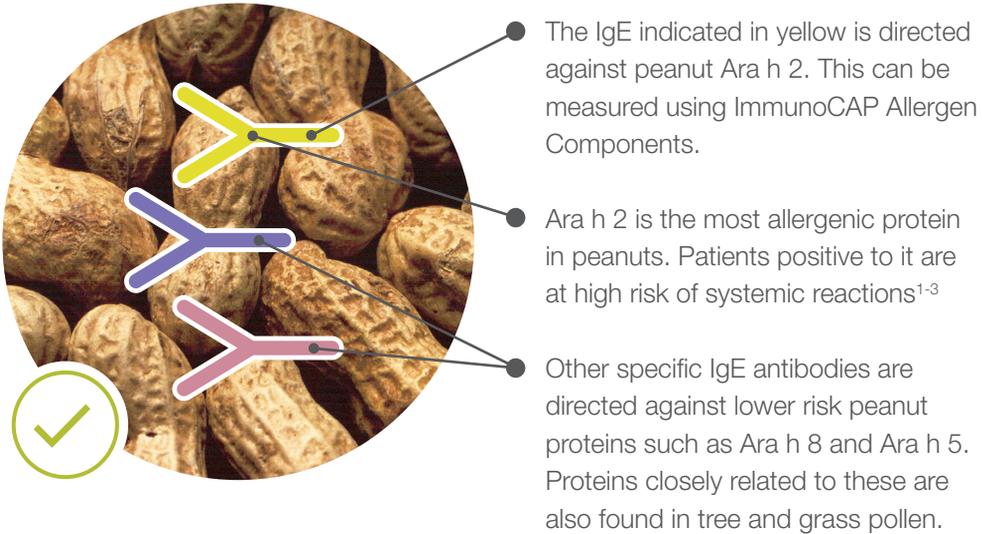
The diagnosis of IgE mediated allergies is made by the physician based on clinical history for the individual patient in conjunction with clinical findings and test results, e.g. specific IgE sensitization tests such as skin prick and/or blood tests and sometimes allergen provocations. Until recently the sensitization tests in use were based on extracts of allergen sources, but in the past years the use of component resolved diagnosis has become increasingly common in clinical practice. Molecular allergology brings a new level of understanding to physicians who seek to improve on existing diagnostic technologies<sup>1-3</sup>.

While traditional extract-based IgE blood tests measure the “sum” of sensitization to all protein components in whole allergens, e.g. peanut, molecular allergology makes it possible to investigate important individual proteins within a peanut for specific IgE sensitization. IgE antibody profiles to these molecules vary significantly from patient to patient and they also differ geographically, due to local differences of exposure<sup>1-3</sup>.

Molecular diagnostics reveals more factual information about what a patient is allergic to, as individual proteins and profiles can indicate different clinical characteristics<sup>1-3</sup>.



**Figure 1:** Illustration of the common misconception that there is one IgE antibody produced by the human body for a whole peanut allergen.



**Figure 2:** Illustration of the reality that there are lots of different IgE antibodies produced which bind to individual proteins in peanut, like Ara h 1, Ara h 2 and Ara h 8.

Ara h 2/Ara h 6 are the proteins that seems to have the highest allergenic potential of all proteins in peanut. Antibodies produced by patients in response to specific allergen proteins can be measured using single or multiplex allergen component tests, indicating the patients' immunological response in their current allergy status. High levels of IgE to Ara h 2/Ara h 6 will often indicate a patient at high risk of systemic symptoms if peanuts are eaten<sup>1-3</sup>.

## Clinical relevance

Allergen component diagnostics measures IgE to specific allergen components, uncovering additional information about an underlying allergy. Not only do they indicate specific allergen reactivity in the way that whole extracts do but they are also indicators for:

1. Understanding patient risk for allergic reactions – adding confidence to your assessment<sup>1-3</sup>.
2. Aiding the selection of the proper treatment extract of Allergen Specific Immunotherapy (AIT) – useful for

example in venom and aero-allergy patient selection<sup>1-3</sup>.

3. Understanding cross-reactions between species – helping to understand multiple sensitizations e.g. in pollen food syndrome<sup>1-3</sup>.

The intention of this first guidebook is to give the physician, dietician or scientist a background to molecular allergology. A straightforward summary of allergen components and an aid to interpretation of results can be found in part 2 of this series.

Much of the clinical value of component testing up to now has been demonstrated within food allergy, especially with plant foods such as nuts, fruits and legume seeds. The majority of information in this reference guide therefore focuses on food allergen components, although an overview of other allergen components which provide clinical value, such as those in pollen, furry animals, mites, latex and insect venoms, is also included.

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1. Matricardi PM et al. EAACI Molecular Allergy User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23:1-250.
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3. Canonica GW et al. A WAO - ARIA - GA<sup>2</sup>LEN consensus document on molecular-based allergy diagnostics. World Allergy Organ J. 2013 Oct 3;6(1):17.

## Protein families

Introducing molecular allergy into daily clinical practice will change the paradigm of thinking from that of biological allergen sources to allergenic proteins and protein families.

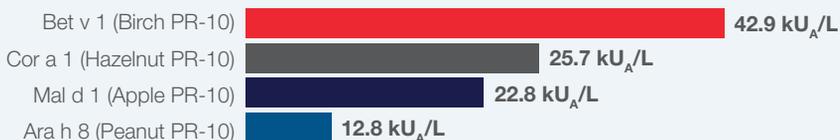
Protein families referred to in this guide are families with similar functions and structures found in many allergen sources<sup>1-8</sup>. For example, plant seeds contain storage proteins such as vicilins, transport proteins such as lipid transfer proteins and defense proteins such as

PR-10s (pathogenesis-related family number 10 proteins). Lipocalins and serum albumins are examples of protein families found in mammalian allergen sources<sup>1-8</sup>.

Below is an example showing the IgE test results of a patient with suspect plant food allergy.

The below test results could be interpreted in three different ways:

### IgE test results of a patient with suspect plant food allergy



- Traditional thinking: four different specific IgE reactions to four different plant sources.
- On the molecular level: IgE to one protein family group, i.e. PR-10 allergy – also indicating cross-reactive IgE.
- The patient is also likely to be sensitized to other PR-10 proteins not measured. From the above extrapolations can be made of other PR-10 sensitization and may be relevant to the patient's clinical history to other allergens, e.g. almond contains PR-10 proteins.
- This same way of thinking can for example be applied to profilin or nsLTP (lipid transfer protein) profiles (if positive).

More on protein families and their clinical relevance will be discussed later in this guide.

## Interpretation of results

In this guide, interpretation has been simplified as much as possible in terms of presence of specific IgE. The presence of allergen-specific IgE usually indicates a risk of allergy symptoms and **a result of  $\geq 0.1$  kU<sub>A</sub>/L indicates sensitization**. Some molecular allergens are associated with a higher risk for systemic reactions, while others are considered to pose no or a very low probability for severe reactions. A high IgE-level to an allergen such as Ara h 2 or Cor a 14 often means a high risk of symptomatic allergy<sup>1-3</sup>.

However for different patients identical results for the same allergens may not be associated with clinically equivalent manifestations, due to differences in individual patient sensitivities. This may also be true for one individual patient at different occasions due to presence or absence of reaction promoting cofactors<sup>1-3</sup>.

## Always consider test results in association with a clinical history.

### References

1. Matricardi PM et al. EAACI Molecular Allergology User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23:1-250.
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# Allergen component nomenclature

## The WHO/IUIS Committee

Allergen and allergen components are identified and categorized by a joint partnership of The World Health Organization (WHO) and The International Union of Immunological Sciences (IUIS). The WHO/IUIS Allergen Nomenclature Sub-committee is responsible for maintaining and developing a unique, unambiguous and systematic nomenclature for allergenic proteins. The systematic nomenclature is based on the Linnaean system and is applied to all allergens<sup>1</sup>. For further information check the IUIS allergen nomenclature website at: **allergen.org**.

Allergen components are given a name based on an abbreviation of the Latin name of the allergen source (the first three letters of the first word and first letter of the second). The allergen protein is also given a number based on the order of discovery (when registered/ approved by the IUIS committee)<sup>1</sup>. An example of peanut allergen component nomenclature:

Peanut – *Arachis hypogaea* – Ara h 2

Thermo Fisher Scientific, the leading provider of allergen components, also gives the test a prefix 'n' for native sourced allergen proteins or an 'r' for recombinant sourced allergen proteins that are used in the IgE tests.

You can look up all WHO IUIS recognized allergens at **allergen.org**.

### References

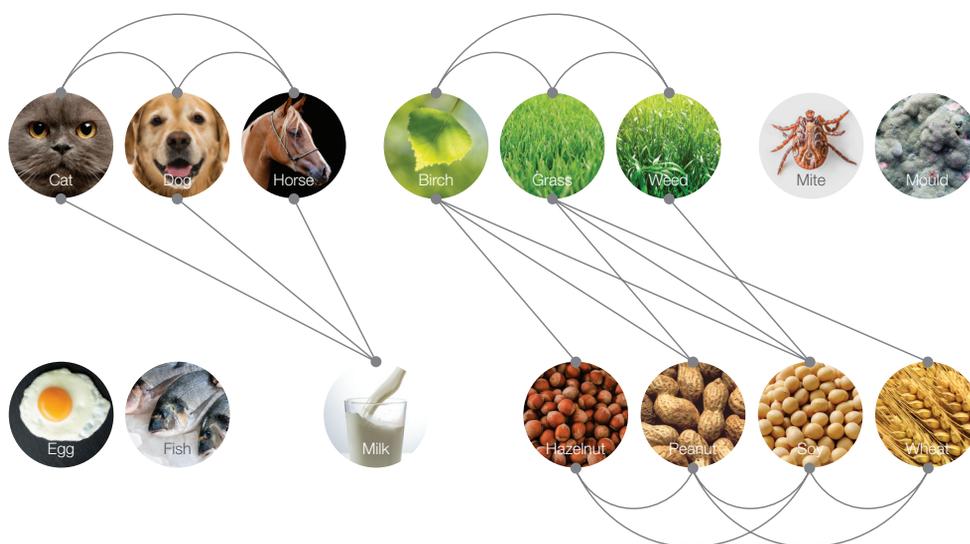
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# Specific and cross-reactive allergens

Molecular allergens can be split into allergens with high and low potential for triggering clinical symptoms. These allergens can then also be further grouped into molecules specific to an allergen source and molecules with great similarities even between distantly related allergen sources. Such allergens are said to be cross-reactive. Differentiating between sensitization to specific and cross-reactive allergen components helps us to better understand the characteristics of an individual's allergy profile<sup>1-3</sup>.

The below figure demonstrates a typical allergen test panel. Many of the allergens could give rise to IgE cross-reactions. For instance, dog, cat and horse all contain members of the lipocalin protein family together with serum albumin which is also found in milk. Birch, grass and weeds contain profilins, which are found in legumes such as soy and peanut, as well as in wheat and hazelnut. IgE cross-reactions can confound extract based test results, which makes it difficult to understand what the primary allergen causing the symptoms is. ImmunoCAP

**Figure 3: Illustration of a typical allergen test profile**



Allergen Component tests and the multiplex ImmunoCAP ISAC 112 help to improve diagnostic clarity<sup>1-3</sup>.

You can learn more about the significance of these types of allergens at: [allergyai.com](http://allergyai.com).

This website contains an educational course which describes the basics of molecular allergy and includes patient case examples.

#### References

1. Matricardi PM et al. EAACI Molecular Allergology User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23:1-250.
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## Other clinical considerations

### Allergen load

The patient's clinical history remains the most important part of allergy diagnosis. Component testing will reveal crucial information but as with any IgE test it should be used in support of the clinical history. Only the clinical history can reveal how much of each food allergen the patient has ingested. For example, when consuming large amounts of allergens at the same time, such as when drinking a soy milk drink can affect the symptom outcome<sup>1-3</sup>.

Low risk allergens such as PR-10 proteins found in soy milk, when consumed in great amounts can provoke more serious allergy symptoms in some patients (such as drinking soy milk<sup>1-2</sup>).

A patient sensitized to several allergen sources will often be sensitized to several allergen components. This will contribute to the overall allergen load. For example, if a patient is positive to multiple peanut storage components such as Ara h 1, Ara h 2 and Ara h 3, he or she is likely to have a higher IgE load and therefore possibly be at more risk for severe reactions than someone who is mono-sensitized<sup>1-5</sup>.

### Diagnostic performance

Extract-based tests (whole allergens) contain a mix of many different proteins from an allergen source (e.g. peanut) and measure the sum of IgE antibodies to these, which gives high sensitivity, but sometimes can create difficulties in interpretation of results<sup>1-5</sup>.

ImmunoCAP Allergen Component-based tests, both singleplex and multiplex, contain pure proteins, measure only specific IgE to single molecules and give results with high diagnostic specificity<sup>1-5</sup>.

Allergen component tests therefore have technical diagnostic superiority at measuring IgE to important individual proteins of interest, such as to Ara h 2 in peanut or Cor a 14 in hazelnut. They simply measure IgE specific to one protein and offer reliable results in terms of minimal variation – like all ImmunoCAP products. However, it must be remembered that an allergen component test only measures one type of specific IgE and that most patients will have IgE antibodies to several molecules contained in the allergen source<sup>1-5</sup>.

Presence of allergen specific IgE implies a risk of allergic disease and its significance must be evaluated within the clinical context. Generally the higher the level of IgE antibodies the higher the probability of a clinically manifest allergic reaction<sup>1-5</sup>.

However, for different patients identical results for the same allergens may not be associated with clinically equivalent manifestations, due to differences in individual patient sensitivities. This may also be true for one individual patient at different occasions due to presence or absence of reaction promoting cofactors<sup>1-5</sup>.

Absence of detectable allergen specific IgE antibodies does not necessarily exclude the potential for an allergy-like reaction<sup>1-2</sup>. For example in food allergy, circulating IgE antibodies may remain undetectable despite a convincing clinical history. The antibodies may be directed towards allergens that are revealed or altered during industrial processing, cooking or digestion and therefore do not exist in the original food for which the patient is tested<sup>1-2</sup>.

#### ***Limitations of ImmunoCAP products test results:***

Samples with results below limit of quantitation obtained with ImmunoCAP Allergen Components are recommended to be tested with the corresponding extract based ImmunoCAP Allergen and/or additional relevant ImmunoCAP Allergen Components, if not already performed and a clinical indication is present. The extract based testing can cover additional allergen components present in the allergen source material to which the patient may be sensitized, but which are not presently available as ImmunoCAP Allergen Components or in ImmunoCAP ISAC 112.

A result below limit of quantitation obtained with an extract based ImmunoCAP Allergen never excludes the possibility of obtaining measurable concentrations of specific IgE when testing with ImmunoCAP Allergen Components from the same allergen

source. This is due to the fact that some components may be present in very low amounts in the natural extract.

In most cases it is recommended that testing starts with whole allergens to achieve high sensitivity to be followed up with allergen component tests for further specificity and as an aid in risk assessment if the test for the whole allergen is positive<sup>1-5</sup>.

Further information at [allergyai.com](http://allergyai.com).

## References

1. Matricardi PM et al. EAACI Molecular Allergy User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23:1-250.
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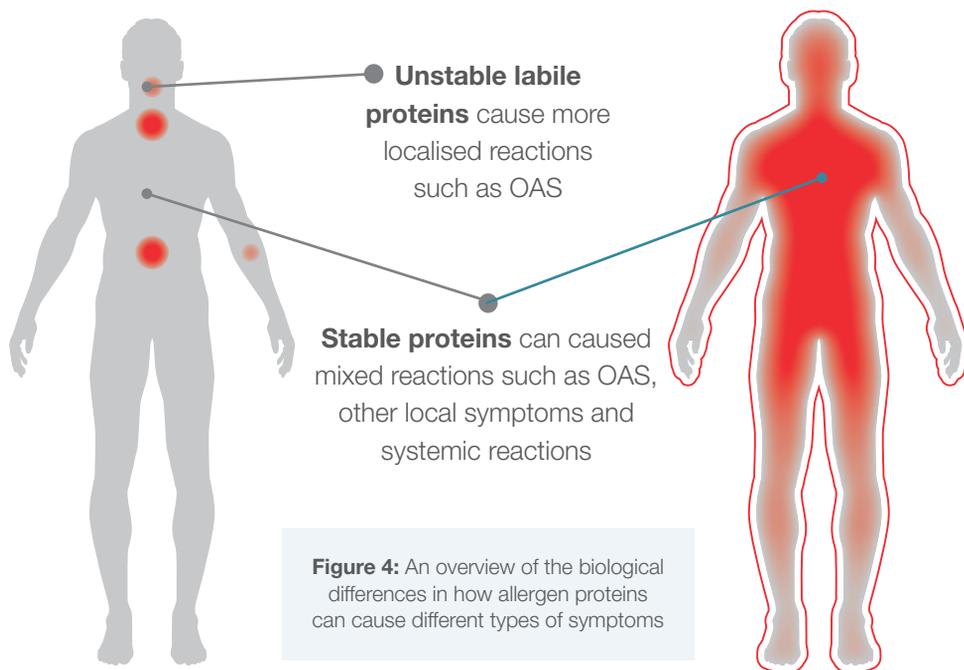
# Food allergy

Food is made up of complex matrices of natural constituents such as proteins, fats and carbohydrates. The way that the human body processes food creates by-products of the original food structure. The natural state of proteins can be changed even before we eat them, most obviously by cooking but also by storage and processing e.g. liquidizing or concentrating (as for fruit juices)<sup>1-2</sup>.

There are many different metabolic processes that occur as soon as food enters the digestive system. Enzymatic digestion starts straight away in the mouth; acidic pH and gastric juices play a role as food enters the stomach and

further digestion takes place in the gut until the food is absorbed as smaller nutrients<sup>1-2</sup>.

Fats are metabolized into fatty acids; carbohydrates are eventually broken down into small sugar molecules, while proteins are digested into their constituents - amino acids. Most allergens are proteins, made up of amino acid chains, and within these structures are regions called epitopes. It is these recognition sites that specific IgE molecules bind to. This can lead to the release of histamine and other mediators, resulting in allergy symptoms<sup>1-2</sup>.



### Molecules of high allergenic potential

Some proteins are more resistant than others to metabolic processes, due to their robust chemical structures; e.g. storage proteins from peanut (Ara h 1, Ara h 2, Ara h 3 and Ara h 6) or ovomucoid from hen's egg (Gal d 1). As these allergens have higher resistance to digestion, their allergenic potential is also higher as their epitope structures stay intact longer. As a result, these proteins cause more systemic symptoms than unstable proteins (figure 4)<sup>1-10</sup>.

### Molecules of low allergenic potential

Certain allergen molecules such as PR-10s and profilins (present in nuts, fruits and pollen) are more labile in structure and therefore susceptible to digestive processes such as heating/cooking and enzyme activity in the gastrointestinal

tract. Such labile proteins start to break down already in the mouth, causing less problematic reactions such as oral allergy syndrome (OAS). As the epitope binding regions in these proteins are destroyed, these molecules tend not to induce systemic symptoms<sup>1-10</sup>.

### Allergen profile variability

If molecules vary in their potential to trigger allergy it raises the question:

**Q: 'If a patient is IgE tested using a whole extract (the source) how do you know which proteins within the source they are sensitized to?'**

**A: 'The simple answer is that a whole extract test does not provide all the answers!'**

The above question and answer is quite thought-provoking. A whole extract IgE test (the source) is a mixture of lots of individual proteins. It would be impossible to tell which proteins a patient is IgE positive to unless they were separated individually – as they are when using ImmunoCAP Allergen Component tests. Also, all patients vary in which components they are sensitized to<sup>1-10</sup>.

ImmunoCAP offers a large portfolio of different allergen components, enabling the mapping of individual patient profiles and improving diagnostic clarity. ImmunoCAP ISAC 112 is a multiplexing test that measures IgE to a total of 112 allergen components and through cross-reactivity one can extrapolate sensitizations to other clinically relevant allergen sources<sup>6</sup>.

Patients testing positive to a whole extract (e.g. positive skin prick test to peanut or serum IgE to peanut) can be sensitized to either allergen proteins of high allergenic potential or of low/no allergenic potential. By using molecular diagnostics it is possible to better differentiate between them, i.e. classify patients into low- and high-risk groups. There are of course also cases where the patient is sensitized to both high-risk and low-risk allergens and can display symptoms such as OAS together with systemic symptoms<sup>1-10</sup>.

Furthermore, in a given situation other factors such as amount of allergen, stress, ongoing infections etc have an impact on the actual clinical reaction<sup>1-2</sup>.

### **Specific allergens and primary food allergy**

Identifying IgE to specific molecules often indicates the cause of allergy symptoms. In food allergy, the allergens that initially trigger the immune system to produce specific IgE antibodies are mostly food proteins more resistant to digestion. Such primary sensitization to stable proteins is therefore often associated with systemic allergy symptoms<sup>1-10</sup>.

### **Cross-reactive sensitization and pollen-food syndrome**

Allergen components that have highly similar structures in several different species can give rise to extensive cross-reactivity, these are referred to as “pan-allergens”. Pan-allergens are commonly found in plants and plant derived foods and they can be found even in distantly related species such as celery and birch trees<sup>1-10</sup>.

Sensitization to pan-allergens may be both asymptomatic and symptomatic, but the symptoms elicited are often of a milder form, such as OAS. In pollen-allergic patients for instance, IgE antibodies primarily targeted towards proteins in pollen (e.g. birch Bet v 1) readily cross-react with similar proteins in food, causing a broad sensitization profile which can be considered “secondary” to the pollen sensitization. In clinical allergy,

this is often referred to as pollen-food syndrome and in the context of latex, the latex-fruit syndrome<sup>1-10</sup>.

Cross-reactive allergens exist also in other sources, such as venoms of stinging insects, fish, mites and shrimp. For example, dust mite and shrimp share a cross-reactive protein called tropomyosin<sup>1-5</sup>.

When sensitization to cross-reactive allergens is detected, the primary sensitizer should always be sought after in order to understand what is driving the patients' allergy. Using a range of specific and cross-reactive allergen component tests it is in most cases possible to differentiate primary and secondary reactions<sup>1-10</sup>.

## References

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# Plant components

Plant protein families are shared between species; the closer the species are related, the more similar the components can be. This increases the potential for IgE molecules directed against e.g. pollen allergen epitopes to bind to similar allergen epitopes in food. This immunological mechanism is often the cause for broad sensitization patterns seen in many allergic patients. The dominant sensitizing plant aeroallergens in Northern Europe are pollen from birch and temperate grass species such as Timothy grass, while in Southern Europe olive and grass pollen are the main culprits of hay fever symptoms. Patients with hay fever may often experience local symptoms from certain plant-derived foods, due to cross-reactive proteins common to different plants<sup>1-10</sup>.

Plant proteins involved in allergy include storage proteins, LTPs, PR-10s and profilins. Another type of molecular structure to take into account is CCDs (cross-reactive carbohydrate determinants). Further references regarding plant food proteins can be found towards the end of this section<sup>1-10</sup>.

## Storage proteins

Storage proteins are biological reserves of amino acids used by plants to grow, found in e.g. legumes, seeds and nuts. Storage proteins are structurally complex and commonly regarded as much more

stable to heat and proteases compared to allergens such as PR-10s and profilins. There is evidence that 2S albumins (e.g. Ara h 2 and Ara h 6 in peanut and Ber e 1 in Brazil nut) are some of the most stable plant food molecules and therefore the most clinically important. The 2S Albumins such as Ara h 2 molecules are not easily destroyed by gastric fluids and thus will be immunologically functional in the gastrointestinal tract with the potential to trigger systemic reactions such as asthma, urticaria, angioedema or anaphylaxis<sup>5</sup>. Storage proteins are more or less specific to their source and do not cross-react except for very closely related allergen sources (e.g. between legumes such as soy and peanut)<sup>1-5</sup>.

## LTPs (Lipid Transfer Proteins)

LTPs are very stable small molecules widespread in plant food such as fruits and nuts. They are found concentrated in the skin of *Rosaceae* fruits, especially in the peel of peach – the pulp contains less of the allergen. LTPs from different species can be highly cross-reactive. IgE sensitization to LTPs has mostly been described in Southern Europe, in patients with severe reactions to peach and other fruits belonging to the *Rosaceae* family (pear, cherry, apple etc.). LTP allergy has also been described in connection with nuts such as walnut and hazelnut and in peanut<sup>1-5, 8</sup>.

The LTP sensitization pattern in Northern Europe is not completely understood and not as well documented as in Southern Europe, where LTP sensitization is very common. The protein characteristics of LTPs explain their clinical relevance due to their high resistance to heat and protease digestion. However, LTP sensitization is also associated with local reactions including OAS<sup>1-5, 8</sup>.

### **PR-10 (Pathogenesis-Related family number 10) proteins**

The plant defense proteins of the PR-10 family are present in pollen of *Fagales* tree species (e.g. birch, hazel, alder and beech) and can also be found in the pulp of fruit. Bet v 1 is the major allergen in birch pollen and is highly similar to other PR-10 proteins in plant foods such as *Rosaceae* fruits (peach, apple and cherry etc.), as well as to PR-10s in nuts and legumes.

