SECOND EDITION

Péter Csonka

MOLECULAR ALLERGOLOGY

User's Guide for Allergen Component IgE Tests

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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. This guide is based on Finnish diagnostic and treatment guidelines and all statements may not be valid in other countries.

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MOLECULAR ALLERGOLOGY

User's Guide for
Allergen Component IgE Tests

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Contents

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Definitions

allergen component	An individual allergen, most commonly a protein, contained in an allergen source. Components that are presently commercially available are indicated in bold in this guide.
allergen source	An organic substance (pollen, nut) containing numerous different proteins, some of which are allergens.
alpha-gal	Galactose-alpha-1,3-galactose
CCD	Cross-reactive carbohydrate determinant
cross-allergens **cross-reactive allergens**	Allergens may also cross-react with each other if an antibody that recognizes both of them exists. The more closely proteins resemble each other by having similar amino acid sequences, the more likely they are to cross-react.
IgE	Immunoglobulin E
labile allergen	Allergenicity and binding to specific IgE is reduced or eliminated by heat and digestion
major allergen	An allergen to which more than 50% of allergic patients are sensitized
minor allergen	Minor allergens are often less prevalent in triggering allergy
molecular allergology	Allergology at the level of allergen components, not just allergen sources
Pollen food syndrome	Redness and itching of the mouth area, swollen lips. Previously known as Oral allergy syndrome (OAS)
PR-10	Pathogenesis-related protein family 10
prick test	A skin prick test
prick-prick test	A skin prick test in which the substance being tested (e.g. an apple) is pricked with a lancet, which is then used to prick the patient's skin
stable allergen	Allergenicity persists despite exposure to heat or digestive enzymes. Stable proteins are also more likely to cause severe, systemic reactions.

Introduction

Our understanding of allergies has grown rapidly over the past few decades. As recently as the 1980s, strict allergen avoidance was considered necessary to reduce allergies.

Recommendations and prohibitions were compiled in numerous lists of what should be avoided to be on the safe side. Despite these recommendations, allergy prevalence has not decreased. On the contrary, doctor visits due to suspected allergies have continued to increase in number. New diagnostic tools are available to confirm or rule out allergies more accurately than before. Nowadays, we are well-equipped to diagnose clinically significant allergic sensitization in order to select the best treatment approach.

Basic mechanisms of allergy

The most common form of allergy is atopic IgE-mediated allergy. Approximately 40% of Finnish young adults have been sensitized to at least one allergen, though not all of them exhibit actual symptoms. Genes, the environment, and lifestyles all influence who develops an allergic disease. Atopic diseases may manifest differently as a person ages: the sensitization profile may change and the symptoms may become milder or stronger. Atopic dermatitis or food allergy may appear at only a few months of age, but the symptoms usually lessen or resolve by the time a child reaches school age. Allergic rhinitis is rare in children under 2 years of age, and sensitization to seasonal allergens occurs gradually. Daily exposure increases the likelihood of sensitization to pets, for example. A child who has atopic dermatitis and/or food allergies as an infant also has an elevated risk of allergic rhinitis and asthma. On the other hand, allergic symptoms may not appear for the first time until adulthood.

Incidence rates of allergic diseases are difficult to estimate accurately due to regional differences between populations, environments and lifestyles. Also, allergic sensitization has been measured using various methods. The incidence of sensitization based on skin prick tests, for example, may not reflect the actual incidence of allergies. Furthermore, the incidence rates of self-reported symptoms are not confirmed in all publications by challenge testing or other means.

Factors that affect the onset of allergic disease include:
1) genes; 2) environment (change to cleaner surroundings, antibiotic therapy, geographic location, eating habits); and 3) route of exposure (airway mucosa, digestive tract, skin).

Several stages are required for allergic symptoms to develop (Figure 1). Exposure to an antigen source – a dog, for example – activates the production of IgE antibodies to dog allergens (sensitization). The antibodies attach to the surface of inflammatory cells, without yet causing significant symptoms in most cases. When the patient is exposed to a dog again, its allergens bind specifically to the anti-dog IgE antibodies on the surface of the patient's inflammatory cells. This causes inflammatory substances inside the cells to be released, resulting in symptoms. **Symptoms do not develop without sensitization, but sensitization does not always lead to symptoms.** Thus an IgE antibody assay does not measure allergy directly, but rather sensitization, or the likelihood of allergy. Indeed, it would be more appropriate to speak of **sensitization testing** rather than allergy testing (Figure 2).