In a typical birch allergy scenario, birch pollen causes a primary sensitization to PR-10 proteins. This can cause typical hay fever-like symptoms such as an itchy/blocked nose, runny eyes etc. As a further consequence, patients who ingest PR-10 proteins found in nuts or fruit can react due to IgE cross-reactions. Food allergy caused via cross-reactivity is sometimes referred to as secondary food allergy. Again this is likely to result in local symptoms such as OAS, but depending on the amount of the cross-reactive protein more severe reactions may also occur (e.g. Gly m 4 induced soy milk reactions)<sup>1-5, 9</sup>.

### **Profilin proteins**

Profilin proteins occur in many different plant species and cause broad sensitization patterns. They are found for example in pollen (e.g. birch or grass), fruit (e.g. apple, cherry, melon and banana) and vegetables, nuts and latex. It has been proposed that just one profilin from one plant species is enough for testing IgE sensitization to profilin, due to the close similarity and extensive cross-reactivity of this protein group. Profilins from birch (Bet v 2) and/or Timothy grass (Phl p 12) are often used in measuring IgE to profilin. Profilins are sensitive to heat and proteases and will thus primarily give rise to OAS as the clinical manifestation of food allergy. It is widely accepted that profilins have less clinical relevance than PR-10 proteins, although in some cases profilin sensitization may cause severe reactions<sup>1-5, 10</sup>.

### **CCDs (Cross-reactive Carbohydrate Determinants)**

Some molecular structures such as CCDs are shared between many species and can be found in insect venoms, pollen and plant foods. CCDs are not proteins but specific parts of carbohydrate chains attached to proteins. The clinical impact of specific IgE to CCDs is considered very low although positive IgE test results are frequent<sup>1-7</sup>.

CCDs help us to understand poly-sensitization to multiple plant foods and latex or double positivity between bee and wasp venoms. It is also worth

noting that natural plant allergen extract preparations contain CCD molecules while recombinant sources typically are CCD-free and hence more specific<sup>1-7</sup>.

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# Interpreting results from cross-reactive protein families

## Example 1

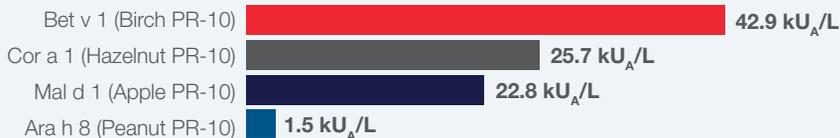
A variety of allergen component tests could be used when resolving a patient's birch-food allergy. Is it a primary food allergy? Bet v 1 is a dominating primary sensitizing allergen in a birch allergic patient and could produce cross-reactions between other plant food species.

The example below demonstrates a patient profile of PR-10 sensitization with a suspected case of IgE-mediated peanut allergy. In this example, all other

risk allergens such as Ara h 2 in peanut or Cor a 14 from hazelnut were IgE-negative.

Like all ImmunoCAP Specific IgE tests, ImmunoCAP Allergen Components give results in kU<sub>A</sub>/L (ImmunoCAP ISAC 112 gives semi-quantitative results in ISU-E). Primary sensitizing allergens from within the same protein family (in this example PR-10) will normally give the highest specific IgE level. Other secondary IgE sensitizations will give similar specific IgE readings but normally lower levels than

### Example 1: PR-10 sensitization with a suspected case of IgE-mediated peanut allergy



the primary sensitizing allergen due to reduced protein homology (and therefore reduced IgE binding)<sup>1-6</sup>.

#### Clinical interpretation:

- Food-pollen syndrome caused by a primary PR-10 birch-pollen allergy
- Likely symptoms local/mild or none e.g. oral allergy to hazelnut, peach and peanut

“Secondary” reactions due to cross-reactivity can occur via plant allergens such as CCDs and profilins. On the other hand, if a patient has a primary sensitization to an allergen component that does not cross-react (such as a storage protein) then this serves as a diagnostic marker of risk for severe

reactions which is covered further in this guide<sup>1-6</sup>.

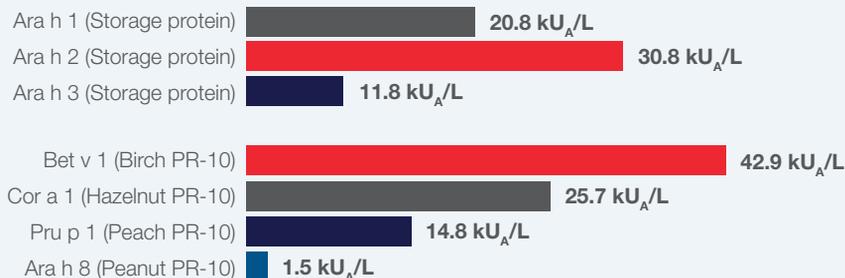
### Example 2

Using the example of suspected peanut allergy (see figure Example 2 below) the IgE results could be interpreted like this:

#### Clinical interpretation:

- Primary sensitization to peanut allergens Ara h 1, Ara h 2 and Ara h 3
- Ara h 2 is the most important peanut allergen; the patient is at higher risk of severe, systemic symptoms
- The patient also has concomitant birch sensitization and perhaps other allergy symptoms such as rhinitis, asthma and oral itching

### Example 2:



- Food pollen syndrome – caused from a primary PR-10 birch-related pollen allergy. Likely reactions to these foods are local/mild e.g. oral allergy, or none
- Both systemic and local symptoms might occur

**Always use the test results in combination with a clinical history. The presence of specific IgE is not always associated with clinical symptoms but represents a risk of allergic reactions on allergen exposure.**

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## Summary of plant food components

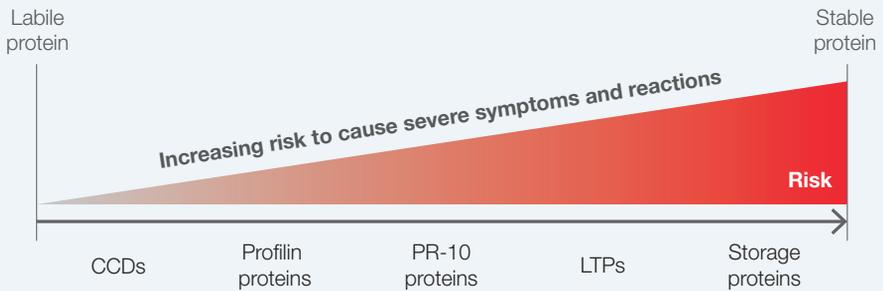
Plant protein families are common to many species and the closer the species are related the more similar the proteins can be. But also in distantly related species there are proteins that are very similar which can give rise to cross-reactivity. Thus, IgE molecules directed against pollen allergen epitopes can bind to similar allergen epitopes in foods such as peanuts, tree nuts, fruits and vegetables<sup>1-5</sup>.

The majority of food allergen components in plants belong to four main protein groups. These are storage proteins, LTP, PR-10 and profilin proteins. In addition, CCDs (Cross-reactive Carbohydrate Determinants) are allergenic structures found in pollen and plant food, as well as in insects and venoms<sup>1-5</sup>.

Protein family	Risk for systemic reactions?	Do I have to consider many different allergen sources?
● <b>Storage proteins</b>	<b>High.</b> Storage proteins are heat and digestion stable which explains their ability to more often cause systemic reaction in addition to oral allergy syndrome (OAS).	<b>No.</b> Storage proteins are not cross-reactive, except for very closely related allergen sources (e.g. between legumes such as soy and peanut).
● <b>LTP</b>	<b>Moderate to High.</b> LTPs are heat and digestion stable which explains their ability to more often cause systemic reaction in addition to OAS.	<b>Yes.</b> Partly cross-reactive (the degree of structural similarity varies between LTPs in plant food and pollen).
● <b>PR-10</b>	<b>Low.</b> Often cause only local symptoms such as OAS due to their sensitivity to heat and digestion, but a few cases with systemic reactions have been reported e.g. for soy Gly m 4 and Celery Api g 1.	<b>Yes.</b> Cross-reactive (the degree of structural similarity varies between PR-10 in plant food and birch-related pollen).
● <b>Profilin</b>	<b>Low.</b> Often have little clinical relevance in allergic diseases. However, profilins may cause local reactions in some patients allergic to plant foods including citrus fruits, banana and tomato, and a few cases with systemic reactions have been reported e.g. for melon and lychee.	<b>Yes.</b> Highly cross-reactive (high degree of structural similarity between profilins in pollen, plant food and latex).
● <b>CCD</b>	<b>Very low.</b> Usually not associated with clinical reactions but may induce IgE antibody responses in some patients.	<b>Yes.</b> Highly cross-reactive (same CCD structure in pollen, plant food and venoms).

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**Figure 5:**

An overview of the biological differences in how allergen proteins can cause different types of symptoms

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# Plant allergen components in some common foods

Allergen source/ Component family	Storage proteins						
	Profilin	PR-10	LTP	2S Albumin	Vicilin-like 7S globulin	Legumin-like 11S globulin	Other
Peanut	Ara h 5	<b>Ara h 8</b>	<b>Ara h 9, 16, 17</b>	<b>Ara h 2, 6, 7</b>	<b>Ara h 1</b>	<b>Ara h 3</b>	Ara h 10-15
Soy	Gly m 3	<b>Gly m 4</b>		Gly m 8	<b>Gly m 5</b>	<b>Gly m 6</b>	Gly m 7
Hazelnut	Cor a 2	<b>Cor a 1</b>	<b>Cor a 8</b>	<b>Cor a 14</b>	Cor a 11	<b>Cor a 9</b>	
Walnut	Jug r 7	Jug r 5	<b>Jug r 3, 8</b>	<b>Jug r 1</b>	<b>Jug r 2, 6</b>	Jug r 4	
Pecan				Car i 1	Car i 2	Car i 4	
Cashew				<b>Ana o 3</b>	Ana o 1	<b>Ana o 2</b>	
Pistachio				Pls v 1	Pls v 3	Pls v 2, 5	Pls v 4
Brazil nut				<b>Ber e 1</b>		Ber e 2	
Sesame				<b>Ses i 1, 2</b>	Ses i 3	Ses i 6, 7	Ses i 4, 5
Sunflower seed	Hel a 2		Hel a 3	<i>Hel a 2 S Albumin</i>			
Rape seed	<i>Bra n 8</i>			Bra n 1			<i>Bra n 4, 7</i>
Cabbage	<i>Bra o 8</i>		Bra o 3				
Mustard	Sin a 4		Sin a 3	Sin a 1		Sin a 2	
Buckwheat				<b>Fag e 2</b>	Fag e 3		Fag e 4
Kiwi	Act d 9	<b>Act d 8, 11</b>	Act d 10	Act d 13		Act d 12	<b>Act d 1, 2, 5</b>
Melon	Cuc m 2	Cuc m 3					Cuc m 1
Tomato	Sola l 1	Sola l 4	Sola l 3, 6, 7				Sola l 2, 5
Apple	Mal d 4	<b>Mal d 1</b>	<b>Mal d 3</b>				Mal d 2
Pear	Pyr c 4	Pyr c 1	Pyr c 3				Pyr c 5
Almond	Pru du 4	Pru du 1	Pru du 3			Pru du 6	Pru du 5
Peach	<b>Pru p 4</b>	<b>Pru p 1</b>	<b>Pru p 3</b>				Pru p 2, 7
Apricot		Pru ar 1	Pru ar 3				
Plum	<i>Pru d 4</i>	<i>Pru d 1</i>	Pru d 3				Pru d 2, 7
Cherry	Pru av 4	Pru av 1	Pru av 3				Pru av 2

**Bold** Available as single ImmunoCAP Allergen Component

**Bold** Available on ImmunoCAP ISAC only

**Normal** WHO/IUIS listed

*Italic* Described in peer reviewed literature

Likely but not yet described

Allergen source/ Component family	Storage proteins						
	Profilin	PR-10	LTP	2S Albumin	Vicilin-like 7S globulin	Legumin-like 11 S globulin	Other
Strawberry	Fra a 4	Fra a 1	Fra a 3				
Raspberry		Rub i 1	Rub i 3				
Carrot	Dau c 4	Dau c 1	<i>Dau c 3</i>				Dau c 5
Celery	Api g 4	<b>Api g 1</b>	Api g 2, 6				Api g 3, 5
Wheat	Tri a 12		<b>Tri a 14</b>				<b>Tri a 19, Gliadin, many more</b>
Barley	Hor v 12						Hor v 15-17, 20
Rice	Ory s 12						
Maize	Zea m 12		Zea m 14				Zea m 8

#### Plants often driving sensitization

Birch	<b>Bet v 2</b>	<b>Bet v 1</b>					
Timothy	<b>Phl p 12</b>						
Latex	<b>Hev b 8</b>		Hev b 12				<b>Hev b 5, 6, 11</b>

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# Other allergen components

Allergen Component testing also provides useful information about other allergen sources such as non-plant foods, furry animals, mites, molds, pollen and venoms from stinging insects. Below is a brief overview, although further information on clinical interpretation and what ImmunoCAP Allergen Components are available can be found in guidebook 2 – ‘The Allergen Components’. The below is intended as an introduction to other allergen component areas, including references below for each allergen section.

## Egg and milk

Foods such as milk and egg are associated more with pediatric allergy, and children tend to outgrow these allergies at a young age<sup>1-7</sup>. However, in a recent longitudinal egg allergy study in the UK it was shown that many children don't outgrow their egg allergy until well past 5 years of age, in fact the median age in this study was 10 years for egg allergy resolution<sup>5</sup>.

Egg and milk contain allergen components that are markers for reactivity to different forms of allergy. The allergenicity of hen's egg Gal d 1 (Ovomucoid) and cow's milk Bos d 8 (Casein) is not destroyed by heating, and patients negative to Gal d 1 and/or Bos d 8 IgE tests have been observed to tolerate cooked forms of egg and milk<sup>1-7</sup>. Allergy persistency is associated with

IgE to the same allergens, and therefore IgE to Gal d 1 and Bos d 8 can be used as markers of clinical reactions and tolerance development to egg and milk, respectively<sup>1,2,5-7</sup>.

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## Red meat

Recently a previously unrecognized clinical syndrome has been reported where systemic reactions occur several hours after the ingestion of mammalian meat (beef, pork, lamb and offal, e.g. kidney)<sup>1-8</sup>. Most cases have concerned adults, but recent reports also include children<sup>6</sup>. Whereas food allergy

symptoms generally occur shortly after ingestion, this type of red meat allergy is associated with symptoms delayed 3-6 hours. The most common symptoms include gastrointestinal problems, urticaria and anaphylaxis<sup>1-8</sup>.

A carbohydrate, the oligosaccharide Galactose-alpha-1, 3-Galactose (alpha-gal), appears to be the allergen causing the reactions<sup>1-8</sup>. Alpha-gal is present in many mammalian proteins including beef, pork and lamb<sup>1-2,5</sup>. The primary hypothesis in the attempts to explain the causes of IgE antibody responses to alpha-gal is that previous tick bites may be a causative factor<sup>1-2,7,8</sup>. Measuring specific IgE to alpha-gal is a tool that can be used to support the diagnosis of this type of red meat allergy and also sensitization to the cancer drug cetuximab which contains the alpha gal epitope<sup>1-9</sup>.

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#### Shellfish and crustaceans

Shellfish and particularly prawns make up one of the major allergenic food groups<sup>1-5</sup>. Tropomyosin (Pen a 1, Pen m 1) is considered a major allergen in shrimp and crustacean allergy<sup>1-6</sup>. Tropomyosin proteins are highly cross-reactive actin-binding proteins located in muscle fibers amongst many invertebrate species such as shrimps (Pen a 1), and other crustacean foods such as crab, lobster and molluscs as well as dust mites (Der p 10) and cockroaches (Bla g 7). Due to its wide-spread occurrence, tropomyosin can be both inhaled and ingested. About 10% of dust mite-allergic patients have IgE to tropomyosin. Some studies suggested that dust mite immunotherapy or respiratory exposure to dust mite tropomyosin may induce tropomyosin sensitization causing food allergy to shrimps<sup>1-3</sup>.

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## Fish

Parvalbumins such as Gad c 1 (cod, white fish) and Cyp c 1 (carp) are major fish allergen components and markers of fish sensitization<sup>1-6</sup>. Fish-allergic patients can sometimes tolerate certain fish species while reacting to others. However, as parvalbumins from different fish species are structurally closely related and highly cross-reactive, analysis of IgE antibody binding to them is generally not informative in regard to discriminating between allergies to different species of fish. A positive test result to either of Gad c 1 and Cyp c 1 nevertheless indicates a risk of severe reactions to fish<sup>1-6</sup>. Parvalbumins are expressed in lower amounts in certain fish species such as tuna, swordfish and some mackerels. This perhaps explains why some fish-allergic patients can tolerate these species<sup>4-6</sup>.

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## Furry Animals

Furry animals such as dogs, cats and horses produce some of the most prevalent allergens in our environment and are released into the surroundings through animal saliva, dander and urine. Like many other allergen sources furry animals contain both specific and cross-reactive allergen components<sup>1-3</sup>.

Clinically uteroglobin and lipocalins have been identified as the most important major allergen components from cat, dog and horse<sup>1-7</sup>. Serum albumins are often considered to have less clinical relevance in allergy to furry animals, they are minor allergens which cause multiple positivity due to cross-reactivity when using extract tests<sup>1-3</sup>. However serum albumins are important food allergens in meat<sup>1-3,8</sup>.

**60-70% of pet sensitized patients are sensitized to several pet extracts - specific or due to cross-reactivity sensitization<sup>11</sup>**

**Typical allergens<sup>12</sup>**



— Cat —

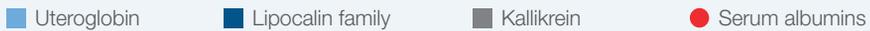


— Dog —



— Horse —

*Specific components in squares*



Protein family	Summary	Clinical Importance
<b>Uteroglobin</b>	Uteroglobin, a steroid-inducible cytokine-like molecule with anti-inflammatory and immunomodulatory properties.	<b>High.</b> Fel d 1 the major cat allergen belongs to this family.
<b>Lipocalin family</b>	Small, specific molecules. Although highly conserved they display limited sequence identity of between 20 – 30%.	<b>High.</b> Lipocalins are often major allergens and constitute an important primary allergen.
<b>Kallikrein</b>	Kallikreins are peptidases. Prostate specific antigen (PSA) is a kallikrein which liquefies semen and allows sperm to swim freely.	<b>High.</b> Associated with male dogs (Can f 5). A major allergen.
<b>Serum albumin</b>	Large globular proteins present in dander, saliva, meat and milk.	<b>High.</b> Highly cross reactivity, minor allergen and is seldom of clinical importance.

Children with problematic severe asthma often have higher levels of IgE antibodies towards cat, dog and horse compared with children with controlled asthma<sup>5-6</sup>. Revealing the primary allergen source driving the allergy could help improve allergy management such as allergen reduction/avoidance strategies, and be an aid to select the proper Allergen Specific Immunotherapy (AIT). AIT success is more likely if sensitization to specific components is identified and appropriate therapy administered<sup>3,9-10</sup>.

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### House dust mites

Allergy to house dust mites (HDM)

is a main cause of respiratory allergies in most parts of the world, and exposure to HDM is a major trigger of asthma exacerbations<sup>1-4</sup>.

*Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) are the most common HDM species, both containing the major allergens - group 1 and 2 proteins. The homology between the two mite species is very high and cross-reactions are common<sup>1-3</sup>.

Der p 1/Der f 1 and Der p 2 /Der f 2 have for a long time been known to be major mite specific allergens<sup>1-4</sup>. Recently several other mite allergens have been identified and Der p 23 has been recognized as also being a major mite component with high clinical relevance<sup>5-6</sup>. Sensitization to increasing numbers of mite components seem to indicate more severe disease<sup>6</sup>.

Tropomyosin (Der p 10) is the main cross-reactive allergen between mites, shellfish, cockroaches and helminths.

Tropomyosin is a minor allergen in mite allergy but considered a major allergen in shellfish allergy<sup>1-3</sup>.

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## Pollen

#### Grasses

All grasses belong to the same botanical family, *Poaceae*, therefore cross-reactivity between different species is common and the closer the relations (e.g. within subfamilies), the higher the degree of cross reactivity<sup>1-4</sup>. Grass pollen allergy is common worldwide, and many atopic patients show sensitization to grass pollen<sup>1-6</sup>. Grass pollen season

overlaps with weed pollen such as mugwort and ragweed in most parts of Europe and with tree pollen (olive, plane) in Southern Europe<sup>1-3,5</sup>. Group 1 and group 5 allergens (e.g. Phl p 1 and Phl p 5 from Timothy) are dominating grass pollen allergens and markers of primary sensitization in a majority of patients<sup>1-6</sup>. Sensitization to Phl p 1 usually precedes other grass pollen component sensitizations in the development of hay fever symptoms<sup>6</sup>. In warmer areas, other grass species such as Bermuda grass are common and they also contain group 1 allergens e.g. Cyn d 1<sup>1-5</sup>. Sensitization to cross-reactive allergens such as profilin (Phl p 12) and polcalcin (Phl p 7) is usually not frequent but several grass allergens carry CCD which can cause cross reactivity in extract based testing<sup>1-7</sup>.

When no specific grass sensitization is detected other pollen or food specific components should be investigated<sup>1-3,5</sup>.

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## Trees

Opposed to grasses, trees belong to several different botanical families, often even to different orders, and there is less cross-reactivity between specific tree allergens. However all tree pollen contain profilin and most contain polcalcins and CCDs, giving rise to possible cross-reactivity on the extract level<sup>1-3</sup>.

Due to Bet v 1 sensitization (the major birch allergen) many birch pollen allergic patients react to several pollen, such as the closely related alder, hazel, beech and oak<sup>1-3,6</sup>. In addition, many of these patients have concomitant pollen-related food allergies due to PR-10 cross-reactivity (Bet v 1) and may react to various fruits, nuts and vegetables (e.g. apple, pear, cherry or hazelnut)<sup>1-3</sup>. In most cases, symptoms are restricted to oral reactions and the food is often tolerated when cooked since PR-10 allergens are heat labile<sup>1-3</sup>.

Olive and ash are botanically very closely related (*Oleaceae* family) and there is extensive cross-reactivity between these species<sup>1-5,7</sup>. Olive tree pollen allergy is quite common and is one of the most

important causes of seasonal respiratory allergy in the Mediterranean area<sup>5,7</sup>. Ole e 1 is the major marker for primary olive pollen sensitization<sup>1-5,7</sup>. The European ash (*Fraxinus excelsior*) is common in most of Europe but ash tree pollen may often be overlooked as a cause of pollinosis<sup>1-2,5</sup>. Ole e 1 serves as a very good marker allergen for ash due to the high cross reactivity<sup>1-5,7</sup>.

Plane trees are known as “street trees” and are found planted practically anywhere in the world<sup>1-2</sup>. Recombinant Pla a 1 is a specific marker allergen discriminating between genuine plane tree pollen sensitization and cross-reactivity<sup>1-5</sup>. Pla a 3 is a LTP which cross-reacts with other LTPs in e.g. fruits<sup>1-3</sup>. Pla a 3 is presently not available as a single ImmunoCAP Allergen Component. However, Pla a 3, as well as the plane-tree specific and major allergen PI a 1 and Pla a 2 are available on the ImmunoCAP ISAC 112 chip.

Cypresses and cedars are common ornamental trees<sup>1-5</sup>. There are several species of cypress and cedars and since they are closely related cross-sensitization is extensive. Cypress trees bloom in the winter and may cause winter respiratory allergy which is often misdiagnosed since symptoms are occurring during winter and are very similar to perennial allergies like dust mite allergy<sup>1-3,8,9</sup>. Cup a 1 is a specific marker for primary sensitization to *Cupressaceae* pollen. The Cup a 1 allergen is very similar to major allergens

of Mediterranean cypress (Cup s 1) Mountain cedar (Jun a 1) Japanese cypress Cha o 1) and Japanese cedar (Cry j 1) and there is an extensive cross-reactivity between species<sup>1-4,8,9</sup>.

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## Weeds

Weed allergy diagnosis can be unclear and difficult to make due to frequent poly-sensitizations and inconclusive anamnesis because of overlapping flowering seasons with other pollen

such as birch and grass<sup>1-3</sup>. Cross reactions are expected between different weed species when botanically closely related, however many weeds belong to unrelated botanical families and therefore specific marker allergens are available, e.g. Amb a 1 from Ragweed, Art v 1 from Mugwort, Par j 1 from Parietaria, Pla l 1 from English plantain and Sal k 1 from Saltwort<sup>1-5</sup>. Saltwort is a weed common in dry, semi-arid areas and is becoming more and more common in southern parts of Europe due to climate change.

Apart from profilin and CCDs, mugwort and ragweed pollen contain some other cross-reactive allergens. Cross-reactive IgE antibodies can lead to clinically significant allergic reactions<sup>5</sup>.

Pollen-food syndromes driven by weed pollen are mainly generated by mugwort and ragweed pollen. In addition to Oral Allergy Syndrome (OAS) more severe allergy is reported such as the celery-mugwort-spice syndrome<sup>1-2,6</sup>.

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## Molds

There is current evidence to demonstrate a close association between fungal sensitization and asthma severity<sup>1-5</sup>. Many airborne fungi are involved such as *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium*, and exposure may be indoors, outdoors or both. Fungal sensitization is common in asthmatic patients and the term “severe asthma with fungal sensitization” (SAFS) has been proposed<sup>1-5</sup>. However, it is recognised that enhanced and precise definition of fungal sensitization will require improvements in diagnostic testing and this can be facilitated by component testing<sup>1-9</sup>.

*Alternaria alternata* is a major outdoor as well as indoor aeroallergen in many parts of the world. Sensitivity to *Alternaria* has been increasingly recognized as a risk factor for the development and persistence of asthma, asthma severity, and potentially fatal asthma exacerbations<sup>2-6</sup>. Alt a 1 is the major *Alternaria* allergen. Alt a 1 is considered a specific marker of primary sensitization to *Alternaria Alternata* and useful in asthma diagnostics<sup>2-6</sup>.

*Aspergillus fumigatus* is an opportunistic fungus causing allergic and invasive aspergillosis in humans and animals<sup>1-4,7-9</sup>. Genuine *A. fumigatus* sensitization is not always easily identifiable and IgE sensitization tests are used as part of routine workup for diagnosing Allergic Bronchopulmonary Aspergillosis (ABPA). The use of allergen components for *A. fumigatus* can aid the identification of primary *A. fumigatus* sensitization<sup>1-4,7-9</sup>.

Asp f 1, Asp f 2 and Asp f 4 are species specific allergens while Asp f 3 and Asp f 6 are described as cross-reactive allergens<sup>1,2,7-9</sup>. Recent studies investigating ABPA demonstrated that ImmunoCAP Allergen Components could differentiate ABPA from asthma and sensitised patients. ABPA has been particularly linked to Asp f 4 and Asp p 6<sup>7-9</sup> – see book 2 for further details.

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## Venoms

Many patients with suspected honey bee and/or common wasp allergy test positive to both species when using extract testing. True double allergic reactivity to both bee and wasp is not clinically common. In many cases double venom IgE positivity can be caused by cross-reactions to CCDs<sup>1-5</sup>. Recombinant venom components do not carry CCD and therefore provide greater diagnostic specificity, useful when making decisions such as to start AIT<sup>1-7</sup>. Ves v 1 and Ves v 5 are major allergens from common wasp and Pol d 5 is a marker for sensitization to paper wasp. The picture for honey bee sensitivity seems more complex than for wasp and can involve more varied sensitization patterns to major components. Api m 1, Api m 2, Api m 3, Api m 5 and Api m 10 are all major allergens within bee venom allergy. It has recently been shown that using an increasing number of bee components can improve diagnostic sensitivity<sup>1-7</sup>. Low level specific IgE below 0.35 kU<sub>A</sub>/l

can be relevant when using components and may be indicative of venom allergy, so measuring down to 0.1 kU<sub>A</sub>/l can be important<sup>1,6</sup>.

Patients with suspected venom allergy should also be tested with ImmunoCAP Tryptase<sup>5,8-9</sup>. Patients with high basal levels of tryptase should be investigated for mastocytosis since these patients have higher risk for severe reactions during venom immunotherapy<sup>5,8-9</sup>.

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## Latex

Primary latex allergy should be identified using specific allergen components as many positive extract test results arise as a result of cross-reactive pollen sensitization involving profilin, CCDs or PR-10 allergens<sup>1-6</sup>. The association of latex allergy and allergy to plant-derived foods is referred to as the latex-fruit syndrome and includes a large number of plant foods such as avocado, banana, chestnut, kiwi, peach, tomato, potato and bell pepper. The latex allergen Hev b 6 is considered the main culprit in this syndrome<sup>1-2</sup>.

IgE antibodies to Hev b 1, Hev b 3, Hev b 5 and Hev b 6 are markers for primary latex allergy<sup>1-6</sup>. Sensitization to these components is frequent in surgery-related latex-allergy, especially among children having undergone multiple and extensive surgery, such as those with spina bifida. Sensitization to Hev b 5 and Hev b 6 is associated with occupational exposure to latex e.g. in healthcare workers and food-handling personnel using latex gloves<sup>1-5</sup>. Latex allergens Hev b 8 (profilin) and Hev b 6 can be used for examining cross-reactivity to pollen and plant foods, respectively<sup>1-4</sup>. If an exclusive sensitization to the profilin Hev b 8 is seen, allergic symptoms to latex are hardly to be expected<sup>5,6</sup>.

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# Immunotherapeutics – Aeroallergens and venoms

## Understanding cross-sensitization and identifying the right allergen source

Clinically it is obviously important to correctly identify the allergen source causing symptoms before starting immunotherapy and this is not always easy<sup>1-6</sup>. Patients can be cross-sensitized to several allergen species; therefore sometimes it is not clear what the disease-eliciting source is. This applies to pollen allergies as well as to animal, dust mite and venom allergy. Molecular allergen tests can help streamline the identification process<sup>1-6</sup>. Specific molecules from, for example, grass can differentiate and identify true grass-allergic patients.

Determining a patient's molecular profile will also help to indicate if they are likely to respond satisfactorily to immunotherapy<sup>3, 6-7</sup>. Immunotherapy products vary from manufacturer to manufacturer; they contain molecules from the allergen source. But which ones and in what quantity? Most products contain larger quantities of the major allergens such as Bet v 1 in birch or Phl p 1 and Phl p 5 in timothy grass and Der p 1 in mite extracts, while sometimes much lower quantities of other allergens are included<sup>7</sup>. Patients who are positive only

to the minor allergens are therefore less likely to respond satisfactorily<sup>1-7, 10-11</sup>.

Many patients with suspected venom allergy can be positive for both bee and wasp whole allergens. Double positivity can be caused by CCDs rather than true double sensitization<sup>1-3, 8-11</sup>. ImmunoCAP recombinant venom components are CCD-free, which enables the physician to distinguish between positivity from cross-reactions and true venom allergy before selecting the right immunotherapeutic solution. Api m 3 and Api m 10 can be absent or underrepresented in VIT extracts and venom AIT in patients sensitized to these components may be less efficient<sup>10-11</sup>.

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## Common questions regarding allergen components

### **What is a molecular allergen-specific IgE test and does it differ technically from normal specific IgE tests that I request from my laboratory?**

Technically they work in the same way and give results in  $kU_A/L$ , the same as normal whole extract sources such as cat, peanut etc.

### **How many ImmunoCAP Allergen Components are available?**

There are currently over 100 allergen components in the product range. A list is included in this guide, however availability may differ between countries.

### **For each allergen source how do I know that the ImmunoCAP Allergen Components represent the whole allergen extract?**

Generally speaking they don't. For example, there are over 30 proteins reported in the peanut extract, many not clinically relevant or with unknown relevance. The field of molecular allergology is ever-expanding as we gain further scientific information and knowledge. Thermo Fisher Scientific supplies between 2- 4 new components every year. Since all components are not available as single tests it is suggested to use the available components together with the whole extract to cover the spectrum of patients' sensitizations.

### **What is ImmunoCAP ISAC 112?**

ImmunoCAP ISAC 112 is a microarray chip which tests for IgE to 112 allergen components simultaneously. It is a multiplex test giving semi-quantitative

results on a patient's allergen component sensitization profile. It has been found useful for the diagnosis of the following, but this list is not exhaustive: complex allergy, OAS, and cases of multi-sensitization, idiopathic anaphylaxis and high total IgE patients. More information on ImmunoCAP ISAC is available in Go Molecular, Book 2.

### **Where can I get access to ImmunoCAP ISAC 112?**

Your local immunology laboratory may have ImmunoCAP ISAC in-house, otherwise the lab should be able to refer your sample for testing. Therefore contact your local lab to find out what is possible.

### **Is it possible to have an ImmunoCAP Whole Allergen test result that is negative and an ImmunoCAP Allergen Component test result that is positive (from the same source)?**

This is possible in some cases. The whole allergen contains a mix of proteins, representing the natural composition at the source, while the allergen component is one single pure protein. Overall the component tests give higher specificity and sometimes even more sensitivity. Using a combination of both whole extract and components (where possible) is currently considered the best strategy for diagnosis.

# Glossary

**Allergen component** – single immunogenic protein from an allergen source e.g. Ara h 2 from peanut.

**Cross-reactivity/Cross-sensitization**

– IgE antibodies directed against one allergen may cross-react to structurally related allergens from other allergen sources. Cross-reactive antibodies can cause a variety of different clinical outcomes.

**Epitope** – Defined substructure of a protein to which an antibody binds.

**ImmunoCAP** – an in vitro test for the measurement of specific IgE antibodies. ImmunoCAP is one of the market leaders and has been established for several decades. ImmunoCAP is also available for testing for other immunoglobulins (e.g. IgA/ IgG).

**Pan-allergen** – evolutionarily conserved and widely distributed allergen, ubiquitous component of several sources of allergens. IgE antibodies to a pan-allergen may cross-react with homologous allergens and thus also give rise to symptoms to many different allergens in a patient.

**Primary sensitizing allergen** –

an allergen originally triggering the immune system to produce specific IgE antibodies. For example Bet v 1 from birch or Ara h 2 from peanut.

**Minor and major allergens** – Major allergen components are those to which at least 50% of relevant patients are sensitized. Minor allergens are often less prevalent in triggering allergy. For instance, in birch allergy the major allergen is Bet v 1 (PR-10), whilst a minor allergen is Bet v 2 (profilin).

**Secondary sensitization** – IgE

antibodies directed to a primary sensitizer cross-react due to the similarity of the proteins/allergens and give rise to cross-reactive sensitization. This occurs in food-pollen syndrome for example, when an individual is sensitized to birch PR-10 (Bet v1) and the IgE antibodies then cross-react to peanut PR-10 (Ara h 8).

**Allergen extract** – refers to the crude mixture of proteins that is obtained by extraction of an allergen source (e.g. birch pollen or peanut).

# Educational resources

**allergyai.com** – Home Page of Immunodiagnostics Division, Thermo Fisher Scientific

**allergen.org** – International Union for Immunological Sciences/WHO Allergen Database

Matricardi PM et al. EAACI Molecular Allergology User's Guide. *Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology*. 2016;27 Suppl 23:1-250.

Kleine-Tebbe J and Jakob T Editors: *Molecular Allergy Diagnostics. Innovation for a Better Patient Management*. Springer International Publishing Switzerland 2017. ISBN 978-3-319-42498-9 ISBN 978-3-319-42499-6 (eBook), DOI 10.1007/978-3-319-42499-6

Canonica GW et al. A WAO – ARIA – GA2LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 2013;6(1):17.

# Using ImmunoCAP Allergen Component tests

The term 'ImmunoCAP Allergen Component' is used for singleplex ImmunoCAP products based on molecular allergens purified from either their natural source (native) or biotechnologically produced as recombinant proteins bound to the conventional ImmunoCAP solid phase.

By using tests for single allergen components as a complement to more traditional specific IgE antibody tests, further clinically relevant and quantitative information can be gained as an aid to the physician in making a diagnosis of allergy.

Allergen components are also available in a multiplex microarray format, ImmunoCAP ISAC 112. Here each test contains 112 components giving 112 semi-quantitative specific IgE results, thus presenting a snapshot of the patient's complete sensitization profile in one test.

More information on ImmunoCAP ISAC 112 is available in Book 2.

The interpretation of sensitizations to allergen components that is described in this book, (as well as in book 2) is the same for both single and multiplex formats.

ImmunoCAP Allergen Components, singleplex as well as multiplex, are useful tools for the physician when investigating and explaining allergic reactions in more detail and to determine if cross-reacting IgE antibodies or primary sensitization causes them. However as all test results they must be evaluated by the physician together with the clinical history of the individual patient.

Presence of allergen specific IgE implies a risk of allergic disease and generally the higher the level of IgE antibodies the higher the probability of a clinically manifest allergic reaction<sup>1-5</sup>. However, due to differences in individual patient sensitivities identical results for the same allergens may not be associated with clinically equivalent manifestations. This may also be true for one individual patient at different occasions due to presence or absence of reaction promoting cofactors<sup>1-5</sup>.

Absence of detectable allergen specific IgE antibodies does not necessarily exclude the potential for an allergy-like reaction<sup>1,2</sup>.

### **Limitations of ImmunoCAP products test results:**

Samples with results below limit of quantitation obtained with ImmunoCAP Allergen Components are recommended to be tested with the corresponding extract based ImmunoCAP Allergen and/or additional relevant ImmunoCAP Allergen Components, if not already performed and a clinical indication is present. The extract based testing can cover additional allergen components present in the allergen source material to which the patient may be sensitized, but which are not presently available as ImmunoCAP Allergen Components or in ImmunoCAP ISAC 112.

A result below limit of quantitation obtained with an extract based ImmunoCAP Allergen never excludes the possibility of obtaining measurable concentrations of specific IgE when testing with ImmunoCAP Allergen Components from the same allergen source. This is due to the fact that some components may be present in very low amounts in the natural extract.

### **References**

1. Matricardi PM et al. EAACI Molecular Allergy User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23:1-250.
2. Kleine-Tebbe J and Jakob T Editors: Molecular Allergy Diagnostics. Innovation for a Better Patient Management. Springer International Publishing Switzerland 2017. ISBN 978-3-319-42498-9 ISBN 978-3-319-42499-6 (eBook), DOI 10.1007/978-3-319-42499-6.
3. Canonica GW et.al. A WAO - ARIA - GA<sup>2</sup>LEN consensus document on molecular-based allergy diagnostics. World Allergy Organ J. 2013 Oct 3;6(1):17.
4. Wickman M. When allergies complicate allergies. Allergy 2005;60(S79):14-18.
5. Van Hage M et.al. ImmunoCAP assays: Pros and cons in allergology. J Allergy Clin Immunol 2017;140:974-7.

### **Disclaimer:**

The content of this book is intended as an aid to the physician to interpret allergen specific IgE antibody test results. It is not intended as medical advice on an individual level. A definitive clinical diagnosis of IgE mediated allergic disorders should only be made by the physician based on the clinical history for the individual patient, after all clinical and laboratory findings have been evaluated. It should not be based on the results of any single diagnostic method.

# ImmunoCAP Allergen Component list\*

Product	Latin name	Code	Size	Art. no.	Barcode
<b>Grass pollen</b>					
Cyn d 1 Bermuda grass	<i>Cynodon dactylon</i>	g216	10	14-4972-01	CFA
rPhl p 1 Timothy	<i>Phleum pratense</i>	g205	10	14-5234-01	BSU
rPhl p 2 Timothy	<i>Phleum pratense</i>	g206	10	14-5235-01	COK
nPhl p 4 Timothy	<i>Phleum pratense</i>	g208	10	14-5288-01	C0L
rPhl p 5b Timothy	<i>Phleum pratense</i>	g215	10	14-5338-01	BV3
rPhl p 6 Timothy	<i>Phleum pratense</i>	g209	10	14-5289-01	BSV
rPhl p 7 Timothy	<i>Phleum pratense</i>	g210	10	14-5290-01	BSW
rPhl p 11 Timothy	<i>Phleum pratense</i>	g211	10	14-5291-01	BSX
rPhl p 12 Profilin, Timothy	<i>Phleum pratense</i>	g212	10	14-5292-01	BSY
rPhl p 1, rPhl p 5b Timothy	<i>Phleum pratense</i>	g213	10	14-5312-01	BU1
rPhl p 7, rPhl p 12 Timothy	<i>Phleum pratense</i>	g214	10	14-5313-01	BU2
<b>Weed pollen</b>					
nAmb a 1 Ragweed	<i>Ambrosia artemisiifolia (A. elatior)</i>	w230	10	14-4969-01	CF8
nArt v 1 Mugwort	<i>Artemisia vulgaris</i>	w231	10	14-4970-01	CF9
nArt v 3 LTP, Mugwort	<i>Artemisia vulgaris</i>	w233	10	14-4983-01	CJ2
rPar j 2 LPT, Wall pellitory	<i>Parietaria judaica</i>	w211	10	14-5311-01	C2M
rPla l 1 Plantain	<i>Plantago lanceolata</i>	w234	10	14-5751-01	D1H
nSal k 1 Saltwort	<i>Salsola kali</i>	w232	10	14-4978-01	CFE
<b>Tree pollen</b>					
rBet v 1 PR-10, Birch	<i>Betula verrucosa</i>	t215	10	14-5225-01	BPV
rBet v 2 Profilin, Birch	<i>Betula verrucosa</i>	t216	10	14-5226-01	BR1
rBet v 4 Birch	<i>Betula verrucosa</i>	t220	10	14-5287-01	BT7
rBet v 6 Birch	<i>Betula verrucosa</i>	t225	10	14-5345-01	CF1
rBet v 2, rBet v 4 Birch	<i>Betula verrucosa</i>	t221	10	14-5310-01	BU0
nCup a 1 Cypress	<i>Cupressus arizonica</i>	t226	10	14-4977-01	CFD
rOle e 1 Olive	<i>Olea europaea</i>	t224	10	14-5705-01	CTC
nOle e 7 LTP, Olive	<i>Olea europaea</i>	t227	10	14-4993-01	CKT
rOle e 9, Olive	<i>Olea europaea</i>	t240	10	14-4999-01	CTZ
rPla a 1 Maple leaf sycamore, London plane	<i>Platanus acerifolia</i>	t241	10	14-5957-01	D2H

\*Not all ImmunoCAP Products are available in all regions/ countries

Product	Latin name	Code	Size	Art. no.	Barcode
<b>Microorganisms</b>					
rAlt a 1	<i>Alternaria alternata</i>	m229	10	14-5346-01	CE0
rAsp f 1	<i>Aspergillus fumigatus</i>	m218	10	14-5293-01	BPL
rAsp f 2	<i>Aspergillus fumigatus</i>	m219	10	14-5294-01	BPM
rAsp f 3	<i>Aspergillus fumigatus</i>	m220	10	14-5295-01	BT4
rAsp f 4	<i>Aspergillus fumigatus</i>	m221	10	14-5296-01	BPN
rAsp f 6	<i>Aspergillus fumigatus</i>	m222	10	14-5297-01	BPP
<b>Epidermals and animal proteins</b>					
nBos d 6 BSA, Cow	<i>Bos spp.</i>	e204	10	14-5009-01	BRV
rCan f 1 Dog	<i>Canis familiaris</i>	e101	10	14-4955-01	CBN
rCan f 2 Dog	<i>Canis familiaris</i>	e102	10	14-4956-01	CBP
nCan f 3 Dog serum albumin	<i>Canis familiaris</i>	e221	10	14-5241-01	C14
rCan f 5 Dog	<i>Canis familiaris</i>	e226	10	14-4998-01	CMZ
rFel d 1 Cat	<i>Felis domesticus</i>	e94	10	14-4905-01	BY0
rFel d 2 Cat serum albumin	<i>Felis domesticus</i>	e220	10	14-5240-01	BRX
rFel d 4 Cat	<i>Felis domesticus</i>	e228	10	14-5702-01	CT9
rEqu c 1 Horse	<i>Equus caballus</i>	e227	10	14-5700-01	CN7
nSus s Pig serum albumin, Swine	<i>Sus scrofa</i>	e222	10	14-5242-01	C36
<b>Mites</b>					
rDer p 1 House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d202	10	14-5996-01	DP4
rDer p 2 House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d203	10	14-4967-01	CG2
rDer p 10 Tropomyosin, House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d205	10	14-4985-01	CG5
rDer p 23 House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d209	10	14-6040-01	DWU
<b>Venoms</b>					
rApi m 1 Phospholipase A2, Honey bee	<i>Apis mellifera</i>	i208	10	14-4987-01	CJ7
rApi m 2 Hyaluronidase, Honey bee	<i>Apis mellifera</i>	i214	10	14-6014-01	DUD
rApi m 3, Acid phosphatase, Honey bee	<i>Apis mellifera</i>	i215	10	14-6015-01	DUC
rApi m 5 Dipeptidyl peptidase, Honey bee	<i>Apis mellifera</i>	i216	10	14-6016-01	DUB
rApi m 10 Icarapin, Honey bee	<i>Apis mellifera</i>	i217	10	14-6004-01	DRO
rVes v 1 Phospholipase A1, Common wasp	<i>Vespula vulgaris</i>	i211	10	14-4995-01	CMR
rVes v 5 Common wasp	<i>Vespula vulgaris</i>	i209	10	14-4992-01	CJ8
rPol d 5 Paper wasp	<i>Polistes dominulus</i>	i210	10	14-4994-01	CJ9
<b>Occupational</b>					
rHev b 1 Latex	<i>Hevea brasiliensis</i>	k215	10	14-5324-01	C20
rHev b 3 Latex	<i>Hevea brasiliensis</i>	k217	10	14-5326-01	C2A
rHev b 5 Latex	<i>Hevea brasiliensis</i>	k218	10	14-5327-01	C1Z
rHev b 6.02 Latex	<i>Hevea brasiliensis</i>	k220	10	14-5329-01	C22
rHev b 8 Profilin, Latex	<i>Hevea brasiliensis</i>	k221	10	14-5330-01	C1V
rHev b 11 Latex	<i>Hevea brasiliensis</i>	k224	10	14-5333-01	C29

## ImmunoCAP Allergen Component list continued\*

Product	Latin name	Code	Size	Art. no.	Barcode
<b>Occupational / Enzymes</b>					
Alkalase	<i>Alkalase</i>	k205	10	14-5126-01	C1F
nAna c 2 Bromelain, Pineapple	<i>nAna c 2 Bromelain, Pineapple</i>	k202	10	14-5127-01	BT1
nAsp o 21 alpha-amylase	<i>nAsp o 21 alpha-amylase</i>	k87	10	14-4370-01	595
nCar p 1 Papain, Papaya	<i>nCar p 1 Papain, Papaya</i>	k201	10	14-5130-01	BT0
nGal d 4 Lysozyme, Egg	<i>nGal d 4 Lysozyme, Egg</i>	k208	10	14-5128-01	C0T
Maxatase	<i>Maxatase</i>	k204	10	14-5129-01	C2F
Savinase	<i>Savinase</i>	k206	10	14-5132-01	C2R
nSus s Pepsin, Swine	<i>nSus s Pepsin, Swine</i>	k213	10	14-5258-01	C3B
<b>Foods</b>					
rAct d 8 PR-10, Kiwi	<i>Actinidia deliciosa</i>	f430	10	14-4984-01	CG7
rAna o 3 Cashew nut	<i>Anacardium occidentale</i>	f443	10	14-5760-01	D0W
rApi g 1.01 PR-10, Celery	<i>Apium graveolens</i>	f417	10	14-4957-01	CBR
rAra h 1 Peanut	<i>Arachis hypogaea</i>	f422	10	14-4963-01	CDF
rAra h 2 Peanut	<i>Arachis hypogaea</i>	f423	10	14-4964-01	CDG
rAra h 3 Peanut	<i>Arachis hypogaea</i>	f424	10	14-4965-01	CDH
rAra h 6 Peanut	<i>Arachis hypogaea</i>	f447	10	14-6041-01	DYU
rAra h 8 PR-10, Peanut	<i>Arachis hypogaea</i>	f352	10	14-5341-01	CEZ
rAra h 9 LTP, Peanut	<i>Arachis hypogaea</i>	f427	10	14-4980-01	CFC
rBer e 1 Brazil nut	<i>Bertholletia excelsa</i>	f354	10	14-5343-01	CDS
nBos d 4 alpha-lactalbumin, Milk	<i>Bos spp.</i>	f76	10	14-4522-01	CTP
nBos d 5 beta-lactoglobulin, Milk	<i>Bos spp.</i>	f77	10	14-4523-01	CTR
nBos d 8 Casein, Milk	<i>Bos spp.</i>	f78	10	14-4524-01	CTS
rCor a 1 PR-10, Hazel nut	<i>Corylus avellana</i>	f428	10	14-4981-01	CFB
rCor a 8 LTP, Hazel nut	<i>Corylus avellana</i>	f425	10	14-4968-01	CDP
nCor a 9, Hazel nut	<i>Corylus avellana</i>	f440	10	14-5758-01	DOM
rCor a 14, Hazel nut	<i>Corylus avellana</i>	f439	10	14-5754-01	CZP
rCyp c 1 Carp	<i>Cyprinus carpio</i>	f355	10	14-5344-01	CF0
rGad c 1 Cod	<i>Gadus morhua</i>	f426	10	14-4971-01	CEY
nGal d 1 Ovomucoid, Egg	<i>Gallus spp.</i>	f233	10	14-4805-01	904
nGal d 2 Ovalbumin, Egg	<i>Gallus spp.</i>	f232	10	14-4804-01	903
nGal d 3 Conalbumin, Egg	<i>Gallus spp.</i>	f323	10	14-5222-01	C18
rGly m 4 PR-10, Soy	<i>Glycine max</i>	f353	10	14-5340-01	CDR
nGly m 5 beta-conglycinin, Soy	<i>Glycine max</i>	f431	10	14-4990-01	CLV
nGly m 6 Glycinin	<i>Glycine max</i>	f432	10	14-4991-01	CLU
rJug r 1 Walnut	<i>Juglans regia</i>	f441	10	14-5762-01	D0T
rJug r 3 LTP, Walnut	<i>Juglans regia</i>	f442	10	14-5954-01	D11
rMal d 1 PR-10, Apple	<i>Malus domestica</i>	f434	10	14-5703-01	CWR
rMal d 3 LTP, Apple	<i>Malus domestica</i>	f435	10	14-5704-01	CWS
rPen a 1 Tropomyosin, Shrimp	<i>Penaeus aztecus</i>	f351	10	14-5335-01	C11
rPru p 1 PR-10, Peach	<i>Prunus persica</i>	f419	10	14-4960-01	CBV