What is an allergen?

An allergen is an antigen, usually a protein, that is able to bind to a specific IgE and trigger an allergic reaction. Proteins account for more than half of the dry mass of most cells. Every organic substance is a potential allergen source

Figure 1. Several stages are required for allergic symptoms to develop.

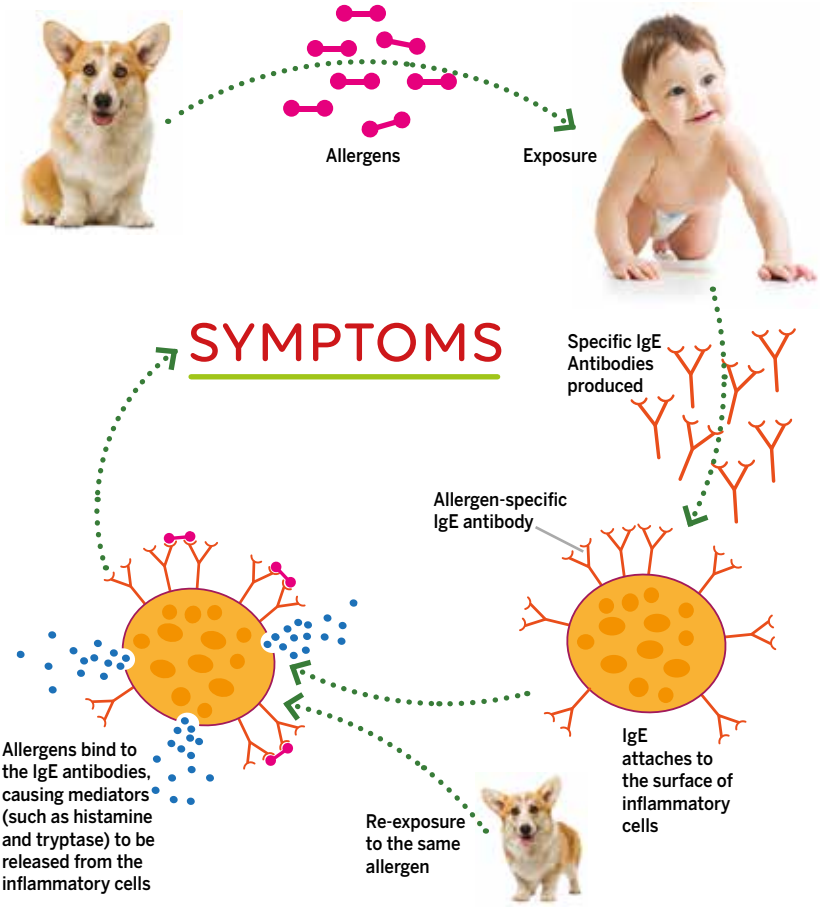
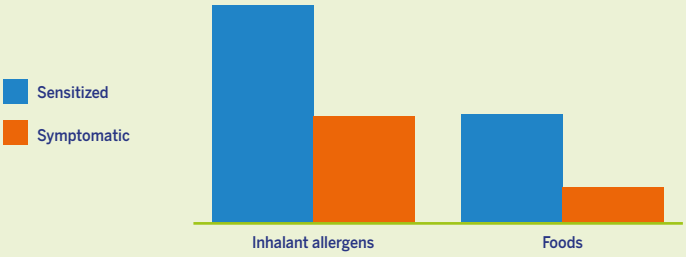


Figure 2.
Elevated levels of antibodies to the allergens tested indicate sensitization, but sensitization does not necessarily lead to clinically relevant symptoms. Particularly in the case of foods, a clear distinction can be seen between sensitization and actual allergy.



and may contain a multitude of proteins with varying properties. A peanut, for instance, is not an individual allergen in itself, but sensitization may occur to any of the proteins it contains (Figure 3). Since the word "allergen" is often used misleadingly in reference to an entire allergen source, individual allergens within an allergen source are called **allergen components** so as to avoid confusion. Components are named according to the Latin genus and species names of the allergen source. Components of the same allergen source are distinguished from each other by numbering them in the order of discovery. In laboratory test abbreviations, the prefix *r* means recombinant, while *n* means nature derived (native). The component IgE tests that are presently commercially available are indicated in bold in this guide.