\*Not all ImmunoCAP Products are available in all regions/ countries

Product	Latin name	Code	Size	Art. no.	Barcode
<b>Foods continued</b>					
rPru p 3 LTP, Peach	<i>Prunus persica</i>	f420	10	14-4961-01	CBW
rPru p 4 Profilin, Peach	<i>Prunus persica</i>	f421	10	14-4962-01	CBX
rTri a 14 LTP, Wheat	<i>Triticum aestivum</i>	f433	10	14-5701-01	CN6
rTri a 19 Omega-5 Gliadin, Wheat	<i>Triticum aestivum</i>	f416	10	14-4954-01	C8H
Gliadin		f98	10	14-5752-01	CXG
<b>Miscellaneous</b>					
nGal-alpha-1,3-Gal (alpha-Gal) Thyroglobulin, bovine		o215	10	14-5997-01	DPC
MUXF3 CCD, Bromelain		o214	10	14-5339-01	CJU

# ImmunoCAP ISAC 112

## Allergen Components

Allergen component	Allergen source common name	Latin name	Protein group
<b>Food allergens</b>			
Gal d 1	Egg white	<i>Gallus domesticus</i>	Ovomucoid
Gal d 2	Egg white	<i>Gallus domesticus</i>	Ovalbumin
Gal d 3	Egg white	<i>Gallus domesticus</i>	Conalbumin/Ovotransferrin
Gal d 5	Egg yolk/chicken meat	<i>Gallus domesticus</i>	Livetin/Serum albumin
Bos d 4	Cow's milk	<i>Bos domesticus</i>	Alpha-lactalbumin
Bos d 5	Cow's milk	<i>Bos domesticus</i>	Beta-lactoglobulin
Bos d 6	Cow's milk and meat	<i>Bos domesticus</i>	Serum albumin
Bos d 8	Cow's milk	<i>Bos domesticus</i>	Casein
Bos d lactoferrin	Cow's milk	<i>Bos domesticus</i>	Transferrin
Gad c 1	Cod	<i>Gadus callarias</i>	Parvalbumin
Pen m 1	Shrimp	<i>Penaeus monodon</i>	Tropomyosin
Pen m 2	Shrimp	<i>Penaeus monodon</i>	Arginine kinase
Pen m 4	Shrimp	<i>Penaeus monodon</i>	Sarcoplasmic Ca-binding protein
Ana o 2	Cashew nut	<i>Anacardium occidentale</i>	Storage protein, 11S globulin
Ber e 1	Brazil nut	<i>Bertholletia excelsa</i>	Storage protein, 2S albumin
Cor a 1.0401	Hazelnut	<i>Corylus avellana</i>	PR-10 protein
Cor a 8	Hazelnut	<i>Corylus avellana</i>	Lipid transfer protein (nsLTP)
Cor a 9	Hazelnut	<i>Corylus avellana</i>	Storage protein, 11S globulin
Jug r 1	Walnut	<i>Juglans regia</i>	Storage protein, 2S albumin
Jug r 2	Walnut	<i>Juglans regia</i>	Storage protein, 7S globulin
Jug r 3	Walnut	<i>Juglans regia</i>	Lipid transfer protein (nsLTP)
Ses i 1	Sesame seed	<i>Sesamum indicum</i>	Storage protein, 2S albumin
Ara h 1	Peanut	<i>Arachis hypogaea</i>	Storage protein ,7S globulin
Ara h 2	Peanut	<i>Arachis hypogaea</i>	Storage protein, 2S albumin
Ara h 3	Peanut	<i>Arachis hypogaea</i>	Storage protein, 11S globulin
Ara h 6	Peanut	<i>Arachis hypogaea</i>	Storage protein, 2S albumin
Ara h 8	Peanut	<i>Arachis hypogaea</i>	PR-10 protein
Ara h 9	Peanut	<i>Arachis hypogaea</i>	Lipid transfer protein (nsLTP)
Gly m 4	Soybean	<i>Glycine max</i>	PR-10 protein
Gly m 5	Soybean	<i>Glycine max</i>	Storage protein, Beta-conglycinin
Gly m 6	Soybean	<i>Glycine max</i>	Storage protein, Glycinin
Fag e 2	Buckwheat	<i>Fagopyrum esculentum</i>	Storage protein, 2S albumin
Tri a 14	Wheat	<i>Triticum aestivum</i>	Lipid transfer protein (nsLTP)
Tri a 19.0101	Wheat	<i>Triticum aestivum</i>	Omega-5 gliadin
Tri a aA_TI	Wheat	<i>Triticum aestivum</i>	
Act d 1	Kiwi	<i>Actinidia deliciosa</i>	
Act d 2	Kiwi	<i>Actinidia deliciosa</i>	Thaumatin-like protein
Act d 5	Kiwi	<i>Actinidia deliciosa</i>	
Act d 8	Kiwi	<i>Actinidia deliciosa</i>	PR-10 protein
Api g 1	Celery	<i>Apium graveolens</i>	PR-10 protein
Mal d 1	Apple	<i>Malus domestica</i>	PR-10 protein
Pru p 1	Peach	<i>Prunus persica</i>	PR-10 protein
Pru p 3	Peach	<i>Prunus persica</i>	Lipid transfer protein (nsLTP)

Allergen component	Allergen source common name	Latin name	Protein group
<b>Aeroallergens</b>			
Cyn d 1	Bermuda grass	<i>Cynodon dactylon</i>	Grass group 1
Phl p 1	Timothy grass	<i>Phleum pratense</i>	Grass group 1
Phl p 2	Timothy grass	<i>Phleum pratense</i>	Grass group 2
Phl p 4	Timothy grass	<i>Phleum pratense</i>	
Phl p 5	Timothy grass	<i>Phleum pratense</i>	Grass group 5
Phl p 6	Timothy grass	<i>Phleum pratense</i>	
Phl p 7	Timothy grass	<i>Phleum pratense</i>	Polcalcin
Phl p 11	Timothy grass	<i>Phleum pratense</i>	
Phl p 12	Timothy grass	<i>Phleum pratense</i>	Profilin
Aln g 1	Alder	<i>Alnus glutinosa</i>	PR-10 protein
Bet v 1	Birch	<i>Betula verrucosa</i>	PR-10 protein
Bet v 2	Birch	<i>Betula verrucosa</i>	Profilin
Bet v 4	Birch	<i>Betula verrucosa</i>	Polcalcin
Cor a 1.0101	Hazel pollen	<i>Corylus avellana</i>	PR-10 protein
Cry j 1	Japanese cedar	<i>Cryptomeria japonica</i>	
Cup a 1	Cypress	<i>Cupressus arizonica</i>	
Ole e 1	Olive	<i>Olea europaea</i>	
Ole e 7	Olive	<i>Olea europaea</i>	Lipid transfer protein (nsLTP)
Ole e 9	Olive	<i>Olea europaea</i>	
Pla a 1	Plane tree	<i>Platanus acerifolia</i>	
Pla a 2	Plane tree	<i>Platanus acerifolia</i>	
Pla a 3	Plane tree	<i>Platanus acerifolia</i>	Lipid transfer protein (nsLTP)
Amb a 1	Ragweed	<i>Ambrosia artemisiifolia</i>	
Art v 1	Mugwort	<i>Artemisia vulgaris</i>	
Art v 3	Mugwort	<i>Artemisia vulgaris</i>	Lipid transfer protein (nsLTP)
Che a 1	Goosefoot	<i>Chenopodium album</i>	
Mer a 1	Annual mercury	<i>Mercurialis annua</i>	Profilin
Par j 2	Wall pellitory	<i>Parietaria judaica</i>	Lipid transfer protein (nsLTP)
Pla l 1	Plantain (English)	<i>Plantago lanceolata</i>	
Sal k 1	Saltwort	<i>Salsola kali</i>	
Can f 1	Dog	<i>Canis familiaris</i>	Lipocalin
Can f 2	Dog	<i>Canis familiaris</i>	Lipocalin
Can f 3	Dog	<i>Canis familiaris</i>	Serum albumin
Can f 5	Dog	<i>Canis familiaris</i>	Arginine esterase
Equ c 1	Horse	<i>Equus caballus</i>	Lipocalin
Equ c 3	Horse	<i>Equus caballus</i>	Serum albumin
Fel d 1	Cat	<i>Felis domesticus</i>	Uteroglobulin
Fel d 2	Cat	<i>Felis domesticus</i>	Serum albumin
Fel d 4	Cat	<i>Felis domesticus</i>	Lipocalin
Mus m 1	Mouse	<i>Mus musculus</i>	Lipocalin
Alt a 1	Alternaria	<i>Alternaria alternata</i>	
Alt a 6	Alternaria	<i>Alternaria alternata</i>	Enolase
Asp f 1	Aspergillus	<i>Aspergillus fumigatus</i>	
Asp f 3	Aspergillus	<i>Aspergillus fumigatus</i>	
Asp f 6	Aspergillus	<i>Aspergillus fumigatus</i>	Mn superoxide dismutase
Cla h 8	Cladosporium	<i>Cladosporium herbarum</i>	
Blo t 5	House dust mite	<i>Blomia tropicalis</i>	
Der f 1	House dust mite	<i>Dermatophagoides farinae</i>	
Der f 2	House dust mite	<i>Dermatophagoides farinae</i>	
Der p 1	House dust mite	<i>Dermatophagoides pteronyssinus</i>	
Der p 2	House dust mite	<i>Dermatophagoides pteronyssinus</i>	
Der p 10	House dust mite	<i>Dermatophagoides pteronyssinus</i>	Tropomyosin
Lep d 2	Storage mite	<i>Lepidoglyphus destructor</i>	

Aeroallergens continued overleaf...

## ImmunoCAP ISAC 112 Allergen Components continued

Allergen component	Allergen source common name	Latin name	Protein group
<b>Aeroallergens continued</b>			
Bla g 1	Cockroach	<i>Blattella germanica</i>	
Bla g 2	Cockroach	<i>Blattella germanica</i>	
Bla g 5	Cockroach	<i>Blattella germanica</i>	
Bla g 7	Cockroach	<i>Blattella germanica</i>	Tropomyosin
<b>Other</b>			
Api m 1	Honey bee venom	<i>Apis mellifera</i>	Phospholipase A2
Api m 4	Honey bee venom	<i>Apis mellifera</i>	Melittin
Pol d 5	Paper wasp venom	<i>Polistes dominulus</i>	Venom, Antigen 5
Ves v 5	Common wasp venom	<i>Vespula vulgaris</i>	Venom, Antigen 5
Ani s 1	Anisakis	<i>Anisakis simplex</i>	
Ani s 3	Anisakis	<i>Anisakis simplex</i>	Tropomyosin
Hev b 1	Latex	<i>Hevea brasiliensis</i>	
Hev b 3	Latex	<i>Hevea brasiliensis</i>	
Hev b 5	Latex	<i>Hevea brasiliensis</i>	
Hev b 6.01	Latex	<i>Hevea brasiliensis</i>	
Hev b 8	Latex	<i>Hevea brasiliensis</i>	Profilin
MUXF3	Sugar epitope from Bromelain		CCD-marker



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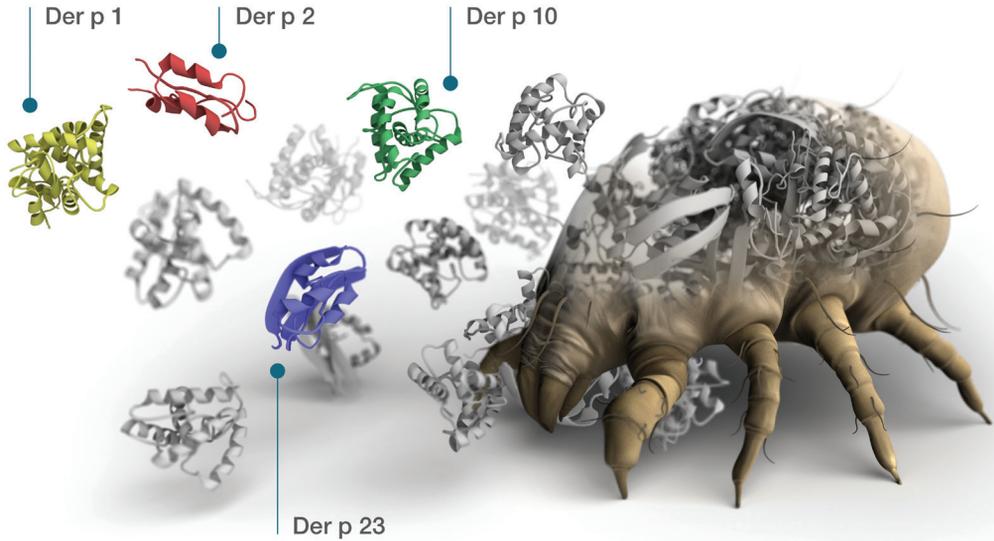
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# Go molecular!

## A clinical reference guide to molecular allergy

### Part 2: The allergen components

Second edition | By Neal Bradshaw

For more information on this topic  
[allergyai.com](http://allergyai.com)

# Preface

In the previous 2013 edition of Go Molecular, I produced a straight forward clinical reference guide book to describe common allergens and their constituent components. This guide is an update to the original but keeps the focus on understanding component test results, as well as what tests are actually commercial available (since this is an important practical aspect of molecular allergy!).

Since 2013 the science of molecular allergy has exploded with many new studies both using single and multiplex allergen testing formats. There is a lot of new clinical evidence to consider, emerging allergens like alpha-gal and the availability of new ImmunoCAP™ Allergen Components such as Ara h 6. Beyond

the new science, the content in this new version of Go Molecular has been aimed to provide improved diagnostic explanations in the form of tables, with concise clinical interpretation comments. Also new is a section on aero-allergen components, an introduction to micro-array, as well as new information on diagnostic gaps regarding certain food components.

If you need further supporting information relating to molecular allergy then I can recommend visiting our webpage:

**[allergyai.com](http://allergyai.com)**.

## **Neal Bradshaw**

Portfolio Manager - Allergy  
Thermo Fisher Scientific

### **Disclaimer:**

The content of this book is intended as an aid to the physician to interpret allergen specific IgE antibody test results. It is not intended as medical advice on an individual level. A definitive clinical diagnosis of IgE mediated allergic disorders should only be made by the physician based on the clinical history for the individual patient after all clinical and laboratory findings have been evaluated. It should not be based on the results of any single diagnostic method. Further information about molecular allergy and our testing portfolio can be found at: [allergyai.com](http://allergyai.com).

# Contents

Foreword	4	Pollen – Trees	50
Introduction	5	Birch 50-51, Other trees 51, Olive/European Ash 51, London plane tree 52, Cypress 52	
What's in this guidebook?	8	Pollen – Weeds	54
Allergen Components from plant sources	10	Common Ragweed, Wall Peillitory, English plantain, Mugwort, Saltwort 54-56	
Food allergens components in some common foods	12	Molds	56
Food allergens from plant sources	14	<i>Alternaria alternata</i> 56-57, <i>Aspergillus fumigatus</i> 58-59	
Peanut 14-15, Soybean 16-17, Hazelnut 18-19, Walnut 20-21, Cashew 22-23, Brazil nut 24-25, Fruits and <i>Rosaceae</i> family 26-27, Wheat 28-29		Venoms	60
Food allergens from animal sources	30	Honey bee, Common Wasp/Yellow Jacket, Paper Wasp 60-62	
Hen's egg 30-31, Cow's milk 32-33, Red meat - Galactose-alpha-1, 3-Galactose (alpha-gal) 34-35		Occupational allergens	62
Shellfish and crustaceans	36	Latex 62-63	
Shrimp 36-37		Introduction to Allergen Micro Array	64
Fish allergens	38	ImmunoCAP ISAC 112	
Cod, Carp 38-39		Facts on ImmunoCAP ISAC 112	65
Inhalant allergen components	39	Advantages of ImmunoCAP ISAC 112	
Furry Animals	40	Recommended further educational resources	68
Cat 41-42, Dog 42-43, Horse 44-45		ImmunoCAP Allergen Components list	70
House dust mites	46	ImmunoCAP ISAC 112 Allergen Components	74
Pollen – Grasses	48		
Bermuda grass, Timothy grass 48-49			

# Foreword

With the advent of allergen components, allergy has got much more complicated. However whole allergen diagnostics, with skin prick testing or serum specific IgE, commonly don't allow us to unravel the complexity that some of our allergy patients exhibit. Using allergen components to understand the molecular allergology of these complex patients has a real potential to improve our clinical decision-making. The use of component resolved diagnostics may optimise our investigation plans and improve our diagnoses, management plans and the advice we give to our allergy patients. All this though relies on clinicians acquiring an understanding of molecular diagnostics. This is a rapidly evolving

area with, for example, the whole peanut allergen suddenly been replaced by more than 10 individual components with different clinical impacts. The second edition of this book is very welcome with its updated information about each of the various allergen components. Importantly, their clinical implications are explained allowing us to use information about allergic sensitisation to each individual component to improve the management of our patients.

**Professor Graham Roberts**

Professor of Paediatric Allergy and  
Respiratory Medicine  
University of Southampton

# Introduction

Since the last version of this book testing with allergen components has become a more standard diagnostic tool, providing an essential part of an allergy diagnosis work-up. Molecular allergology has refined the way that clinicians tailor their approach to patient management by redefining the patient diagnostic journey. Allergen components have made understanding allergy more scientific, moving towards precision medicine. This helps improve the understanding of a patient's true clinical reactivity, as well as making decisions to improve their quality of life.

Tests incorporating allergen components are defined entities, in that you know exactly what allergen protein you have in the test. Sometimes allergen component protein is present in a higher amount in an allergen component test when compared to a corresponding extract based test. This can make allergen component tests analytically even more sensitive and specific at measuring important IgEs of interest.

By using tests with allergen components you add another tool to the diagnostic armoury, which may make it possible to understand more about the underlying allergies. Allergen component tests are not diagnostic magic bullets;

rather they are an enhancement over conventional extract tests, giving more factual information. The results have to be interpreted like any other specific IgE test and cannot be solely relied upon to determine a diagnosis; results should always be used in conjunction with an allergy-focused clinical history and physical examination and the diagnosis is then made by the physician.

Testing with allergen components helps in:

1. Understanding patient risk – adding confidence to your assessment<sup>1-5</sup>
2. Aiding in the selection of the proper treatment extract of Allergen Specific Immunotherapy (AIT) – useful for example in venom and aero-allergy patient selection<sup>1-5</sup>
3. Understanding cross-reactions between species – helping to understand multiple sensitizations e.g. in pollen food syndrome<sup>1-5</sup>

Many ImmunoCAP Allergen Components are available in our product range and familiarity with them is essential to understand their clinical implications. To help you implement testing with allergen components more supporting information on molecular allergy is available at:

**[allergyai.com](http://allergyai.com)**.

The allergen component tests themselves are not technically different to other specific IgE tests that are routinely ordered from your lab such as milk, egg, cat or peanut allergens. Extracts like these are made up of lots of different allergen components. Allergen component tests differ as each test involves measuring specific IgE to pure single recombinant or native allergen proteins from a source. For example Pru p 3 is an nsLTP (non-specific lipid transfer protein) from peach. Antibodies produced by patients in response to specific allergen proteins can be measured using ImmunoCAP single (ImmunoCAP Allergen Component) or multiplex (ImmunoCAP ISAC 112) component tests. Both platforms therefore can be used to give an overview of the patients immunological response in their current allergy status.

Presence of allergen specific IgE implies a risk of allergic disease and its significance must be evaluated within the clinical context. Generally the higher the level of IgE antibodies the higher the probability of a clinically manifest allergic reaction<sup>1-5</sup>.

However for different patients identical results for the same allergens may not be associated with clinically equivalent manifestations, due to differences in individual patient sensitivities. This may also be true for one individual patient at different occasions due to presence or absence of reaction promoting cofactors<sup>1-5</sup>.

Absence of detectable allergen specific IgE antibodies does not necessarily exclude the potential for an allergy-like reaction<sup>1-2</sup>. For example in food allergy, circulating IgE antibodies may remain undetectable despite a convincing clinical history. The antibodies may be directed towards allergens that are revealed or altered during industrial processing, cooking or digestion and therefore do not exist in the original food for which the patient is tested<sup>1-2</sup>.

#### *Limitations of ImmunoCAP products test results:*

Samples with results below limit of quantitation obtained with ImmunoCAP Allergen Components are recommended to be tested with the corresponding extract based ImmunoCAP Allergen and/or additional relevant ImmunoCAP Allergen Components, if not already performed and a clinical indication is present. The extract based testing can cover additional allergen components present in the allergen source material to which the patient may be sensitized, but which are not presently available as ImmunoCAP Allergen Components or on ImmunoCAP ISAC 112.

A result below limit of quantitation obtained with an extract based ImmunoCAP Allergen never excludes the possibility of obtaining measurable concentrations of specific IgE when testing with ImmunoCAP Allergen Components from the same allergen source. This is due to the fact that some components may be present in very low amounts in the natural extract.

**In most cases it is recommended that testing starts with whole allergens to achieve high sensitivity to be followed up with allergen components for further specificity, and as an aid in risk assessment if the whole allergen test for specific IgE is positive<sup>1-5</sup>.**

**There is more information found in book 1 of this series or on the Thermo Fisher Scientific molecular allergy course: [allergyai.com](http://allergyai.com)**

#### References

1. Matricardi PM et al. EAACI Molecular Allergology User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23:1-250.
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# What's in this guide book?

The purpose of this guide is to offer an 'all in one' reference to each allergen source and its components in a single practical booklet. Molecular allergology involves many different allergen proteins and it can be difficult to remember them all and what the results mean. It is also difficult to remember all the relevant allergen codes, allergen nomenclature, what tests are helpful to make a risk assessment and what is actually available in the product range. I hope this booklet addresses these issues to make life a little easier!

## **Description, Latin name and allergen nomenclature**

Each section of the booklet describes a different allergen source and a little background. A comprehensive list of all of whole allergens, allergen components and an aid to clinical interpretation of the main components can be found at: **[allergyai.com](http://allergyai.com)**.

## **Major and minor allergen components**

You will often find references and descriptions for major and minor allergens. Major allergen components are defined as allergens that account for over 50% of sensitization within an allergic population<sup>1-2</sup>. This may differ in different geographical regions due to different exposures to allergens. Minor allergens are often less prevalent in triggering

allergy (these are often panallergens which are more likely to cross-react with homologous allergens). For instance in birch pollen allergy the major allergen is Bet v 1 (PR-10-pathogenesis related family number 10), whilst a minor allergen is Bet v 2 (profilin)<sup>1-2</sup>.

## **ImmunoCAP IgE test products available and new product updates**

Thermo Fisher Scientific supplies many existing and often new clinically relevant allergen components. Products available at the time of going to press are listed in each section. If you are interested in the latest updates and product releases register by contacting us at: **[allergyai.com](http://allergyai.com)**.

Most of the information given in this guide is for single ImmunoCAP Allergen Components but is of course also valid for components on the multiplex product ImmunoCAP ISAC 112 and may also be informative for whole extract allergens. The allergen code is also provided which can be useful when ordering from a testing laboratory. Whole allergens are still a useful sensitization guide and offer value by covering components from the allergen source not yet available as pure component tests. For example, we currently have six allergen components for peanut but over 15 have been described. We provide the most scientifically documented,

clinically relevant component tests where possible. A common practice is to request testing for the whole allergen and ask the laboratory to reflex test for related components if the whole allergen is positive – a good use of time and resources.

### **Interpretation of results**

In this guide, interpretation has been simplified as much as possible using a table format. The presence of allergen-specific IgE is a risk factor for allergy symptoms and a result higher than  $0.1 \text{ kU}_A / \text{L}$  indicates sensitization. Traditionally the higher the IgE antibody level the greater the likelihood of being symptomatic allergic. Some allergen components are associated with a much higher risk for severe symptoms, whilst some allergens are considered giving no or very low risk. A high-titre, high-risk allergen such as Ara h 2 or Cor a 14 would often carry a high risk for patients to suffer from severe symptoms. However for different patients identical results for the same allergens may not be associated with clinically equivalent manifestations, due to differences in individual patient sensitivities. This may also be true for one individual patient at different occasions due to presence or absence of reaction promoting cofactors<sup>1-2</sup>.

**Always consider test results in association with the clinical history for the individual patient.**

### **References**

References are inserted after each section.

A comprehensive overview of molecular allergology covering the introduction part is provided in:

1. Matricardi PM et al. EAACI Molecular Allergology User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23: 1-250.
2. Kleine-Tebbe J and Jakob T Editors: Molecular Allergy Diagnostics. Innovation for a Better Patient Management. Springer International Publishing Switzerland 2017. ISBN 978-3-319-42498-9 ISBN 978-3-319-42499-6 (eBook), DOI 10.1007/978-3-319-42499-6.

# Allergen components from plant sources

Plant protein families are shared between species; the closer the species are related botanically the more similar the proteins are likely to be. This increases the potential for IgE antibodies directed against pollen allergen epitopes to bind to similar allergen epitopes in food. There

are five main types of allergen groups indicated in the table below. These are Storage proteins, LTP, PR-10 and Profilin which are all proteins, and CCDs which are cross-reactive carbohydrate determinants:

Protein family	Risk for systemic reactions?	Do I have to consider many different allergen sources?
● <b>Storage proteins</b>	<b>High.</b> Storage proteins are heat and digestion stable which explains their ability to more often cause systemic reaction in addition to oral allergy syndrome (OAS).	<b>No.</b> Storage proteins are not cross-reactive, except for very closely related allergen sources (e.g. between legumes such as soy and peanut).
● <b>LTP</b>	<b>Moderate to High.</b> LTPs are heat and digestion stable which explains their ability to more often cause systemic reaction in addition to OAS.	<b>Yes.</b> Partly cross-reactive (the degree of structural similarity varies between LTPs in plant food and pollen).
● <b>PR-10</b>	<b>Low.</b> Often cause only local symptoms such as OAS due to their sensitivity to heat and digestion, but a few cases with systemic reactions have been reported e.g. for soy Gly m 4 and Celery Api g 1.	<b>Yes.</b> Cross-reactive (the degree of structural similarity varies between PR-10 in plant food and birch-related pollen).
● <b>Profilin</b>	<b>Low.</b> Often have little clinical relevance in allergic diseases. However, profilins may cause local reactions in some patients allergic to plant foods including citrus fruits, banana and tomato, and a few cases with systemic reactions have been reported e.g. for melon and lychee.	<b>Yes.</b> Highly cross-reactive (high degree of structural similarity between profilins in pollen, plant food and latex).
● <b>CCD</b>	<b>Very low.</b> Usually not associated with clinical reactions but may induce IgE antibody responses in some patients.	<b>Yes.</b> Highly cross-reactive (same CCD structure in pollen, plant food and venoms).

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# Plant allergen components in some common foods

Allergen source/ Component family	Storage proteins						
	Profilin	PR-10	LTP	2S Albumin	Vicilin-like 7S globulin	Legumin-like 11 S globulin	Other
Peanut	Ara h 5	<b>Ara h 8</b>	<b>Ara h 9, 16, 17</b>	<b>Ara h 2, 6, 7</b>	<b>Ara h 1</b>	<b>Ara h 3</b>	Ara h 10-15
Soy	Gly m 3	<b>Gly m 4</b>		Gly m 8	<b>Gly m 5</b>	<b>Gly m 6</b>	Gly m 7
Hazelnut	Cor a 2	<b>Cor a 1</b>	<b>Cor a 8</b>	<b>Cor a 14</b>	Cor a 11	<b>Cor a 9</b>	
Walnut	Jug r 7	Jug r 5	<b>Jug r 3, 8</b>	<b>Jug r 1</b>	<b>Jug r 2, 6</b>	Jug r 4	
Pecan				Car i 1	Car i 2	Car i 4	
Cashew				<b>Ana o 3</b>	Ana o 1	<b>Ana o 2</b>	
Pistachio				Pls v 1	Pls v 3	Pls v 2, 5	Pls v 4
Brazil nut				<b>Ber e 1</b>		Ber e 2	
Sesame				<b>Ses i 1, 2</b>	Ses i 3	Ses i 6, 7	Ses i 4, 5
Sunflower seed	Hel a 2		Hel a 3	Hel a 2 S Albumin			
Rape seed	<i>Bra n 8</i>			Bra n 1			<i>Bra n 4, 7</i>
Cabbage	<i>Bra o 8</i>		Bra o 3				
Mustard	Sin a 4		Sin a 3	Sin a 1		Sin a 2	
Buckwheat				<b>Fag e 2</b>	Fag e 3		Fag e 4
Kiwi	Act d 9	<b>Act d 8, 11</b>	Act d 10	Act d 13		Act d 12	<b>Act d 1, 2, 5</b>
Melon	Cuc m 2	Cuc m 3					Cuc m 1
Tomato	Sola l 1	Sola l 4	Sola l 3, 6, 7				Sola l 2, 5
Apple	Mal d 4	<b>Mal d 1</b>	<b>Mal d 3</b>				Mal d 2
Pear	Pyr c 4	Pyr c 1	Pyr c 3				Pyr c 5
Almond	Pru du 4	Pru du 1	Pru du 3			Pru du 6	Pru du 5
Peach	<b>Pru p 4</b>	<b>Pru p 1</b>	<b>Pru p 3</b>				Pru p 2, 7
Apricot		Pru ar 1	Pru ar 3				
Plum	<i>Pru d 4</i>	<i>Pru d 1</i>	Pru d 3				Pru d 2, 7
Cherry	Pru av 4	Pru av 1	Pru av 3				Pru av 2

**Bold** Available as single ImmunoCAP Allergen Component

**Bold** Available on ImmunoCAP ISAC only

*Normal* WHO/IUIS listed

*Italic* Described in peer reviewed literature

*Likely but not yet described*

Allergen source/ Component family	Storage proteins						
	Profilin	PR-10	LTP	2S Albumin	Vicilin-like 7S globulin	Legumin-like 11 S globulin	Other
Strawberry	Fra a 4	Fra a 1	Fra a 3				
Raspberry		Rub i 1	Rub i 3				
Carrot	Dau c 4	Dau c 1	<i>Dau c 3</i>				Dau c 5
Celery	Api g 4	<b>Api g 1</b>	Api g 2, 6				Api g 3, 5
Wheat	Tri a 12		<b>Tri a 14</b>				<b>Tri a 19, Gliadin, many more</b>
Barley	Hor v 12						Hor v 15-17, 20
Rice	Ory s 12						
Maize	Zea m 12		Zea m 14				Zea m 8

**Plants often driving sensitization**

Birch	<b>Bet v 2</b>	<b>Bet v 1</b>					
Timothy	<b>Phl p 12</b>						
Latex	<b>Hev b 8</b>		Hev b 12				<b>Hev b 5, 6, 11</b>

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1. Matricardi PM et al. EAACI Molecular Allergy User's Guide. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2016;27 Suppl 23:1-250.
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# Food allergens from plant sources

## Peanut

### ***Arachis hypogaea* (Ara h)**

Peanut allergy is of great interest and has increased in prevalence over the last few decades. Peanut is a problematic allergen source that is consumed in many different forms such as peanut butter, as snacks, in confectionery and in baked goods. Peanuts also yield cooking oils (both refined and crude, aromatic and non-aromatic) which may contain trace amount of allergens.

It is commonly accepted that Ara h 1, Ara h 2, Ara h 3 and Ara h 6 are major peanut allergens<sup>1-4</sup>. These allergens are heat stable and resistant to gastric acid fluid degradation. 2S albumin proteins such as Ara h 2 and Ara h 6 are considered to be the most important peanut allergens but IgE also to Ara h 1 and/or Ara h 3 increases risk of severe symptoms<sup>1-5</sup>. Ara h 2 and Ara h 6 allergen components provide the most accurate peanut test in terms of predictive value in the aid of diagnosis<sup>1,4,6-12</sup>. A minority of patients are mono-sensitised to Ara h 6 and not positive to Ara h 2; a combination of the two seems to provide the optimal performance<sup>10,12</sup>.

IgE antibodies in birch pollen allergy patients sensitised to Bet v 1 (PR-10) or Bet v 2 (profilin) can cross-react with Ara h 8 (PR-10) or Ara h 5 (profilin) in peanut respectively<sup>13-14</sup>. IgE to timothy grass profilin (Phl p 12) can also cross-react with peanut profilin Ara h 5<sup>13-14</sup>.

### **Available ImmunoCAP Allergen Products**

Peanut – Whole allergen – f13

Component		Code
rAra h 1	7S globulin, storage protein	f422
rAra h 2	2S albumin, storage protein	f423
rAra h 3	11S globulin, storage protein	f424
rAra h 6	2S albumin, storage protein	f447
rAra h 8	PR-10 protein	f352
rAra h 9	nsLTP	f427

### **Clinical relevance**

Understanding risk and cross-reactions.

## Interpreting the results

f13	Ara h 1	Ara h 2	Ara h 3	Ara h 6	Ara h 8	Ara h 9	Interpretation
+/-	+						Indicates a primary peanut allergy. The patient is at high risk of severe, systemic symptoms, especially if Ara h 2 or Ara h 6 are positive. <sup>1-14</sup>
+/-		+					
+/-			+				
+/-				+			
+/-					+		The patient is at risk for local reactions, however, the probability of severe, systemic reactions is low. <sup>13-14</sup>
+/-						+	IgE to nsLTP is a risk marker of both systemic and local reactions. The patient may be reacting to other nsLTPs due to cross- reactions which can cause systemic symptoms to both cooked and uncooked foods. <sup>13-14</sup>

For other sources of common plant allergen cross-reactions also consider CCD and profilins.

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## Soybean

### **Glycine max (Gly m)**

Soy is widely used worldwide because it is cheap to produce and because of its high biological value and high quality protein content. It is used as soy protein flour, flakes, concentrates and isolates as well as soy oil. It can be a hidden allergen in processed foods such as meat products, sausages, bakery goods, chocolate and breakfast cereals<sup>1-2</sup>.

The presence of specific IgE to Gly m 5 and Gly m 6 may indicate primary soy allergy and risk of severe systemic reactions<sup>3,4</sup>. Gly m 8, a 2S Albumin, has recently been reported to be an important marker of soy allergy<sup>5-7</sup>. Since 2002 soy allergic reactions have increasingly been linked to birch pollen sensitized individuals<sup>8</sup>. Gly m 4 (PR-10) is labile to heat, processing and digestion and consumption of processed soy usually causes no or only mild symptoms in Gly m 4 sensitised patients. However, with unprocessed soy in drinks (soy milk) and dietary protein powders (e.g. such as those sold in gyms) it is actually possible

to ingest a large amount of Gly m 4 at one time. Since these products contain high quantities of Gly m 4 this can lead to a risk for severe systemic reactions due to high allergen load, especially in pollen-allergic patients during pollen season when there is simultaneous exposure to birch pollen, which contains a cross-reactive PR-10 protein (Bet v 1)<sup>7,9</sup>. Gly m 4 content can be very low in extract- based tests. Therefore the use of allergen component tests for Gly m 4 is recommended as supplement to whole allergen testing<sup>9</sup>.

### **Available ImmunoCAP Allergen Products**

Soybean – Whole allergen – f14

Component		Code
rGly m 4	PR-10 protein	f353
nGly m 5	β-conglycinin, storage protein	f431
nGly m 6	glycinin, storage protein	f432

### **Clinical relevance**

Understanding risk and cross-reactions.

## Interpreting the results

f14	Gly m 4	Gly m 5	Gly m 6	Interpretation
+/-	+			A high allergen load of PR-10 can result in systemic symptoms. Consider checking how much consumption of soy has occurred (the allergen load) especially if the patient is Bet v 1 positive. For example does the patient regularly drink soya milk, perhaps in the pollen season? <sup>7-10</sup>
+/-		+		Indicates a primary soy allergy. The patient is at risk of severe, systemic symptoms <sup>3-4,8,10</sup>
+/-			+	

For other sources of common plant allergen cross-reactions also consider CCD and profilins.

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## Hazelnut

### ***Corylus avellana* (Cor a)**

Hazelnut is widely used and can be a “hidden” allergen; for example as an ingredient in confectionery such as chocolate or nougat. Allergic reactions to hazelnuts range from OAS to severe anaphylactic reactions<sup>1-2</sup>.

Cor a 9 and Cor a 14 are both storage proteins which are resistant to digestion and have been demonstrated in clinical studies to be major allergens which cause systemic symptoms<sup>3-9</sup>. Presence of specific IgE antibodies to Cor a 8 (nsLTP) is also an indication of severe reactions in patients with a suspected allergy to hazelnut, although nsLTP allergy in northern European countries is less common compared to southern Europe<sup>10</sup>. In geographical areas in which birch is endemic (including the UK), hazelnut allergy has been mainly associated with cross-reactive IgE to Birch, Bet v 1 (PR-10) and Bet v 2 (profilin), which usually causes mild symptoms<sup>11-14</sup>.

### Available ImmunoCAP Allergen Products

Hazelnut – Whole allergen – f17

Component		Code
rCor a 1	PR-10	f428
rCor a 8	nsLTP	f425
nCor a 9	11S globulin, storage protein	f440
Cor a 14	2S albumin, storage protein	f439

### Clinical relevance

Understanding risk and cross-reactions.

## Interpreting the results

f17	Cor a 1	Cor a 8	Cor a 9	Cor a 14	Interpretation
+/-	+				Probability is low for systemic reactions and local symptoms such as OAS are more likely. The patient may be reacting to other PR-10-containing pollens and plant foods due to cross-reactions <sup>11-16</sup>
+/-		+			Mixed allergy is possible, including systemic and local symptoms such as OAS. The patient may be reacting to other nsLTPs contained in other plant foods/pollens due to cross-reactions. This can cause systemic symptoms to both cooked and uncooked foods <sup>10,15-16</sup>
+/-			+		Primary hazelnut allergy, the patient is at high risk of severe, systemic allergy <sup>3-9,15-16</sup>
+/-				+	

For other sources of common plant allergen cross-reactions also consider CCD and profilins.

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## Walnut

### *Corylus avellana* (Cor a)

Walnut is botanically closely related to pecan. Walnuts are often eaten as an ingredient in baked goods and as additive in other dishes e.g. meat, poultry, fish and pasta as well as in salads and ice cream. Walnut oil can be allergenic, although this depends on the extraction method and the purity of the end product<sup>1</sup>.

Jug r 1, a 2S albumin storage protein that is resistant to digestion, has been associated with primary walnut allergy and systemic symptoms<sup>2-4</sup>. Presence of specific IgE antibodies to Jug r 3, an nsLTP, indicates that local symptoms as well as systemic reactions can occur<sup>5-7</sup>. The walnut component Jug r 2, a vicilin-like storage protein, is available on ImmunoCAP ISAC 112.

### Available ImmunoCAP Allergen Products

Walnut – Whole allergen – f256

Component		Code
rJug r 1	2S albumin, storage protein	f441
rJug r 3	nsLTP	f442

### Clinical relevance

Understanding risk and cross-reactions.

## Interpreting the results

f256	Jug r 1	Jug r 3	Interpretation
+/-	+		Primary walnut allergy, the patient is at high risk of severe, systemic allergy <sup>2-4,8-11</sup>
+/-		+	Mixed allergy is possible, including systemic and local symptoms such as OAS. The patient may be sensitized to other nsLTGs contained in other plant foods/pollens due to cross-reactions which can cause systemic symptoms in cooked and uncooked foods <sup>5-7,10-11</sup>

*\*Walnut/Pecan share a high homology between proteins and the two allergens are highly cross reactive<sup>2-3,8-9</sup>. Patients sensitised to pecan nuts are very likely to also be IgE-reactive to walnut and vice versa. Jug r 1 and Jug r 3 are therefore risk markers for both pecan and walnut allergy.*

*For other sources of common plant allergen cross-reactions also consider CCD and profilins.*

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## Cashew

### ***Anacardium occidentale* (Ana o)**

The cashew nut comes from the cashew nut tree, a member of the *Anacardiaceae* family, and is botanically closely related to pistachio. Cashew nut is commonly used as a thickening agent in soups, meats and stews and particularly features in Indian cuisine.

Three storage proteins have been identified so far: Ana o 1, Ana o 2 and Ana o 3 (no nsLTP identified yet). Ana o 3 is a 2S albumin storage protein and is described as a primary cashew nut allergen associated with severe symptoms<sup>1-4</sup>. Significant cross-reactivity has been reported between pistachio nut and cashew nut<sup>3,5-9</sup>. Ana o 3 therefore can act as a risk marker for severe reactions also for pistachio.

The Rutaceae family (e.g. lemon, tangerine, orange) is closely related to the *Anacardiaceae* family to which cashew belongs. Cross-reactions of cashew-allergic individuals reacting to lemon and orange seeds hidden in juices and dressings have been described<sup>10-11</sup>. The cashew component Ana o 2, a vicilin-like storage protein, is available on ImmunoCAP ISAC 112.

### **Available ImmunoCAP Allergen Products**

Cashew – Whole allergen – f202

Component		Code
rAna o 3	2S albumin, storage protein	f443

### **Clinical relevance**

Understanding risk and cross-reactions.

## Interpreting the results

f202	Ana o 3	Interpretation
+/-	+	Primary sensitization to cashew nut. The patient is at high risk of severe, systemic symptoms <sup>1-4,12-13</sup>

*\*Cashew and pistachio are closely botanically related and show extensive cross reactivity also between storage proteins. Patients sensitised to cashew Ana o 3 are most likely also reacting with symptoms to pistachio nuts<sup>3,5-9</sup>.*

*For other sources of common plant allergen cross-reactions also consider CCD and profilins.*

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## Brazil nut

### ***Bertholletia excelsa* (Ber e)**

Prevalence of Brazil nut allergy is becoming more common<sup>1</sup> and is associated with severe reactions<sup>2-5</sup>. A number of allergenic proteins has been isolated from Brazil nut. Like other tree nuts and seeds, Brazil nut contains storage proteins. Ber e 1 is a 2S albumin protein and a major allergen<sup>1,10</sup>. The 2S albumin group has been described extensively in many other legumes and tree nuts such as peanut (Ara h 2) and hazelnut (Cor a 14)<sup>6</sup>.

Ber e 1, 2S albumin in Brazil nut has been found to be largely intact following gastric digestion<sup>7,10</sup>. High stability is a hallmark for allergens able to provoke a systemic allergic reaction in sensitized

individuals<sup>8-9</sup>. A small UK study in 2015 identified rBer e 1 as an improvement in clinical test performance versus the whole allergen Brazil nut extract<sup>1</sup>. A further Brazil nut storage protein allergen, Ber e 2, an 11S globulin-like protein has also been identified.

### **Available ImmunoCAP Allergen Products**

Brazil nut – Whole allergen – f18

Component		Code
rBer e 1	2S albumin, storage protein	f354

### **Clinical relevance**

Understanding primary Brazil nut allergy.

## Interpreting the results

f18	rBer e 1	Interpretation
+/-	+	Major allergen. Primary sensitization to Brazil nut. The patient is at high risk of severe, systemic symptoms <sup>1-7,11</sup>

*For other sources of common plant allergen cross-reactions also consider CCD and profilins.*

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## Fruits and Rosaceae Family

Fruit allergen sources are quite widespread but many fruit allergies are caused by members of the *Rosaceae* family and often are initiated by a primary sensitization to pollen<sup>1</sup>. LTPs are major allergen components in fruit and have often been considered to be more associated with Southern European regions<sup>1</sup>, although recent studies have identified LTP allergy also in Central<sup>2</sup> and Northern Europe<sup>2-3</sup>. Due to high structural homology, Pru p 3 (nsLTP) can be a useful general marker for *Rosaceae* allergy<sup>1</sup> and is associated with systemic symptoms as well as oral allergy<sup>4</sup>. Furthermore patients sensitized to more than five LTPs often have a higher prevalence of food-induced systemic symptoms<sup>5</sup>. LTP levels are concentrated in the skin/fuzz and outer layers of fruits and by removing the peel exposure to the allergen can be reduced<sup>1</sup>. Patients sensitized to nsLTP without concomitant sensitization to profilin or PR-10's are prone to suffer from more severe symptoms<sup>5-6</sup>. Pru p 7 is another stable peach allergen that has been identified to cause severe symptoms<sup>7-10</sup>.

Pru p 1 (PR-10) is found in skin and pulp and mainly give local Oral Allergy Syndrome<sup>1</sup>. PR-10s cross-react extensively with Bet v 1 homologues in other fruits and also to a lower degree, PR-10 proteins in legumes such as soy and peanut, and vegetables such as celery and carrot<sup>1</sup>.

### Available ImmunoCAP Allergen Products

Stone Fruit Whole allergen – e.g. Apple (f49), Apricot (f237), Peach (f95), Pear (f94), Plum (f255), Almond (f20), Raspberry (f343), Strawberry (f44)

Component		Code
rPru p 1	PR-10	f419
rPru p 3	nsLTP	f420
rPru p 4	Profilin	f421
rMal d 1	PR-10	f434
rMal d 3	nsLTP	f435

### Clinical relevance

Understanding risk and cross-reactions.

## Interpreting the results

Stone fruit allergen	Pru p 1/Mal d 1	Pru p 3/Mal d 3	Pru p 4	Interpretation
+/-	+			Probability is low for systemic reactions and local symptoms such as OAS are more likely. The patient may be sensitised and reacting to other PR-10-containing pollens and plant foods due to cross-reactions <sup>1,4,11</sup>
+/-		+		Mixed allergy is possible, including systemic and local symptoms such as OAS. The patient may be sensitized and reacting to other nsLTPs contained in other plant foods/pollens due to cross-reactions which can cause systemic symptoms to both cooked and uncooked foods <sup>1,3-6,11</sup>
+/-			+	Low probability for severe reactions, highly cross-reactive. Positive results can explain broad sensitizations to other plant allergens that contain profilin, including latex, banana, tomato, potato, avocado, timothy grass, peanut etc <sup>1,11</sup>

For other sources of common plant allergen cross-reactions also consider CCD.

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## Wheat

### *Triticum aestivum* (Tri a)

Wheat is one of the five most common foods that trigger allergic reactions in children. In Germany, Japan, and Finland it has been reported as the third most common allergen, after milk and egg<sup>1</sup>. The WHO IUIS allergen list now includes 27 wheat allergens<sup>1</sup>.

Wheat contains several allergens such as profilin and CCD, which causes wheat extract tests to be positive due to cross-reactions<sup>2</sup>. As wheat is a grass, it cross-reacts with grass pollen<sup>3-4</sup>, and with other cereals since many also belong to the grass family<sup>3-5</sup>. Most wheat allergic patients have IgE antibodies to multiple components<sup>5</sup>.

Gliadins are non-water soluble proteins but are readily dissolved by stomach acid and are considered as true food allergens. IgE antibodies to gliadin (containing a mix of  $\alpha$ ,  $\gamma$ ,  $\beta$  and  $\omega$  gliadins), Tri a 19 ( $\omega$ -5 gliadin) or Tri a

14 (nsLTP), are associated with allergic reactions to ingested wheat<sup>6-17</sup>. The wheat proteins,  $\alpha$ ,  $\gamma$ ,  $\beta$  and  $\omega$  gliadins (especially  $\omega$ -5 gliadin) have also been reported as major allergens in Wheat - Dependent Exercise-Induced Anaphylaxis (WDEIA)<sup>7-13</sup>. Moreover,  $\omega$ -5 gliadin has been shown to be a specific risk marker in children with immediate allergy to ingested wheat<sup>14-17</sup>.

### Available ImmunoCAP Allergen Products

Wheat – Whole allergen – f4

Component		Code
Gliadin	mix of $\alpha$ , $\gamma$ , $\beta$ and $\omega$ gliadins	f98
rTri a 19	$\omega$ -5 gliadin	f416
rTri a 14	nsLTP	f433

### Clinical relevance

Increasing diagnostic specificity, understanding patient risk, indicators of immediate wheat allergy and of wheat-dependent exercise-induced anaphylaxis (WDEIA).

### Interpreting the results

f4	f98 gliadin	Tri a 14	Tri a 19	Interpretation
+/-	+			Indicates immediate wheat food allergy with the patient at high risk of severe, systemic reactions and of WDEIA <sup>3,8-18</sup>
+/-		+		Systemic and local symptoms such as OAS are possible. The patient may be sensitised to other nsLTPs contained in other plant foods/pollens due to cross-reactions which can cause systemic symptoms to both cooked and uncooked foods <sup>3,18</sup>
+/-			+	$\omega$ -5 gliadin* (omega-5) gives even higher specificity than gliadin f98 and is associated with immediate wheat allergy and WDEIA <sup>3,8-18</sup>

\* $\omega$ -5 gliadin has a natural limited presence on the ImmunoCAP Allergen f4, wheat and some wheat allergic patients, especially WDEIA patients, are negative to the f4-test but positive to  $\omega$ -5 gliadin

*For other sources of common plant allergen cross-reactions also consider CCD and profilins.*

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# Food allergens from animal sources

## Hen's egg

### ***Gallus domesticus* (Gal d)**

Hen's egg allergy affects up to 2.5% of young children and is potentially life-threatening<sup>1</sup>. Ovomuroid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin/conalbumin (Gal d 3) and lysozyme (Gal d 4) have been identified as the most important allergens in egg white<sup>2-3</sup>. The use of egg white components is clinically helpful for a fine tuned approach to diagnosis of egg allergy<sup>3</sup>. In particular to help answer the following questions: a) Distinguishing between sensitization and clinical allergy; b) allergy to raw or partially cooked eggs c) allergy to all forms of egg (raw and cooked)<sup>3</sup>. Ovomuroid (Gal d 1) has been identified to be the major egg allergen, making up 10% of the egg white protein. Gal d 1 has several important characteristics which makes it more allergenic, such as its stability to cooking and digestion by proteases. Patients with elevated IgE to ovomucoid are at risk for allergic reactions to both raw and cooked egg products<sup>3-8</sup>. Specific IgE to Gal d 1 is also a risk factor for persistent hen's egg allergy<sup>3,9-11</sup>. Over time, egg tolerance is associated with a decrease in IgE to egg white and to ovomucoid<sup>12</sup>. In a recent Danish longitudinal study all positive re-challenge cases correlated with an increase in IgE to ovomucoid<sup>12</sup>.