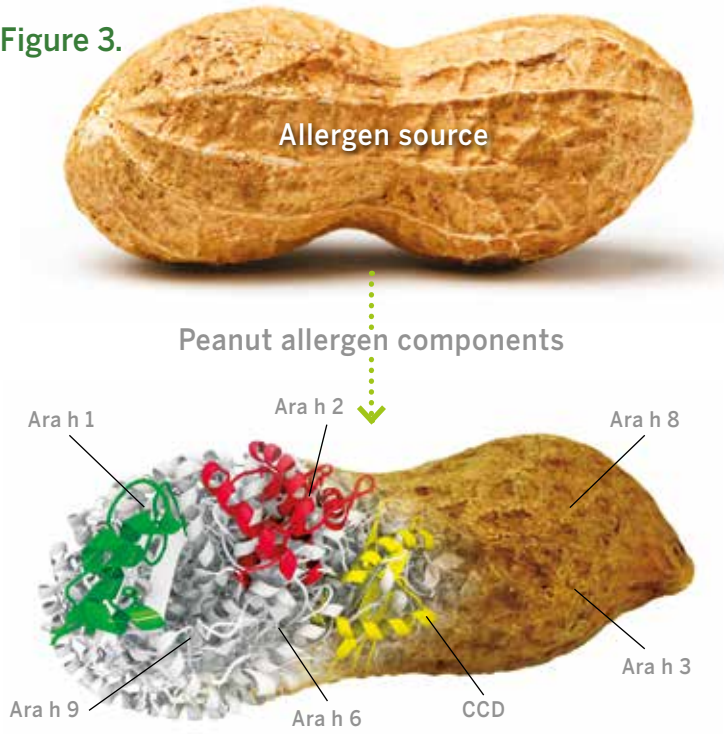
Not all allergens are proteins. Some drugs (such as beta-lactams or chlorhexidine) can form an immunogenic hapten complex by binding to a carrier protein. Among glycans, **CCD (cross-reactive carbohydrate determinant)** and **alpha-gal** can also bind to IgE.

Major allergens and cross-reactive allergens

An allergen source contains proteins of greater and lesser importance in terms of allergic sensitization and symptoms. Allergens to which more than 50% of patients with the allergy are sensitized are usually classified as major allergens, while others are classified as minor allergens. The most important sensitizing allergen of an allergen source is usually a major allergen, and is often linked to clinically relevant symptoms as well. A major allergen is often quite specific for the allergen source.

Allergens may also cross-react with each other if an antibody that recognizes both of them exists (Figure 5 on page 31). The more closely proteins resemble each other by having similar amino acid sequences, the more likely they are to cross-react. Usually the antibody has a preference for the sensitizing allergen that caused a stronger initial sensi-

Figure 3.



Peanut is not an allergen in itself, but contains numerous proteins that are called allergen components. **Ara h 8** is a protein similar to a major allergen of birch. **Ara h 1, 2, 3** and **6** are storage proteins. **Ara h 9** is a lipid transfer protein (LTP). CCD is a carbohydrate determinant.

tization response. Species lineage and taxonomical relationships have some influence on the extent of cross-reactions as well.

It is also useful to consider the properties of allergens belonging to various **protein families**. For example, the most important allergen (major allergen) of birch is **Bet v 1**. More than 95% of birch allergic patients are sensitized to it. The major protein in apple is **Mal d 1**, but symptoms linked to raw apple most often result from primary sensitization to the **Bet v 1** protein, which markedly resembles the **Mal d 1** allergen. Thus **Mal d 1** of apple is said to be an allergen that cross-reacts with birch (a birch homolog), and is not the actual primary sensitizer in this case (see also the pro-

tein families section, and PR-10 cross-allergies on page 13). Depending on the protein family, an allergen that causes severe symptoms may also cross-react with other proteins from an allergen source that belong to the same family (see e.g. the storage protein or nsLTP section on page 17). The more stable the protein, the more likely it is to be associated with significant symptoms (as described in more detail below).

Stable vs. labile allergens

A protein's three-dimensional structure and function may be altered under unfavorable circumstances (e.g. exposure to heat or an acidic or alkaline environment). **Stable components** will remain allergenic despite being subjected to heat or to digestive enzymes, and are also more likely to cause severe, systemic reactions. **Labile components**, on the other hand, will bind to specific IgE to a lesser extent or not at all when they have been heated or digested.

Major allergens and cross-allergens can both be either stable or labile. An individual allergen source contains both stable and labile allergen components. For example, casein in milk (**Bos d 8**) and ovomucoid in hen's egg (**Gal d 1**) are stable proteins. But alpha-lactalbumin (**Bos d 4**) and beta-lactoglobulin (**Bos d 5**) in milk, and ovalbumin (**Gal d 2**) in eggs, are labile proteins. Bet v 1 in birch causes mucosal symptoms within seconds in a person who has been sensitized to it. A birch homolog in hazelnuts (**Cor a 1**), for example, may similarly cause an itchy mouth in someone who is sensitized to birch, but not a systemic reaction. Since birch homologs resembling the Bet v 1 protein (in the PR- 10 family) are labile to heat, foods that contain birch cross-allergens usually cause no symptoms if cooked. In contrast, stable hazelnut allergens (**Cor a 9** and **Cor a 14**) can produce severe reactions.

The nature and severity of symptoms are affected by an allergen's concentration in the allergen source, its stabil-

ity, and the body surface it comes into contact with (airway, eye, mucosa, digestive tract, skin). Stable allergens are more clinically significant than labile allergens. The component a person ultimately becomes sensitized to varies from one individual to the next.

Protein families

Proteins can be classified into families based on their structural and functional properties. There are more than 16,000 protein families, about 40 of which are associated with allergies. The most important families are presented in Table 1. Proteins that belong to the same family can cause significant cross-reactions. In addition to producing allergic symptoms, cross-reactions may be evident in skin prick tests and serum IgE antibody tests based on extracts prepared from whole allergen sources. For example, someone who is allergic to birch may have positive test results for all foods containing birch homologs (see Table 2 on page 19) without any definite or serious symptoms. The family classification helps shed light on how severe a patient's symptoms could potentially be, how likely cross-reactions are, and which substances could trigger cross-reactions.

PR-10 proteins

• The major birch allergen **Bet v 1** is the most significant protein of the PR-10 family in the Nordic countries. It has strong cross-reactivity with the pollen of other broadleaf trees in the order *Fagales* (Table 3 on page 19).
• More than half of people with a *Fagales* tree allergy also develop symptoms from cross-reactive foods (Table 2 on page 19), which contain a PR-10 protein that resembles the major birch allergen. Cross-reactions are most frequently seen with foods belonging to the rose (*Rosaceae*), parsley (*Apiaceae*) or legume families (*Fabaceae*). For example, eating a raw apple may cause an itchy mouth, or peeling a potato may irritate the hands. Since PR-10 proteins denature when exposed to heat or digestive enzymes, these fruits

Table 1. Protein families.

Protein family	Allergen source	Description	Stability	Component examples
PR-10 (Bet v 1)	Pollen from plants in the birch and beech families, fruits, vegetables, nuts	A significant cross-allergen	Labile	**Aln g 1** (alder) **Api g 1** (celery) **Bet v 1** (birch) Cas s 1 (chestnut) **Cor a 1** (hazelnut) Dau c 1 (carrot) Fag s 1 (beech) **Gly m 4** (soy) **Mal d 1** (apple) **Pru p 1** (peach)
2S albumins	Nuts, seeds, legumes	Storage proteins	Stable	**Ana o 3** (cashew) **Ara h 2, Ara h 6** (peanut) **Ber e 1** (Brazil nut) **Cor a 14** (hazelnut) **Jug r 1** (walnut) Pis v 1 (pistachio) **Ses i 1** (sesame seed) Sin a 1 (mustard seed)
7S globulins (vicilins)	Nuts, seeds, legumes	Storage proteins	Stable	**Ara h 1** (peanut) **Gly m 5** (soy) **Jug r 2** (walnut) Ses i 3 (sesame seed)
11S globulins (legumins)	Nuts, seeds, legumes	Storage proteins	Stable	**Ara h 3** (peanut) Ber e 2 (Brazil nut) Fag e 1 (buckwheat) **Gly m 6** (soy) Ses i 6 (sesame seed)