Egg yolk also contains specific allergens such as Livetin/Chicken Serum Albumin (Gal d 5) and YGP42 (Gal d 6)<sup>13-14</sup>. Egg yolk may be somewhat less allergenic than egg white<sup>15</sup> but sensitization to Gal d 5 in egg yolk is related to the bird/egg syndrome<sup>16</sup>. The allergen component Gal d 5 is available on ImmunoCAP ISAC 112.

### **Available ImmunoCAP Allergen Products**

Egg white – Whole allergen – f1

Egg yolk – Whole allergen – f75

Component	Code
nGal d 1 ovomucoid	f233
nGal d 2 ovalbumin	f232
nGal d 3 conalbumin	f323
nGal d 4 lysozyme	k208

### **Clinical relevance**

Clinically helpful for distinguishing between allergy to cooked and raw egg, or exclusively to raw egg.

## Interpreting the results

f1	Gal d 1	Gal d 2	Gal d 3	Gal d 4	Interpretation
+/-	+				High probability of a persistent egg allergy, patient is at high risk to react both to raw and cooked egg <sup>3-12,17</sup>
+/-		+			Indicates a risk to react to raw egg and a probability to have tolerance to extensively heated egg, especially if Gal d 1 is negative or at low levels <sup>3,7,11-12,17</sup>
+/-			+		
+/-				+	

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## Cow's milk

### ***Bos domesticus* (Bos d)**

Milk allergic individuals are often sensitized to more than one milk component and demonstrate varied sensitization profiles<sup>1</sup>. The major allergens in cow's milk are casein,  $\alpha$ -lactalbumin and  $\beta$ -lactoglobulin, although other allergens including Bovine Serum Albumin (BSA) and lactoferrin, are also important since 35-50% of patients are sensitized to these allergens<sup>2</sup>.

Casein makes up 80% of milk proteins and has been characterized to be thermo-stable<sup>3-4</sup> and resistant to digestion<sup>5</sup>. IgE to casein therefore indicates a risk of allergic reactions to all types of milk products including those that are cooked<sup>6-12</sup>. Milk components have shown to be useful in diagnosing tolerance to extensively heated milk proteins in baked foods. Children with cow's milk allergy (CMA) who have high levels of casein IgE are less likely to tolerate baked milk compared to children with low levels of casein IgE<sup>10-13</sup>. Children with persistent milk allergy have demonstrated to predominantly generate IgE antibodies towards casein<sup>12,14-16</sup>. Furthermore a broader allergen component diversity of IgE and IgG4 binding have been found in children with persistent CMA<sup>17</sup>.

A recent study showed patients with a specific type of gastrointestinal cow's milk allergy often have specific IgE against  $\beta$ -lactoglobulin, an important allergen in this particular disease<sup>18</sup>.

Bovine Serum Albumin (BSA) is a minor allergen in milk and a major allergen in beef, therefore milk allergic patients sensitised to Bos d 6 (BSA) may have concomitant beef allergy<sup>19-20</sup>. It has also been seen to cross-react with other serum albumins such as pork and sheep<sup>19-20</sup>.

### **Available ImmunoCAP Allergen Products**

Milk – Whole allergen – f2

Component		Code
nBos d 4	$\alpha$ -lactalbumin	f76
nBos d 5	$\beta$ -lactoglobulin	f77
nBos d 6	BSA	e204
nBos d 8	Casein	f78

### **Clinical relevance**

Milk allergy risk assessment, IgE to casein is an indicator for reactions to both raw and cooked milk products and for milk allergy persistence.

## Interpreting the results

f2	Bos d 4	Bos d 5	Bos d 6	Bos d 8	Interpretation
+/-	+				Indicates a risk to react to raw milk and a probability to have tolerance to cooked/baked milk, especially if Bos d 8 is negative or at low levels <sup>1,10-13,21</sup>
+/-		+			
+/-			+		
+/-				+	High probability of a persistent milk allergy, patient is at high risk to have reactions to both raw and cooked milk <sup>1,3-17,21</sup>

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## Red meat

### Galactose-alpha-1, 3-Galactose (alpha-gal)

Recently a previously unrecognized clinical syndrome has been reported where systemic reactions occur several (often 3-6) hours after the ingestion of mammalian red meat (beef, pork, lamb and offal, e.g. kidney). The most common symptoms include gastrointestinal problems, urticaria and anaphylaxis<sup>1-13</sup>. Co-factors, such as physical exercise or alcohol potentiate symptoms<sup>5,7-8</sup>.

A carbohydrate, the oligosaccharide Galactose-alpha-1, 3-Galactose (alpha-gal), appears to be the allergen causing the reactions<sup>1-6,10,14</sup>. Alpha-gal is present in many mammalian proteins including beef, pork and lamb<sup>7-9</sup>. Measuring specific IgE to alpha-gal is a tool that can be used to support the diagnosis of this type of red meat allergy, which seems to mainly be induced by sensitization by tick bites<sup>10-13</sup>, although alpha gal exposure has been reported via the monoclonal antibody cetuximab, which contains the  $\alpha$ -Gal epitope on its Fab fragment. Severe reactions to cetuximab infusions have been reported in patients with IgE to  $\alpha$ -Gal<sup>14</sup>.

Gelatin which is an ingredient in some candies and drugs also contains  $\alpha$ -Gal and  $\alpha$ -Gal related reactions due to gelatin have been reported<sup>15</sup>.

### Available ImmunoCAP Allergen Products

Beef – Whole allergen – f27

Pork – Whole allergen – f26

Mutton – Whole allergen – f88

Gelatin, bovine – Whole allergen – c74

Component		Code
nGal-alpha-1, 3-Gal (alpha- gal)	Thyroglobulin, bovine	o215

### Clinical relevance

Alpha-gal can be used as an aid to help confirm alpha-gal related red meat allergy.

## Interpreting the results

f27 beef	f26 pork	f88 mutton	c74 gelatin	o215 Alpha-Gal	Interpretation
+/-	+/-	+/-	+/-	+	Suspected cases of $\alpha$ -Gal related allergy is supported by a history of tick bites, delayed symptoms and IgE positivity to several red meats as well as IgE to $\alpha$ -Gal <sup>1-17</sup>

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## Shellfish and crustaceans

### Shrimp – *Penaeus aztecus* (Pen a)

Shellfish and particularly prawns make up one of the major allergen food groups<sup>1-2</sup>. Tropomyosin (Pen a 1, Pen m 1) is considered a major allergen in shrimp and crustacean allergy<sup>3</sup>. Arginine kinase (Pen m 2), myosin light chain and sarcoplasmic calcium binding protein (Pen m 4) have been identified as minor crustacean allergens<sup>4-7</sup>. Pen m 2 and Pen m 4 are available on ImmunoCAP ISAC 112.

60% of individuals with confirmed allergy to shellfish produce specific IgE which binds to tropomyosin<sup>8</sup>. Due to its widespread occurrence, tropomyosin can be both inhaled and ingested. Pen a 1 as well as Pen m 1 is heat stable, causing reactions both to raw and cooked shrimp<sup>9</sup>. Tropomyosin proteins (Pen a 1, Pen m 1), are highly cross-reactive amongst many invertebrate species such as shrimps other crustacean foods such as crab, lobster snail and molluscs as well as dust mites (Der p 10), cockroaches (Bla g 7) and helminths<sup>10</sup>.

Prevalence of dust mite-allergic patients with IgE to tropomyosin is reportedly between 5-18%<sup>6</sup>. Some studies suggested that dust mite immunotherapy

or respiratory exposure to dust mite tropomyosin may induce tropomyosin sensitization causing food allergy to shrimps<sup>11</sup>. Patients with IgE to Der p 10 may potentially have a higher probability of allergic reactions to shellfish (crustaceans and mollusc), insects and parasites<sup>11</sup>.

### Available ImmunoCAP Allergen Products

Shrimp – Whole allergen – f24

Crab – Whole allergen – f23

Blue mussel – Whole allergen – f37

Component		Code
rPen a 1	Tropomyosin	f351
rDer p 10	Tropomyosin	d205

### Clinical relevance

Risk markers, cross-reactive determinations. Specific IgE results to either Pen a 1 or Der p 10 would explain multiple positive results to different shellfish whole extracts.

## Interpreting the results

f24/ f23	Pen a 1	Der p 10	Interpretation
+/-	+		Probability to react to different tropomyosins and to crustacean foods in general – cross-reactions through tropomyosin can cause systemic symptoms <sup>3,8-12</sup>
+/-		+	Some patients sensitised to Der p 10 may react to crustacean tropomyosin such as Pen a 1 in shrimp. These patients are at higher probability of crustacean allergy <sup>6,8,10-12</sup>

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## Fish Allergens

### Cod – *Gadus callarius* (Gad c), Carp – *Cyprinus carpio* (Cyp c)

Increases in global fish consumption have led to rise in the reports of fish related allergy<sup>1</sup>. The route of exposure is not just restricted to ingestion but also manual handling and inhalation which are important factors for consideration in occupational exposure<sup>1</sup>.

Parvalbumins are major allergens in fish (and amphibians such as frogs)<sup>1-3</sup>. This protein allergen group causes a major clinical cross reactivity between fish species, resulting in over 90% of fish allergic patients reacting to almost all fish species<sup>1-4,7-8</sup>. Fish parvalbumin is a highly stable molecule<sup>8</sup> and is resistant to cooking and digestion. Recombinant carp parvalbumin (rCyp c 1) was found to contain 70% of the IgE epitopes present in natural extract of cod, tuna and salmon<sup>2</sup>. This suggested that carp

parvalbumin would make a valid tool in the diagnosis of patients with fish allergy<sup>2</sup>.

Parvalbumins are expressed in lower levels in certain fish species such as tuna, swordfish and some mackerels. This perhaps explains why some fish-allergic patients can tolerate these species<sup>1,6,9</sup>.

### Available ImmunoCAP Allergen Products

Fish whole allergen – e.g. Cod (f3)  
Haddock (f42), Salmon (f41), Mackerel (f206)

Component		Code
rGad c 1	Parvalbumin	f426
rCyp c 1	Parvalbumin	f355

### Clinical relevance

Understanding risk and cross-reactive determinations.

### Interpreting the results

f3	Gad c 1	Cyp c 1	Interpretation
+/-	+		Primary allergen in fish, high probability of allergy to cod and closely related fish (white fish but also other fishes) due to cross-reactions <sup>1-10</sup>
+/-		+	High probability of allergy to carp and closely related fish (oily fish) due to cross-reactions <sup>1-10</sup>

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# Inhalant allergen components

Inhalant sensitization to aeroallergens such as dust mite, animal dander and pollen can cause allergy in two ways. Initially causing primary allergy, often linked to respiratory symptoms. Furthermore pollen sensitized individuals also can suffer from secondary cross-reactions, which can result in local symptoms such as Pollen-Food Syndrome<sup>1</sup>.

Revealing the primary allergen source driving the allergy could help improve allergy management such as exposure reduction strategies<sup>2-3</sup> and be an aid to select the proper Allergen Specific Immunotherapy (AIT). AIT success is more likely if sensitization to specific

components is identified and appropriate therapy containing the right allergens administered<sup>4-6</sup>.

Immunotherapy vaccines vary in their composition of molecular allergens, for example birch immunotherapy vaccines contain mainly the birch major allergen Bet v 1 (PR-10). Quantities of allergen present vary from manufacturer to manufacturer<sup>7-11</sup>. Allergen extracts may be reflective of how much of the allergen is present at the source. The levels of Der p 23 in mite faecal particles and bodies is rather low<sup>12</sup>.

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## Furry animals

Furry animals such as dogs, cats and horses produce some of the most prevalent allergens in our environment and are released into the surroundings through animal saliva, dander and urine. Like many other allergen sources furry animals contain both specific and cross-reactive allergen components.

Clinically uteroglobin and lipocalins have been identified as the most important major allergen components from cat, dog and horse<sup>1-3</sup>. Serum albumins are often considered to have less clinical relevance in allergy to furry animals, they are minor allergens that cause multiple positivity

due to crossreactivity when using extract tests. However serum albumins are important food allergens in meat<sup>4</sup>.

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## Cat

### ***Felis domesticus* (Fel d)**

Sensitization to cat is strongly associated with asthma, especially in environments free of mite and cockroach<sup>1-2</sup>.

Children with cat allergy and problematic severe asthma have higher levels of IgE antibodies towards cat compared with children with controlled asthma<sup>3</sup>. Fel d 1 is the major cat allergen, belonging to the uteroglobin family and is produced in the salivary glands and skin. Multiple sensitizations towards lipocalins (Fel d 4) and uteroglobins (Fel d 1) have been associated with increased bronchial inflammation in severe asthmatics<sup>4-7</sup>.

Allergy to cat dander and pork meat, also referred to as the pork/cat syndrome<sup>8-9</sup>, has been described to be mediated by

cross-reactive IgE antibodies recognizing cat serum albumin (Fel d 2) and pig serum albumin<sup>10</sup>.

### **Available ImmunoCAP Allergen Products**

Cat – Whole allergen – e1

Component		Code
rFel d 1	uteroglobin	e94
rFel d 2	cat serum albumin	e220
rFel d 4	lipocalin	e228

### **Clinical relevance**

Understanding primary sensitization to cat, aiding immunotherapy selection (see Immunotherapy section) and markers of severity. AIT success is more likely if sensitization to specific components is identified<sup>11-13</sup>.

### **Interpreting the results**

e1	Fel d 1	Fel d 2	Fel d 4	Interpretation
+/-	+			Major allergen. Primary sensitization to Cat. Fel d 1 positive patients are suitable for AIT <sup>4-7,11-15</sup>
+/-		+		Minor allergen. IgE to Fel d 2 (cat serum albumin) can indicate cross reactivity and is seldom of clinical importance in inhalant allergy, however Fel d 2 can be a primary sensitizer in Pork-Cat-Syndrome <sup>8-10,14,15</sup>
+/-			+	Major allergen. Fel d 4 indicates primary sensitization to Cat. Fel d 4 sensitized patients are associated with severe asthma symptoms <sup>4-7,14-15</sup>

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## Dog

### ***Canis familiaris* (Can f)**

Like cat allergy, allergy to dogs is considered to be a major risk factor of the development of asthma and rhinitis<sup>1</sup> and allergy to these animals reduces quality of life<sup>2</sup>. Can f 1, lipocalin is a major dog allergen and a primary sensitizer. It is found in all homes with a dog and up to one third of homes without a dog<sup>3</sup>. Many dog allergics are sensitized to Can f 1 and /or Can f 2, both lipocalin allergens, but prevalence differs in different patient populations<sup>4</sup>. Children with severe asthma in a Swedish study<sup>2</sup> demonstrated sensitization to 3 or more lipocalins including Can f 2. Other lipocalins identified to be of clinical importance are Can f 4<sup>5</sup> and Can f 6<sup>6</sup>. Can f 3, dog serum albumin is abundant

in saliva and dander, and is highly cross reactive with other serum albumins from other species such as Fel d 2 from cat<sup>7</sup>. Serum albumins are generally considered minor allergens<sup>7</sup>. Can f 5 is an important allergen from male dogs and IgE antibodies to Can f 5 can be found in up to 70% of patients with dog allergy in certain populations<sup>8-11</sup>.

### **Available ImmunoCAP Allergen Products**

Dog – Whole allergen – e5

Component		Code
rCan f 1	lipocalin	e101
rCan f 2	lipocalin	e102
nCan f 3	dog serum albumin	e221
rCan f 5	kallikrein	e226

## Clinical relevance

Understanding primary sensitization to dog, aiding immunotherapy selection,

markers of severity. AIT success is more likely if sensitization to specific components is identified<sup>12-14</sup>.

## Interpreting the results

e5	Can f 1	Can f 2	Can f 3	Can f 5	Interpretation
+/-	+				Major allergen. Primary sensitization to dog. Positive patients are suitable for AIT <sup>2-4,7,12-15</sup>
+/-		+			Important allergen. Primary sensitization to dog. Can f 2 patients are associated with severe asthma symptoms <sup>2,4,7,15</sup>
+/-			+		Minor allergen. Can f 3 (dog serum albumin) is associated with cross reactivity (e.g. dog or horse) and is seldom of high clinical importance <sup>7,15</sup>
+/-				+	Major allergen. Can f 5 sensitization is associated male dogs. Mono sensitization may suggest female dogs are suitable pets. May be relevant to human seminal fluid allergy cross-reactions <sup>7, 8-11,15</sup>

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## Horse

### ***Equus caballus* (Equ c)**

Horse allergy occurs among people who handle horses regularly, either professionally or for recreational purposes, and results in the induction or exacerbation of asthma, allergic rhinitis, allergic conjunctivitis and occupational asthma. Horse allergens have potential to cause severe allergic reaction but are often overlooked<sup>1-3</sup>. Up to now two lipocalins have been identified in horse - Equ c 1 and Ecu c 2. Equ c 1 is the major horse allergen and up to 76% of patients with horse allergy react<sup>3-4</sup>. Lipocalins are associated with severe childhood asthma<sup>4-5</sup>. As with other furry animals summarized in this book, horses produce serum albumin allergen (Ecu c 3), which is often referred to as a minor allergen<sup>5-6</sup>. Cross-reactions between

patients allergic to horse albumin and other albumins from dog, cat, or guinea pig albumin are common<sup>1</sup>. Horse dander can easily be transferred into homes or public places such as schools by family members to horse riders. Equ c 3 is available on ImmunoCAP ISAC 112.

### **Available ImmunoCAP Allergen Products**

Horse – Whole allergen – e3

Component		Code
rEqu c 1	Lipocalin	e227

### **Clinical relevance**

Understanding primary sensitization to horse, aiding immunotherapy selection, markers of severity. AIT success is more likely if sensitization to specific components is identified<sup>6-9</sup>.

## Interpreting the results

e3	Equ c 1	Interpretation
+/-	+	Major allergen. Primary sensitization to horse. Patients positive to Equ c 1 may be suitable for AIT <sup>3-10</sup>

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## House dust mites

### ***Dermatophagoides pteronyssinus***

#### **(Der p)**

### ***Dermatophagoides farinae*** (Der f)

Allergy to house dust mites (HDM) is a main cause of respiratory allergies, and exposure to HDM is a major trigger of asthma exacerbations<sup>1</sup>.

*Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) are the most common HDM species, both containing the major allergens - group 1 and 2 proteins. The homology between the two mite species is very high and cross-reactions are common<sup>2</sup>.

Together Der p 1 and Der p 2 will identify between 63 and 97% of patients sensitised to Der p extracts<sup>3</sup>. Thus, a significant proportion (up to 37%) of house dust mite sensitised patients may be missed by the use of only group 1 and group 2 specific IgE component tests.

Der p 23 has recently been identified as another major dust mite allergen present on the surface of mite faecal particles, which is the major airborne form of mite allergens<sup>4</sup>. It is present in low levels in the allergen source<sup>4-6</sup>. Up to 74% of *Dermatophagoides pteronyssinus* allergic patients are sensitized to Der p 23<sup>4-5</sup>. Der p 23 appears highly clinically relevant<sup>7</sup>. Early sensitization in children to either: Der p 1, Der p 2 or Der p 23 is associated with asthma development<sup>8</sup>. Asthma patients are sensitized to more

mite allergen components than those without asthma<sup>9</sup>. Sensitization to Der p 1 and Der p 23 before the age of five was predictive of asthma at school-age<sup>9</sup>. Tropomyosin (Der p 10) is the main cross reactive allergen between mites, shellfish, cockroaches and helminths. Therefore in cases where genuine sensitization is unclear specific allergen components can be useful to identify primary allergy<sup>2</sup>. Tropomyosin is a minor allergen in mite allergy but considered a major allergen in shellfish allergy<sup>2</sup>.

### **Available ImmunoCAP Allergen Products**

*Dermatophagoides pteronyssinus* – Whole allergen – d1

*Dermatophagoides farinae* – Whole allergen – d2

Component		Code
rDer p 1	(Group 1) Cysteine protease	d202
rDer p 2	(Group 2) NPC2 protein family (epidermal secretory proteins)	d203
rDer p 10	Tropomyosin	d205
rDer p 23	Peritrophin-like protein	d209

### **Clinical Relevance**

Identifying primary allergens when sensitization is not clear. Aiding choice of allergen immunotherapy. AIT success is more likely if sensitization to specific components is identified<sup>10-12</sup>.

## Interpreting the results

d1 or d2	Der p 1	Der p 2	Der p 10	Der p 23	Interpretation
+/-	+				Major allergen, primary sensitizer. Good indicator for AIT <sup>2-3,5,6,8-14</sup>
+/-		+			Major allergen. Primary sensitizer. May be under represented in AIT potentially leading to reduced efficacy <sup>2,6,8-14</sup>
+/-			+		Minor allergen. Cross reactive to other species including shellfish. 10% prevalence sensitization in children and adults with asthma. May be under represented in AIT potentially leading to reduced efficacy <sup>2,6,14</sup>
+/-				+	Major allergen. Primary sensitizer. Low levels in the natural source <sup>2,4-14</sup>

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## Pollen – Grasses

### Timothy Grass – *Phleum pratense*

#### (Phl p)

### Bermuda grass – *Cynodon dactylon*

#### (Cyn d)

Grass pollen allergy is common worldwide, and in some regions up to 40% of atopics show sensitization to grass pollen<sup>1-3</sup>. Grass pollen season overlaps with weed pollen such as mugwort and ragweed in most parts of Europe and with tree pollen (olive, plane) in Southern Europe<sup>4</sup>. Group 1 and group 5 allergens (Phl p 1, Cyn d 1 and Phl p 5) are dominating grass pollen allergens and markers of primary sensitization. More than 90% of patients with sensitization to grass pollen have IgE abs to Phl p 1 and/or Phl p 5<sup>2,5-7</sup>. Sensitization to Phl p 1 usually precedes other grass pollen component sensitizations in the development of hay fever symptoms<sup>3</sup>.

When no specific grass sensitization is detected in multisensitized patients, other pollen or food specific components should be investigated<sup>2,5,8</sup>. Sensitization to cross-reactive minor allergens such as profilin (Phl p 12) and polcalcin (Phl p 7) is usually not frequent (< 20 %) but sensitization to CCD is rather common and many plant foods contain both profilin and CCD. Sensitization to minor allergens such as Phl p 7 in addition

to major components indicates more complex sensitization profiles and has been associated with more severe symptoms and longer duration of disease<sup>7</sup>.

### Available ImmunoCAP Allergen Products

Bermuda grass – Whole allergen – g2

Timothy grass – Whole allergen – g6

Component		Code
nCyn d 1	grass group 1, CCD bearing protein	g216
rPhl p 1	grass group 1	g205
rPhl p 2	grass group 2	g206
nPhl p 4	CCD-bearing protein	g208
rPhl p 5b	grass group 5	g215
rPhl p 6	grass group 6	g209
rPhl p 7	Polcalcin	g210
rPhl p 11	Ole 1-related protein	g211
rPhl p 12	Profilin	g212
rPhl p 1	+ rPhl p 5b	g213*
rPhl p 7	+ rPhl p 12	g214*
CCD	MUXF3 from Bromelain	o214

*\*Indicates dual allergen component ImmunoCAP available (in certain countries/ regions)*

### Clinical Relevance

Identifying primary grass allergy and utilisation in AIT management<sup>9-14</sup>.

Identifying cross-reactivities.

## Interpreting the results

g2/g6	Cyn d 1	Phl p 1	Phl p 5b	Phl p 7	Phl p 12	Interpretation
+/-	+					Primary sensitization to Bermuda grass when CCD sensitization is excluded. Good candidate for AIT <sup>1-4, 9-15</sup>
+/-		+				Primary sensitization to Timothy. Phl p 1 and Phl p 5b are major allergens. Good candidate for AIT <sup>1-7,9-15</sup>
+/-			+			
+/-				+		Phl p 7 and Phl p 12 are cross reactive minor allergens which may not be available in sufficient amounts in AIT extract. IgE to Phl p 7 and 12 alone indicate low suitability for grass pollen SIT. The primary allergen should be identified <sup>7-15</sup>
					+	

For other sources of common plant allergen cross-reactions also consider CCD.

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## Pollen – Trees

### Birch – *Betula verrucosa* – (Bet v)

Many birch pollen allergic patients are sensitized and react to several pollen, either due to multiple primary sensitizations or due to allergen cross-reactivity<sup>1-3</sup>. Birch is closely related to several other trees such as alder, hazel, beech and oak. In addition, many of these patients have concomitant pollen-related food allergies due to PR-10 cross-reactivity<sup>1,4</sup>. Therefore patients sensitized to Bet v 1 may react to various fruits, nuts and vegetables such as apple, pear or hazelnut<sup>1,4</sup>. In most cases, symptoms to the triggering food are restricted to oral reactions and the food is often tolerated when cooked since PR-10 allergens are heat labile<sup>4-5</sup>.

### Birch AIT treatment

- Patients sensitized to the specific birch component Bet v 1 are more likely to get symptom relief by birch pollen AIT<sup>6-7</sup>

- Patients sensitized to minor, cross-reactive birch components only, have less successful outcomes of birch pollen AIT<sup>6-7</sup>

### Available ImmunoCAP Allergen Products

Birch – Whole allergen – t3

Component		Code
rBet v 1	PR-10	t215
rBet v 2	Profilin	t216
rBet v 4	Polcalcin	t220
rBet v 6	Isoflavone reductase like	t225
rBet v 2	+ rBet v 4	t221*
CCD	MUXF3 from Bromelain	o214

\*Indicates dual allergen component ImmunoCAP available (in certain countries/regions)

### Clinical Relevance

Identifying primary birch allergy and utilisation in AIT management. Explain birch pollen-related food allergies (Bet v 1, Bet v 2, Bet v 6)<sup>1,4</sup>. Clarify sensitization due to cross-reactivity (Bet v 2, Bet v 4, Bet v 6)<sup>4,8</sup>.

### Interpreting the results

t3	Bet v 1	Bet v 2	Bet v 4	Bet v 6	Interpretation
+/-	+				Primary sensitization to Birch. Bet v 1 is a major allergen. Good candidate for AIT. In food allergy cases patient may react to various fruits, nuts and vegetables containing PR-10 allergens <sup>1-12</sup>
+/-		+			Bet v 2, Bet v 4 and Bet v 6 are cross-reactive minor allergens which may not be available in sufficient amounts in AIT extract. IgE to Bet v 2 and Bet v 4 alone indicate low suitability for birch pollen AIT. The primary allergen should be identified <sup>1,6-12</sup>
+/-			+		
+/-				+	

For other sources of common plant allergen cross-reactions also consider CCD.

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## Other trees

### **Olive tree – *Olea europea* – (Ole e) European Ash – *Fraxinus excelsior* – (Fra e)**

Olive and ash are botanically very closely related (*Oleaceae* family) and extensive cross-reactivity between these species occurs<sup>1-4</sup>. Olive fruit allergy is quite rare, whilst olive tree pollen allergy is quite common and is one of the most important causes of seasonal respiratory allergy in the Mediterranean area<sup>5-6</sup>. Ole e 1 is the major marker for primary olive pollen allergy and sensitization prevalence is about 70% within olive allergy patients<sup>7</sup>. Ole e 7 (LTP) allergy

prevalence is 50% and Ole e 9 at 68%<sup>7</sup>. The European ash (*Fraxinus excelsior*) is common in most of Europe but ash tree pollen may often be overlooked as a cause of pollinosis, as the flowering season coincides with that of birch. Ash may locally be as important as birch in the elicitation of spring pollinosis<sup>1,8</sup>. Although Fra e 1 is the major allergen for ash pollen-sensitization, cross-reactivity between Fra e 1 and Ole e 1 in olive is so pronounced that Ole e 1 serves as a very good marker allergen for the diagnosis of ash pollen allergy<sup>7</sup>.

### London plane tree – *Platanus acerifolia* – (Pla a)

Plane trees are known as “street trees” and are found planted practically anywhere in the world. Recombinant Pla a 1 is a specific marker allergen suitable for discriminating between genuine plane tree pollen sensitization and cross-reactivity<sup>7,9</sup>. Pla a 1 is a major plane tree pollen allergen recognized by up to 90% of plane tree-allergic patients<sup>9-10</sup>. Pla a 3 is an nsLTP which cross-reacts with other LTPs in e.g. fruits<sup>11-12</sup> sharing a 50% sequence identity with Pru p 3<sup>12</sup>. Pla a 3 is not available on ImmunoCAP. However, Pla a 3, as well as the plane-tree specific and major allergen Pla a 1 and Pla a 2 are available on ImmunoCAP ISAC 112.

### Cypress – *Cupressus arizonica* – (Cup a)

Cypresses are common ornamental trees found extensively in Southern Europe<sup>13</sup> but also can be found globally including North America and Japan<sup>14</sup>. Cedars are other members of the *Cupressaceae* family and IgE cross-react with similar species<sup>15-16</sup>. Cypress trees bloom in the winter and may cause winter respiratory allergy<sup>7</sup>. Winter pollen allergies are often misdiagnosed since symptoms are occurring during winter and are very similar to perennial allergies like dust mite allergy<sup>7,17</sup>. Rhinitis is the most prevalent symptom of cypress pollen, while conjunctivitis can be quite severe<sup>15</sup>. Component testing may help to better management of the patients<sup>18-19</sup>.

Four allergens from *Cupressus arizonica* have been described, including the major allergen. Cup a 1<sup>13,20-21</sup>; Cup a 2 (polygalacturonase); Cup a 3 (thaumatin); and Cup a 4 (polcalcin). Cup a 1 is a specific marker for primary sensitization to *Cupressaceae* pollen<sup>16</sup>. The Cup a 1 allergen is very similar to major allergens of Mediterranean cypress (Cup s 1), Mountain cedar (Jun a 1), Japanese cypress (Cha o 1) and Japanese cedar (Cry j 1), there is extensive cross-reactivity between these closely related species<sup>7</sup>.

### Available ImmunoCAP Allergen Products

Italian cypress – Whole allergen – t23

Cypress – Whole allergen – t222

Olive – Whole allergen – t9

London plane – Whole allergen – t11

Component		Code
nCup a 1*	Pectate lyase-CCD bearing protein	t226
rOle e 1	Common olive group 1	t224
rOle e 7	LTP	t227
rOle e9	Glucanase	t240
rPla a 1	Invertase inhibitor	t241
CCD	MUXF3 from Bromelain	o214

### Clinical Relevance

Identifying primary allergy to different trees and utilisation in AIT management<sup>22-24</sup>.

## Interpreting the results

Tree Pollen	Component	Protein	Code	Interpretation
Cypress, t23	nCup a 1*	Pectate lyase	t226	Primary sensitizer/major allergen in Cupressaceae trees. Good candidate for AIT <sup>7,13,16,18, 21-25</sup>
Olive/Ash t9 / t25	rOle e 1	Common Olive group 1	t224	Primary sensitizer/major allergen Also marker for ash tree sensitization. Good candidate for AIT <sup>5-7,21-25</sup>
Olive, t9	rOle e 7	LTP	t227	Minor allergen <sup>5-7,25</sup>
Olive, t9	rOle e 9	1 3-beta glucanase	t240	Minor allergen <sup>5-7,25</sup>
London Plane Tree, t11	rPla a 1	Putative Invertase inhibitor	t241	Primary sensitizer/major allergen indicating Plane tree pollen sensitization. Good candidate for AIT <sup>7,9-10,21-25</sup>

\*nCup 1 is purified from a native allergen source and contains CCD

For other sources of common plant allergen cross-reactions also consider CCD, profilins and polcalcins.

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## Pollen – Weeds

### Common Ragweed – *Ambrosia*

#### *artemisiifolia* (Amb a)

### Mugwort – *Artemisia vulgaris* (Art v)

#### Wall Pellitory – *Parietaria judaica*

#### (Par j)

### English Plantain – *Plantago*

#### *lanceolata* (Pla l)

### Saltwort – *Salsola kali* (Sal k)

Weed allergy diagnosis can be unclear and difficult to diagnose due to frequent poly-sensitizations and inconclusive anamnesis due to overlapping flowering seasons with other pollens such as birch and grass<sup>1-2</sup>. Cross-reactions are expected between different weed species when botanically closely related. Apart from profilin and CCDs, mugwort and ragweed pollen contain a number of other cross-reactive allergens. Cross-reactive IgE antibodies can lead to clinically significant allergic reactions<sup>3-4</sup>. Furthermore, mugwort, ragweed, and

Timothy grass pollen share IgE epitopes with glycoprotein containing latex allergens, this presence of common epitopes might in part explain clinical symptoms in patients allergic to pollen on contact with latex<sup>5</sup>.

Pollen-food syndromes driven by weed pollen are mainly generated by mugwort and ragweed pollen. As well as Oral Allergy Syndrome (OAS) more severe allergy is reported such as celery-mugwort-spice syndrome<sup>6-9</sup>.

### Available ImmunoCAP Allergen Products

Common Ragweed – Whole allergen – w1  
 Mugwort – Whole allergen – w6  
 Wall Pellitory – Whole allergen – w21  
 Plantain (English) – Whole allergen – w9  
 Saltwort – Whole allergen – w11

Component		Code
nAmb a 1	Pectate lyase	w230
nArt v 1	Defensin-like protein	w231
nArt v 3	LTP	w233
rPar j 2	LTP	w211
rPla l 1	Ole e 1 like protein	w234
nSal k 1*	Pectin methylesterase	w232

### Clinical Relevance

Identifying primary allergy to different trees and utilisation in AIT management<sup>1-2,10-13</sup>

### Interpreting the results

Weed Pollen	Component	Protein	Code	Interpretation
Ragweed, w1	nAmb a 1	Pectate lyase	w230	Primary sensitizer/major allergen Good candidate for AIT <sup>1-2,10-13</sup>
Mugwort, w6	nArt v 1	Defensin-like protein	w231	Primary sensitizer/major allergen Good candidate for AIT <sup>1-2,10-13</sup>
	nArt v 3	LTP	w233	Major allergen <sup>1-2,13</sup>
Parietaria/ Wall pellitory, w21	rPar j 2	LTP	w211	Primary sensitizer/major allergen Good candidate for AIT <sup>1-2,10-13</sup>
Plantain, w9	rPla l 1	Ole e 1 like protein	w234	Primary sensitizer/major allergen Good candidate for AIT <sup>1-2,10-13</sup>
Saltwort, w11	nSal k 1*	Pectin methylesterase	w232	Primary sensitizer/major allergen Good candidate for AIT <sup>1-2,10-13</sup>

\*nSal k 1 is purified from a native allergen source and contains CCD, nAmb a 1 is also a purified native component but does not contain CCD.

For other sources of common plant allergen cross-reactions also consider CCD, profilins and polcalcins.

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## Molds

There is current evidence to demonstrate a close association between fungal sensitization and asthma severity. Many airborne fungi are involved, including species of *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium*, and exposure may be indoors, outdoors or both. Fungal sensitization is common in asthmatic patients in urban settings and is associated with broader sensitization to non-fungal allergens and to increased risk of life-threatening asthma<sup>1-2</sup>. The term “severe asthma with fungal sensitization” (SAFS) has been proposed. However, it is recognised that enhanced and precise definition of fungal sensitization will require improvements in diagnostic testing<sup>2-4</sup>. This can be facilitated by component testing<sup>5-7</sup>.

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### ***Alternaria alternata* – (Alt a)**

*Alternaria alternata* is a major outdoor as well as indoor aeroallergen in many parts of the world. Sensitivity to *Alternaria* has been increasingly recognized as a risk factor for the development and persistence of asthma, asthma severity, and potentially fatal asthma exacerbations<sup>1-5</sup>. Asthma in children with *Alternaria* sensitization has been reported to persist beyond age 11 years, compared to asthma in individuals who

were negative<sup>6</sup>. *Alternaria*-sensitized patients may also be at risk for allergic rhinitis<sup>7</sup>, and the most severe cases of rhinitis may be attributable to *Alternaria* sensitivity<sup>8-9</sup>.

Alt a 1 is the major *Alternaria* allergen causing sensitization in asthmatics and has been reported as the main elicitor of airborne allergies in patients affected by a mold allergy. Alt a 1 is considered a marker of primary sensitization to *A. alternata*<sup>3,5-7,10</sup>. A vast majority (80-100%) of *Alternaria* sensitized patients have specific IgE to Alt a 1<sup>11-13</sup>. Alt a 1

is a highly allergenic molecule allowing sensitive and specific diagnosis of *Alternaria* allergy<sup>11,14-16</sup>.

### Available ImmunoCAP Allergen Products

*Alternaria alternata* – Whole allergen – m6

Component	Code
rAlt a 1      unknown	m229

### Clinical Relevance

Identifying primary sensitization to *Alternaria*.

### Interpreting the results

m6	Alt a 1	Interpretation
+/-	+	Major allergen. Primary sensitization to <i>Alternaria</i> . Risk marker for severe asthma <sup>1-17</sup>

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### ***Aspergillus fumigatus* – (Asp f)**

*Aspergillus fumigatus* causes the most common form of Allergic Bronchopulmonary Mycosis (ABPM), and is referred to as Allergic Bronchopulmonary Aspergillosis (ABPA). IgE sensitization tests are used as part of routine workup for diagnosing ABPA<sup>1</sup>. Genuine *A. fumigatus* sensitization is not always easily identifiable<sup>1</sup>. Other fungi species share cross reactive pan allergens with *A. fumigatus* which can cause non-specific test results. Therefore the use of specific IgE components for *A. fumigatus* can aid the identification of primary *A. fumigatus* sensitization<sup>2</sup>.

Recent studies investigating ABPA demonstrated that ImmunoCAP Allergen Components could differentiate ABPA individuals from those with asthma and sensitized to *Aspergillus*<sup>3-6</sup>. Asp f 1 is major allergen, species specific and shares no homology with any known fungal genome<sup>4</sup>. Additionally it is not produced in spores but in germination and growth<sup>4-6</sup>. Asp f 2 is further species specific allergen and present in 96%

frequency of sensitization with ABPA<sup>1</sup>. Asp f 4 has also been identified as a specific allergen in studies that used ImmunoCAP components. Asp f 3 and Asp f 6 are described as cross-reactive allergens<sup>3-6</sup>.

### **Available ImmunoCAP Allergen Products**

*Aspergillus fumigatus* – Whole allergen – m3

Component		Code
rAsp f 1	Ribotoxin	m218
rAsp f 2	Unknown	m219
rAsp f 3	Peroxisomal protein	m220
rAsp f 4	Unknown	m221
rAsp f 6	MnSOD	m222

### **Clinical Relevance**

Helping understanding primary *Aspergillus fumigatus* sensitization, differentiating ABPA from asthma and sensitized patients.

## Interpreting the results

m3	Asp f 1	Asp f 2	Asp f 3	Asp f 4	Asp F 6	Interpretation
+/-	+					Primary sensitization to <i>Aspergillus fumigatus</i> <sup>1-2,4,7-8</sup>
+/-		+				Primary sensitization to <i>Aspergillus fumigatus</i> <sup>1-2,4,7-8</sup>
+/-			+			Primary sensitization to <i>Aspergillus fumigatus</i> <sup>1-2,4,7-8</sup>
+/-				+		Likely cross sensitization from other mould species. Primary allergen should be identified <sup>3-8</sup>
+/-					+	Likely cross sensitization from other mould species. Primary allergen should be identified <sup>3-8</sup>

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## Venoms

Up to 50% of patients with suspected honey bee or common wasp allergy test positive when using extract testing<sup>1</sup>. True double allergic reactivity to both bee and wasp is not clinically common<sup>1-3</sup>. In many cases double venom IgE positivity can be caused by cross-reactions to CCDs<sup>1-2</sup>. Recombinant venom components do not carry CCD and therefore provide greater diagnostic specificity, useful when making decision such as to start AIT<sup>4-6</sup>. Low level specific IgE below 0.35 kU<sub>A</sub>/l can be relevant when using components and indicative of venom allergy<sup>6-7</sup>, so measuring down to 0.1 kU<sub>A</sub>/l can be important.

### Common Wasp – *Vespula vulgaris* Paper wasp – *Polistes dominulus*

Ves v 1 and Ves v 5 are major allergens from common wasp and have demonstrated clinical sensitization rates, of between 33.3 - 54% and 84.5 - 100% respectively<sup>7</sup>. The combination of the two tests in a study by Korosec et al provided sensitivity of 92%<sup>9</sup>. Paper wasp is common in Southern Europe and other parts of the world and Pol d 5 is a marker for sensitization to paper wasp<sup>1-2,7</sup>.

### Honey Bee – *Apis mellifera*

The picture for bee sensitivity seems more complex than for wasp and can involve more varied sensitization patterns to major components<sup>7</sup>. Api m 1, Api m 2, Api m 3, Api m 5 and Api m 10 are all major allergens within bee venom allergy<sup>7</sup>. Api m 1 and Api m 10 demonstrate the highest clinical

sensitization rates, ranging from 57 - 97% for Api m 1 and 51.5 - 61.8 for Api m 10<sup>7</sup>. It has recently been shown that using an increasing number of bee components can improve bee sensitivity<sup>8</sup>. Api m 3 and Api m 10 can be absent or underrepresented in VIT extracts<sup>10-11</sup>, thus venom AIT in patients sensitized to these components may be less efficient.

Patients with suspected venom allergy should also be tested for tryptase<sup>2-3,7</sup>. Patients with high basal levels of tryptase should be investigated for mastocytosis since these patients have higher risk for severe reactions during venom immunotherapy<sup>2-3,7,12</sup>. It is recommended that special attention should be paid to patients who have high baseline tryptase measurements<sup>2-3,7,12</sup>.

### Available ImmunoCAP allergen products

Honey bee – Whole allergen – i1  
Common wasp (Yellow jacket) – Whole allergen – i3  
Paper wasp – Whole allergen – i4

Component		Code
rApi m 1	Phospholipase A2	i208
rApi m 2	Hyaluronidase	i214
rApi m 3	Acid phosphatase	i215
rApi m 5	Dipeptidyl peptidase	i216
rApi m 10	Icarapin	i217
rVes v 1	Phospholipase A1	i211
rVes v 5	Antigen 5	i209
rPol d 5	Antigen 5	i210
CCD	MUXF3 from Bromelain	o214

### Clinical Relevance

Helping differentiating primary bee and wasp sensitization from cross-reactivity. An aid to select proper treatment extract in venom AIT<sup>4-9,13</sup>.

### Interpreting the results

i1, i3, i4	Api m 1	Api m 2	Api m 3	Api m 5	Api m 10	Ves v 1	Ves v 5	Pol d 5	CCD	Interpretation
+/-	+									Primary sensitization to Honey bee, Good candidate for AIT. Clinical sensitivity of Honey bee Components combined >90% <sup>4-8,13</sup>
+/-		+								
+/-			+							
+/-				+						
+/-					+					
+/-						+				Primary sensitization to Common wasp, a good candidate for Common wasp AIT. Clinical sensitivity of wasp components combined >90% <sup>4-7,9,13</sup>
+/-							+			
+/-								+		Primary sensitization to paper wasp <sup>4-7,9,13</sup>
+/-									+	If venom components are negative and CCD positive. Further investigations may be necessary to identify underlying source <sup>1-2,7,13</sup>

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## Occupational Allergens

### Latex – *Hevea brasiliensis* (Hev b)

Latex allergy is often associated with an occupational exposure and can trigger contact urticaria but also severe and even life-threatening allergic reactions. IgE to Hev b 5 and Hev b 6 is often linked with occupational aero exposure to latex e.g. in healthcare workers and food handling personnel using latex gloves<sup>1-5</sup>. Hev b 1 and Hev b 3 are insoluble molecules and therefore allergen transmission comes via direct contact e.g. in patients with histories of multiple operations such as spina bifida patients<sup>5-6</sup>. Latex components are useful tools in resolving specific latex sensitization from cross reactivity due to e.g. profilin (Hev b 8) and CCDs<sup>7-9</sup>.

The association of latex allergy and allergy to plant-derived foods is called latex-fruit syndrome. An increasing number of plant sources such as avocado, banana, chestnut, kiwi, peach, tomato, potato and bell pepper have been associated with this syndrome. Hev b 11 is a class 1 chitinase which can be involved in latex food cross-reactions<sup>10,11</sup>. Patients with latex-pollen syndrome are often sensitised to MUXF3 (CCD) and/or Hev b 8 (profilin)<sup>5,12</sup>.

### Available ImmunoCAP allergen products

Latex – Whole allergen – k82

Component		Code
rHev b 1	Rubber elongation factor	k215
rHev b 3	Small rubber particle protein	k217
rHev b 5	Acidic structural protein	k218
rHev b 6.02	Prohevein	k220
rHev b 8	Profilin	k221
rHev b 11	Class 1 chitinase	k224
CCD	MUXF3 from Bromelain	o214

### Clinical relevance

Understanding risk and cross-reactions.

### Interpreting the results

k82	Hev b 1	Hev b 3	Hev b 5	Hev b 6	Hev b 8	Hev b 11	CCD	Interpretation
+/-	+							Primary sensitization to latex <sup>5-6,13</sup>
+/-		+						Primary sensitization latex <sup>5-6,13</sup>
+/-			+					Primary sensitization to latex <sup>5-6,13</sup>
+/-				+		+		Primary sensitization to latex, also associated with latex fruit syndrome. Hev b 6, prohevein and Hev b 11 class 1 chitinase can cross-react with other foods and plants such as avocado, kiwi, chestnut or banana <sup>1-5,13</sup>
+/-					+			Low risk for latex allergy. Likely cross sensitization. Primary allergen should be identified <sup>5,7-9,12-13</sup>
+/-							+	Low risk for latex allergy. Likely cross sensitization. Primary allergen should be identified <sup>5,7-9,12-13</sup>

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# Introduction to Allergen Micro Array

## ImmunoCAP ISAC 112

Allergen micro-arrays have been around since the late 1990s and therefore in some ways are not new products. What is new is that in the last few years' arrays have improved in analytical performance, reporting software and of course there is also a better clinical understanding of how to interpret positive and negative results.

Recent studies and reviews have shown comparable performance of ImmunoCAP ISAC 112 versus other existing techniques such as extract based skin prick tests and specific IgE blood tests<sup>1</sup>. Furthermore ImmunoCAP ISAC 112

can provide further refined information or change diagnosis compared to standard assessment or testing. In a Swedish asthma study ImmunoCAP ISAC 112 provided more refined IgE characterisation in 47% of patients compared to standard extract-based methods<sup>2</sup>. Whereas in a recent atopic dermatitis study 70% of patients had a change in diagnosis when ImmunoCAP ISAC 112 was included in the workup<sup>3</sup>.

Besides applications in research, multiplex in-vitro diagnostics are increasingly being used to answer clinical questions in regular allergy clinics. The combination of microarray, single

component allergens and extract based tests allows a much more comprehensive view of the sensitization status of the patient. Together with clinical history it is possible to quickly identify clinical phenotypes especially in multi-sensitized patients<sup>4-8</sup>.

The currently available multiplex systems, are just the beginning of a development that will significantly affect clinical allergy in the coming years. New allergens and technological advancement will contribute to product changes. Allergen components have been and will be removed and added, based on factors such as new allergen discovery, availability and clinical experience of the current version of a product.

On ImmunoCAP ISAC 112 there are more than 100 allergen components representing many different protein families, which gives a good “snapshot” of a sensitization profile. The profile together with symptoms and clinical history provides a detailed foundation for clinical assessment.

ImmunoCAP ISAC 112 can sometimes generate a lot of IgE results and careful clinical interpretation and knowledge of allergen proteins is essential to interpret a patient report. Much of the content of Go Molecular Books 1 and 2 is relevant to interpreting allergen array. A software tool is available for ImmunoCAP ISAC 112 laboratories, which provides additional interpretational support.

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## Facts on ImmunoCAP ISAC 112

### **ImmunoCAP ISAC 112:**

- Is a multiplex allergen micro-array
- ImmunoCAP ISAC 112 contains 112 allergen components from 51 allergen sources representing different protein families - see separate list of allergens
- Enables simultaneous measurement of IgE to the 112 allergen components in a single step
- Small sample volume needed: just 30µl serum sample or plasma
- Capillary or venous blood can be used
- ImmunoCAP ISAC 112 measures IgE in ISU-E which stands for - ISAC Standard Units Immunoglobulin E
- The results are presented semi-quantitatively in 4 classes each corresponding to a concentration range
- Is a complementary technology that should be used in conjunction with clinical history and other sensitization tests

Technical feature	Clinical Advantages
<b>Wide number of allergen components from many different protein families</b>	<ul style="list-style-type: none"> <li>• Better coverage of allergen sources overall</li> <li>• Wider coverage to identify primary sensitizer(s)</li> <li>• Can make economic sense when a lot of allergen tests are needed</li> </ul>
<b>Multiplexed protein families</b>	<ul style="list-style-type: none"> <li>• Allow extrapolations of probable sensitization to other allergen sources not actually included, by using surrogate allergen components on the array</li> <li>• Help understand cross-reactions between different species</li> <li>• Help understand different syndromes e.g. pollen-food</li> </ul>
<b>Recombinant or purified allergen components</b>	<ul style="list-style-type: none"> <li>• Recombinant/purified native allergen components are pure consisting of only one type of protein making them highly specific for measuring antibodies of one type</li> </ul>
<b>Micro-array platform</b>	<ul style="list-style-type: none"> <li>• Small sample volume needed (30µl), giving more than 100 results</li> </ul>
<b>Good technical performance</b>	<ul style="list-style-type: none"> <li>• ImmunoCAP ISAC 112 shows high sensitivity and specificity<sup>9</sup> and good correlation with other types of testing including specific IgE and skin prick<sup>10-11</sup></li> </ul>

### Advantages of ImmunoCAP ISAC 112

Advantages can obviously be looked at in different perspectives, in the research arena ImmunoCAP ISAC 112 could seem an easy choice of a diagnostic test - you get a lot of allergens test results from just a small amount of precious serum (30µl). These advantages apply to the clinical environment too where blood volumes from children can be limited.

The above table gives an overview of some advantages of microarray.

### Examples of the clinical relevance of ImmunoCAP ISAC 112 include:

- Complex patient cases – patients with complex symptomology e.g. eczema and unstable asthma<sup>5</sup>
- Eczema patients – involving multiple allergens<sup>3,12-15</sup>
- Idiopathic anaphylaxis – ImmunoCAP ISAC 112 identified further useful clinical information in 20% of this group of patients from a UK study<sup>16</sup>
- Multi-sensitized patients – e.g. patients with possible cross-reactions or genuine primary allergens. Many of the papers referenced in the section are citations which investigate multi-sensitized patients<sup>12-19</sup>
- Allergy work up for Immunotherapy patients<sup>17-19</sup>
- Food allergy investigations<sup>20-22</sup>
- Respiratory allergy<sup>23-24</sup>

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# Recommended further educational resources

**allergyai.com** – Home Page of Immunodiagnostics Division, Thermo Fisher Scientific

**allergen.org** – International Union for Immunological Sciences/WHO Allergen Database

Canonica GW, et al. A WAO – ARIA – GA2LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 2013;6(1):17.

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## Using ImmunoCAP Allergen Component tests

ImmunoCAP Allergen Components, singleplex as well as multiplex, are useful tools for the physician when investigating and explaining allergic reactions more in detail and to determine if cross-reacting IgE antibodies or primary sensitization causes them. However as with all test results they must be evaluated by the physician together with the clinical history of the individual patient.

Presence of allergen specific IgE implies a risk of allergic disease and generally the higher the level of IgE antibodies the higher the probability of a clinically manifest allergic reaction<sup>1-5</sup>. However, due to differences in individual patient sensitivities identical results for the same allergens may not be associated with clinically equivalent manifestations. This may also be true for one individual patient at different occasions due to presence or absence of reaction promoting cofactors<sup>1-5</sup>.

Absence of detectable allergen specific IgE antibodies does not necessarily exclude the potential for an allergy-like reaction<sup>1-2</sup>.

### ***Limitations of ImmunoCAP products test results:***

Samples with results below limit of quantitation obtained with ImmunoCAP Allergen Components are recommended to be tested with the corresponding extract based ImmunoCAP Allergen and/or additional relevant ImmunoCAP Allergen Components, if not already performed and a clinical indication is present. The extract based testing can cover additional allergen components present in the allergen source material to which the patient may be sensitized, but which are not presently available as ImmunoCAP Allergen Components or on ImmunoCAP ISAC 112.

A result below limit of quantitation obtained with an extract based ImmunoCAP Allergen never excludes the possibility of obtaining measurable concentrations of specific IgE when testing with ImmunoCAP Allergen Components from the same allergen source. This is due to the fact that some components may be present in very low amounts in the natural extract.

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# ImmunoCAP Allergen Component list\*

Product	Latin name	Code	Size	Art. no.	Barcode
<b>Grass pollen</b>					
Cyn d 1 Bermuda grass	<i>Cynodon dactylon</i>	g216	10	14-4972-01	CFA
rPhl p 1 Timothy	<i>Phleum pratense</i>	g205	10	14-5234-01	BSU
rPhl p 2 Timothy	<i>Phleum pratense</i>	g206	10	14-5235-01	COK
nPhl p 4 Timothy	<i>Phleum pratense</i>	g208	10	14-5288-01	COL
rPhl p 5b Timothy	<i>Phleum pratense</i>	g215	10	14-5338-01	BV3
rPhl p 6 Timothy	<i>Phleum pratense</i>	g209	10	14-5289-01	BSV
rPhl p 7 Timothy	<i>Phleum pratense</i>	g210	10	14-5290-01	BSW
rPhl p 11 Timothy	<i>Phleum pratense</i>	g211	10	14-5291-01	BSX
rPhl p 12 Profilin, Timothy	<i>Phleum pratense</i>	g212	10	14-5292-01	BSY
rPhl p 1, rPhl p 5b Timothy	<i>Phleum pratense</i>	g213	10	14-5312-01	BU1
rPhl p 7, rPhl p 12 Timothy	<i>Phleum pratense</i>	g214	10	14-5313-01	BU2
<b>Weed pollen</b>					
nAmb a 1 Ragweed	<i>Ambrosia artemisiifolia (A. elatior)</i>	w230	10	14-4969-01	CF8
nArt v 1 Mugwort	<i>Artemisia vulgaris</i>	w231	10	14-4970-01	CF9
nArt v 3 LTP, Mugwort	<i>Artemisia vulgaris</i>	w233	10	14-4983-01	CJ2
rPar j 2 LPT, Wall pellitory	<i>Parietaria judaica</i>	w211	10	14-5311-01	C2M
rPla l 1 Plantain	<i>Plantago lanceolata</i>	w234	10	14-5751-01	D1H
nSal k 1 Saltwort	<i>Salsola kali</i>	w232	10	14-4978-01	CFE
<b>Tree pollen</b>					
rBet v 1 PR-10, Birch	<i>Betula verrucosa</i>	t215	10	14-5225-01	BPV
rBet v 2 Profilin, Birch	<i>Betula verrucosa</i>	t216	10	14-5226-01	BR1
rBet v 4 Birch	<i>Betula verrucosa</i>	t220	10	14-5287-01	BT7
rBet v 6 Birch	<i>Betula verrucosa</i>	t225	10	14-5345-01	CF1
rBet v 2, rBet v 4 Birch	<i>Betula verrucosa</i>	t221	10	14-5310-01	BU0
nCup a 1 Cypress	<i>Cupressus arizonica</i>	t226	10	14-4977-01	CFD
rOle e 1 Olive	<i>Olea europaea</i>	t224	10	14-5705-01	CTC
nOle e 7 LTP, Olive	<i>Olea europaea</i>	t227	10	14-4993-01	CKT
rOle e 9, Olive	<i>Olea europaea</i>	t240	10	14-4999-01	CTZ
rPla a 1 Maple leaf sycamore, London plane	<i>Platanus acerifolia</i>	t241	10	14-5957-01	D2H

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Product	Latin name	Code	Size	Art. no.	Barcode
<b>Microorganisms</b>					
rAlt a 1	<i>Alternaria alternata</i>	m229	10	14-5346-01	CE0
rAsp f 1	<i>Aspergillus fumigatus</i>	m218	10	14-5293-01	BPL
rAsp f 2	<i>Aspergillus fumigatus</i>	m219	10	14-5294-01	BPM
rAsp f 3	<i>Aspergillus fumigatus</i>	m220	10	14-5295-01	BT4
rAsp f 4	<i>Aspergillus fumigatus</i>	m221	10	14-5296-01	BPN
rAsp f 6	<i>Aspergillus fumigatus</i>	m222	10	14-5297-01	BPP
<b>Epidermals and animal proteins</b>					
nBos d 6 BSA, Cow	<i>Bos spp.</i>	e204	10	14-5009-01	BRV
rCan f 1 Dog	<i>Canis familiaris</i>	e101	10	14-4955-01	CBN
rCan f 2 Dog	<i>Canis familiaris</i>	e102	10	14-4956-01	CBP
nCan f 3 Dog serum albumin	<i>Canis familiaris</i>	e221	10	14-5241-01	C14
rCan f 5 Dog	<i>Canis familiaris</i>	e226	10	14-4998-01	CMZ
rFel d 1 Cat	<i>Felis domesticus</i>	e94	10	14-4905-01	BY0
rFel d 2 Cat serum albumin	<i>Felis domesticus</i>	e220	10	14-5240-01	BRX
rFel d 4 Cat	<i>Felis domesticus</i>	e228	10	14-5702-01	CT9
rEqu c 1 Horse	<i>Equus caballus</i>	e227	10	14-5700-01	CN7
nSus s Pig serum albumin, Swine	<i>Sus scrofa</i>	e222	10	14-5242-01	C36
<b>Mites</b>					
rDer p 1 House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d202	10	14-5996-01	DP4
rDer p 2 House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d203	10	14-4967-01	CG2
rDer p 10 Tropomyosin, House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d205	10	14-4985-01	CG5
rDer p 23 House dust mite	<i>Dermatophagoides Pteronyssinus</i>	d209	10	14-6040-01	DWU
<b>Venoms</b>					
rApi m 1 Phospholipase A2, Honey bee	<i>Apis mellifera</i>	i208	10	14-4987-01	CJ7
rApi m 2 Hyaluronidase, Honey bee	<i>Apis mellifera</i>	i214	10	14-6014-01	DUD
rApi m 3, Acid phosphatase, Honey bee	<i>Apis mellifera</i>	i215	10	14-6015-01	DUC
rApi m 5 Dipeptidyl peptidase, Honey bee	<i>Apis mellifera</i>	i216	10	14-6016-01	DUB
rApi m 10 Icarapin, Honey bee	<i>Apis mellifera</i>	i217	10	14-6004-01	DRO
rVes v 1 Phospholipase A1, Common wasp	<i>Vespula vulgaris</i>	i211	10	14-4995-01	CMR
rVes v 5 Common wasp	<i>Vespula vulgaris</i>	i209	10	14-4992-01	CJ8
rPol d 5 Paper wasp	<i>Polistes dominulus</i>	i210	10	14-4994-01	CJ9

## ImmunoCAP Allergen Component list continued\*

Product	Latin name	Code	Size	Art. no.	Barcode
<b>Occupational</b>					
rHev b 1 Latex	<i>Hevea brasiliensis</i>	k215	10	14-5324-01	C20
rHev b 3 Latex	<i>Hevea brasiliensis</i>	k217	10	14-5326-01	C2A
rHev b 5 Latex	<i>Hevea brasiliensis</i>	k218	10	14-5327-01	C1Z
rHev b 6.02 Latex	<i>Hevea brasiliensis</i>	k220	10	14-5329-01	C22
rHev b 8 Profilin, Latex	<i>Hevea brasiliensis</i>	k221	10	14-5330-01	C1V
rHev b 11 Latex	<i>Hevea brasiliensis</i>	k224	10	14-5333-01	C29
<b>Occupational / Enzymes</b>					
Alkalase	<i>Alkalase</i>	k205	10	14-5126-01	C1F
nAna c 2 Bromelain, Pineapple	<i>nAna c 2 Bromelain, Pineapple</i>	k202	10	14-5127-01	BT1
nAsp o 21 alpha-amylase	<i>nAsp o 21 alpha-amylase</i>	k87	10	14-4370-01	595
nCar p 1 Papain, Papaya	<i>nCar p 1 Papain, Papaya</i>	k201	10	14-5130-01	BT0
nGal d 4 Lysozyme, Egg	<i>nGal d 4 Lysozyme, Egg</i>	k208	10	14-5128-01	C0T
Maxatase	<i>Maxatase</i>	k204	10	14-5129-01	C2F
Savinase	<i>Savinase</i>	k206	10	14-5132-01	C2R
nSus s Pepsin, Swine	<i>nSus s Pepsin, Swine</i>	k213	10	14-5258-01	C3B
<b>Foods</b>					
rAct d 8 PR-10, Kiwi	<i>Actinidia deliciosa</i>	f430	10	14-4984-01	CG7
rAna o 3 Cashew nut	<i>Anacardium occidentale</i>	f443	10	14-5760-01	D0W
rApi g 1.01 PR-10, Celery	<i>Apium graveolens</i>	f417	10	14-4957-01	CBR
rAra h 1 Peanut	<i>Arachis hypogaea</i>	f422	10	14-4963-01	CDF
rAra h 2 Peanut	<i>Arachis hypogaea</i>	f423	10	14-4964-01	CDG
rAra h 3 Peanut	<i>Arachis hypogaea</i>	f424	10	14-4965-01	CDH
rAra h 6 Peanut	<i>Arachis hypogaea</i>	f447	10	14-6041-01	DYU
rAra h 8 PR-10, Peanut	<i>Arachis hypogaea</i>	f352	10	14-5341-01	CEZ
rAra h 9 LTP, Peanut	<i>Arachis hypogaea</i>	f427	10	14-4980-01	CFC
rBer e 1 Brazil nut	<i>Bertholletia excelsa</i>	f354	10	14-5343-01	CDS
nBos d 4 alpha-lactalbumin, Milk	<i>Bos spp.</i>	f76	10	14-4522-01	CTP
nBos d 5 beta-lactoglobulin, Milk	<i>Bos spp.</i>	f77	10	14-4523-01	CTR
nBos d 8 Casein, Milk	<i>Bos spp.</i>	f78	10	14-4524-01	CTS
rCor a 1 PR-10, Hazel nut	<i>Corylus avellana</i>	f428	10	14-4981-01	CFB
rCor a 8 LTP, Hazel nut	<i>Corylus avellana</i>	f425	10	14-4968-01	GDP
nCor a 9, Hazel nut	<i>Corylus avellana</i>	f440	10	14-5758-01	D0M

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Product	Latin name	Code	Size	Art. no.	Barcode
<b>Foods continued</b>					
rCor a 14, Hazel nut	<i>Corylus avellana</i>	f439	10	14-5754-01	CZP
rCyp c 1 Carp	<i>Cyprinus carpio</i>	f355	10	14-5344-01	CF0
rGad c 1 Cod	<i>Gadus morhua</i>	f426	10	14-4971-01	CEY
nGal d 1 Ovomuroid, Egg	<i>Gallus spp.</i>	f233	10	14-4805-01	904
nGal d 2 Ovalbumin, Egg	<i>Gallus spp.</i>	f232	10	14-4804-01	903
nGal d 3 Conalbumin, Egg	<i>Gallus spp.</i>	f323	10	14-5222-01	C18
rGly m 4 PR-10, Soy	<i>Glycine max</i>	f353	10	14-5340-01	CDR
nGly m 5 beta-conglycinin, Soy	<i>Glycine max</i>	f431	10	14-4990-01	CLV
nGly m 6 Glycinin	<i>Glycine max</i>	f432	10	14-4991-01	CLU
rJug r 1 Walnut	<i>Juglans regia</i>	f441	10	14-5762-01	DOT
rJug r 3 LTP, Walnut	<i>Juglans regia</i>	f442	10	14-5954-01	D11
rMal d 1 PR-10, Apple	<i>Malus domestica</i>	f434	10	14-5703-01	CWR
rMal d 3 LTP, Apple	<i>Malus domestica</i>	f435	10	14-5704-01	CWS
rPen a 1 Tropomyosin, Shrimp	<i>Penaeus aztecus</i>	f351	10	14-5335-01	C11
rPru p 1 PR-10, Peach	<i>Prunus persica</i>	f419	10	14-4960-01	CBV
rPru p 3 LTP, Peach	<i>Prunus persica</i>	f420	10	14-4961-01	CBW
rPru p 4 Profilin, Peach	<i>Prunus persica</i>	f421	10	14-4962-01	CBX
rTri a 14 LTP, Wheat	<i>Triticum aestivum</i>	f433	10	14-5701-01	CN6
rTri a 19 Omega-5 Gliadin, Wheat	<i>Triticum aestivum</i>	f416	10	14-4954-01	C8H
Gliadin		f98	10	14-5752-01	CXG
<b>Miscellaneous</b>					
nGal-alpha-1,3-Gal (alpha-Gal) Thyroglobulin, bovine		o215	10	14-5997-01	DPC
MUXF3 CCD, Bromelain		o214	10	14-5339-01	CJU

# ImmunoCAP ISAC 112

## Allergen Components

Allergen component	Allergen source common name	Latin name	Protein group
<b>Food allergens</b>			
Gal d 1	Egg white	<i>Gallus domesticus</i>	Ovomucoid
Gal d 2	Egg white	<i>Gallus domesticus</i>	Ovalbumin
Gal d 3	Egg white	<i>Gallus domesticus</i>	Conalbumin/Ovotransferrin
Gal d 5	Egg yolk/chicken meat	<i>Gallus domesticus</i>	Livetin/Serum albumin
Bos d 4	Cow's milk	<i>Bos domesticus</i>	Alpha-lactalbumin
Bos d 5	Cow's milk	<i>Bos domesticus</i>	Beta-lactoglobulin
Bos d 6	Cow's milk and meat	<i>Bos domesticus</i>	Serum albumin
Bos d 8	Cow's milk	<i>Bos domesticus</i>	Casein
Bos d lactoferrin	Cow's milk	<i>Bos domesticus</i>	Transferrin
Gad c 1	Cod	<i>Gadus callarias</i>	Parvalbumin
Pen m 1	Shrimp	<i>Penaeus monodon</i>	Tropomyosin
Pen m 2	Shrimp	<i>Penaeus monodon</i>	Arginine kinase
Pen m 4	Shrimp	<i>Penaeus monodon</i>	Sarcoplasmic Ca-binding protein
Ana o 2	Cashew nut	<i>Anacardium occidentale</i>	Storage protein, 11S globulin
Ber e 1	Brazil nut	<i>Bertholletia excelsa</i>	Storage protein, 2S albumin
Cor a 1.0401	Hazelnut	<i>Corylus avellana</i>	PR-10 protein
Cor a 8	Hazelnut	<i>Corylus avellana</i>	Lipid transfer protein (nsLTP)
Cor a 9	Hazelnut	<i>Corylus avellana</i>	Storage protein, 11S globulin
Jug r 1	Walnut	<i>Juglans regia</i>	Storage protein, 2S albumin
Jug r 2	Walnut	<i>Juglans regia</i>	Storage protein, 7S globulin
Jug r 3	Walnut	<i>Juglans regia</i>	Lipid transfer protein (nsLTP)
Ses i 1	Sesame seed	<i>Sesamum indicum</i>	Storage protein, 2S albumin
Ara h 1	Peanut	<i>Arachis hypogaea</i>	Storage protein ,7S globulin
Ara h 2	Peanut	<i>Arachis hypogaea</i>	Storage protein, 2S albumin
Ara h 3	Peanut	<i>Arachis hypogaea</i>	Storage protein, 11S globulin
Ara h 6	Peanut	<i>Arachis hypogaea</i>	Storage protein, 2S albumin
Ara h 8	Peanut	<i>Arachis hypogaea</i>	PR-10 protein
Ara h 9	Peanut	<i>Arachis hypogaea</i>	Lipid transfer protein (nsLTP)
Gly m 4	Soybean	<i>Glycine max</i>	PR-10 protein
Gly m 5	Soybean	<i>Glycine max</i>	Storage protein, Beta-conglycinin
Gly m 6	Soybean	<i>Glycine max</i>	Storage protein, Glycinin
Fag e 2	Buckwheat	<i>Fagopyrum esculentum</i>	Storage protein, 2S albumin
Tri a 14	Wheat	<i>Triticum aestivum</i>	Lipid transfer protein (nsLTP)
Tri a 19.0101	Wheat	<i>Triticum aestivum</i>	Omega-5 gliadin
Tri a aA_TI	Wheat	<i>Triticum aestivum</i>	
Act d 1	Kiwi	<i>Actinidia deliciosa</i>	
Act d 2	Kiwi	<i>Actinidia deliciosa</i>	Thaumatine-like protein
Act d 5	Kiwi	<i>Actinidia deliciosa</i>	
Act d 8	Kiwi	<i>Actinidia deliciosa</i>	PR-10 protein
Api g 1	Celery	<i>Apium graveolens</i>	PR-10 protein
Mal d 1	Apple	<i>Malus domestica</i>	PR-10 protein
Pru p 1	Peach	<i>Prunus persica</i>	PR-10 protein
Pru p 3	Peach	<i>Prunus persica</i>	Lipid transfer protein (nsLTP)

Allergen component	Allergen source common name	Latin name	Protein group
<b>Aeroallergens</b>			
Cyn d 1	Bermuda grass	<i>Cynodon dactylon</i>	Grass group 1
Phl p 1	Timothy grass	<i>Phleum pratense</i>	Grass group 1
Phl p 2	Timothy grass	<i>Phleum pratense</i>	Grass group 2
Phl p 4	Timothy grass	<i>Phleum pratense</i>	
Phl p 5	Timothy grass	<i>Phleum pratense</i>	Grass group 5
Phl p 6	Timothy grass	<i>Phleum pratense</i>	
Phl p 7	Timothy grass	<i>Phleum pratense</i>	Polcalcin
Phl p 11	Timothy grass	<i>Phleum pratense</i>	
Phl p 12	Timothy grass	<i>Phleum pratense</i>	Profilin
Aln g 1	Alder	<i>Alnus glutinosa</i>	PR-10 protein
Bet v 1	Birch	<i>Betula verrucosa</i>	PR-10 protein
Bet v 2	Birch	<i>Betula verrucosa</i>	Profilin
Bet v 4	Birch	<i>Betula verrucosa</i>	Polcalcin
Cor a 1.0101	Hazel pollen	<i>Corylus avellana</i>	PR-10 protein
Cry j 1	Japanese cedar	<i>Cryptomeria japonica</i>	
Cup a 1	Cypress	<i>Cupressus arizonica</i>	
Ole e 1	Olive	<i>Olea europaea</i>	
Ole e 7	Olive	<i>Olea europaea</i>	Lipid transfer protein (nsLTP)
Ole e 9	Olive	<i>Olea europaea</i>	
Pla a 1	Plane tree	<i>Platanus acerifolia</i>	
Pla a 2	Plane tree	<i>Platanus acerifolia</i>	
Pla a 3	Plane tree	<i>Platanus acerifolia</i>	Lipid transfer protein (nsLTP)
Amb a 1	Ragweed	<i>Ambrosia artemisiifolia</i>	
Art v 1	Mugwort	<i>Artemisia vulgaris</i>	
Art v 3	Mugwort	<i>Artemisia vulgaris</i>	Lipid transfer protein (nsLTP)
Che a 1	Goosefoot	<i>Chenopodium album</i>	
Mer a 1	Annual mercury	<i>Mercurialis annua</i>	Profilin
Par j 2	Wall pellitory	<i>Parietaria judaica</i>	Lipid transfer protein (nsLTP)
Pla l 1	Plantain (English)	<i>Plantago lanceolata</i>	
Sal k 1	Saltwort	<i>Salsola kali</i>	
Can f 1	Dog	<i>Canis familiaris</i>	Lipocalin
Can f 2	Dog	<i>Canis familiaris</i>	Lipocalin
Can f 3	Dog	<i>Canis familiaris</i>	Serum albumin
Can f 5	Dog	<i>Canis familiaris</i>	Arginine esterase
Equ c 1	Horse	<i>Equus caballus</i>	Lipocalin
Equ c 3	Horse	<i>Equus caballus</i>	Serum albumin
Fel d 1	Cat	<i>Felis domesticus</i>	Uteroglobulin
Fel d 2	Cat	<i>Felis domesticus</i>	Serum albumin
Fel d 4	Cat	<i>Felis domesticus</i>	Lipocalin
Mus m 1	Mouse	<i>Mus musculus</i>	Lipocalin
Alt a 1	Alternaria	<i>Alternaria alternata</i>	
Alt a 6	Alternaria	<i>Alternaria alternata</i>	Enolase
Asp f 1	Aspergillus	<i>Aspergillus fumigatus</i>	
Asp f 3	Aspergillus	<i>Aspergillus fumigatus</i>	
Asp f 6	Aspergillus	<i>Aspergillus fumigatus</i>	Mn superoxide dismutase
Cla h 8	Cladosporium	<i>Cladosporium herbarum</i>	
Blo t 5	House dust mite	<i>Blomia tropicalis</i>	
Der f 1	House dust mite	<i>Dermatophagoides farinae</i>	
Der f 2	House dust mite	<i>Dermatophagoides farinae</i>	
Der p 1	House dust mite	<i>Dermatophagoides pteronyssinus</i>	
Der p 2	House dust mite	<i>Dermatophagoides pteronyssinus</i>	
Der p 10	House dust mite	<i>Dermatophagoides pteronyssinus</i>	Tropomyosin
Lep d 2	Storage mite	<i>Lepidoglyphus destructor</i>	

## ImmunoCAP ISAC 112 Allergen Components continued

Allergen component	Allergen source common name	Latin name	Protein group
<b>Aeroallergens continued</b>			
Bla g 1	Cockroach	<i>Blattella germanica</i>	
Bla g 2	Cockroach	<i>Blattella germanica</i>	
Bla g 5	Cockroach	<i>Blattella germanica</i>	
Bla g 7	Cockroach	<i>Blattella germanica</i>	Tropomyosin
<b>Other</b>			
Api m 1	Honey bee venom	<i>Apis mellifera</i>	Phospholipase A2
Api m 4	Honey bee venom	<i>Apis mellifera</i>	Melittin
Pol d 5	Paper wasp venom	<i>Polistes dominulus</i>	Venom, Antigen 5
Ves v 5	Common wasp venom	<i>Vespula vulgaris</i>	Venom, Antigen 5
Ani s 1	Anisakis	<i>Anisakis simplex</i>	
Ani s 3	Anisakis	<i>Anisakis simplex</i>	Tropomyosin
Hev b 1	Latex	<i>Hevea brasiliensis</i>	
Hev b 3	Latex	<i>Hevea brasiliensis</i>	
Hev b 5	Latex	<i>Hevea brasiliensis</i>	
Hev b 6.01	Latex	<i>Hevea brasiliensis</i>	
Hev b 8	Latex	<i>Hevea brasiliensis</i>	Profilin
MUXF3	Sugar epitope from Bromelain		CCD-marker







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