Protein family	Allergen source	Description	Stability	Component examples
Non-specific lipid transfer proteins (nsLTP)	Nuts, seeds, fruits	Defend plants against fungi, bacteria, etc.	Stable	Act d 10 (kiwi) Api g 2 (celery) **Ara h 9** (peanut) Art v 6 (mugwort) **Cor a 8** (hazelnut) Gly m 1 (soy) **Jug r 3** (walnut) Mus a 3 (banana) Pru d 1 (plum) **Pru p 3** (peach) Sola 3 (tomato)
Profilins	Pollens, fruits, vegetables, latex	Significant cross-allergen	Labile	Api g 4 (celery) Ara h 5 (peanut) **Bet v 2** (birch) **Hev b 8** (latex) Mal d 4 (apple) Ole e 2 (olive) **Phl p 12** (timothy grass) **Pru p 4** (peach)
Cereal prolamins	Wheat, barley, rye	A storage protein in cereal grains. Only in cereals	Stable	**Tri a 19** (Wheat) Tri a 21 (Wheat) Tri a 26 (Wheat)
Parvalbumins	Fish	Concentrations differ considerably between fish species.	Stable	**Cyp c 1** (carp) **Gad c 1** (cod) Sal s 1 (salmon) Thu a 1 (tuna)
Tropomyosins	Crustaceans, mollusks, nematodes, mites, cockroaches	A cross-allergen	Stable	**Bla g 1** (cockroach) **Der p 10** (dust mite) **Pen m 1** (shrimp)

Table 1.

Protein family	Allergen source	Description	Stability	Component examples
Serum albumins	Animal saliva, dander, serum	A significant cross-allergen (minor allergen) in animal allergies	Partly labile	**Bos d 6** (cow) **Can f 3** (dog) Cav p 4 (guinea pig) **Equ c 3** (horse) **Fel d 2** (cat) **Gal d 5** (chicken) **Sus s 1** (pig)
Lipokalins	Mammals, mites, cockroaches	The most significant protein family in animal allergies (dander, secretions). Also in the serum of mammals (β-lactoglobulin)	Partly labile	Bos d 2 (cow) **Bos d 5** (cow) **Can f 1** (dog) **Can f 2** (dog) **Equ c 1** (horse) **Fel d 4** (cat)
Bifunctional inhibitors	Cereals	Only in cereals, such as wheat, barleyand rice.	Stabile	Tri a 29 (wheat) Hor v 15 (barley)
Polkalsins	Pollens	Calcium-binding proteins; specific biologic function is not yet known	Labile	**Bet v 4** (birch) Orz s 7 (rice) **Phl p 5** (timothy grass) Tri a 7 (wheat)

The component IgE tests that are presently commercially available are indicated in bold text.

and vegetables generally cause no symptoms if cooked and may only produce local mucosal symptoms if raw.

• Due to their solubility in water, PR-10 proteins produce oropharyngeal symptoms almost immediately. Pollen food allergy (previously known as oral allergy syndrome). Since PR-10 proteins are highly labile (denatured by heat or low pH), systemic allergic reactions develop very rarely. Strong reactions have mainly been described to soy (**Gly m 4**) in patients who consumed large amounts of minimally processed soy products (such as a soy beverage).

• A birch IgE test or skin prick test is often sufficient for diagnosing sensitization to birch and other PR-10 proteins (see the birch tree allergy section on page 34 for details).

Since PR-10 proteins are labile, commercial food extracts for skin prick tests are unnecessary as well as unreliable. In some cases, a cross-reaction with food may be confirmed using the prick-prick method (see the fruit and vegetable allergy sections on page 54). Also, traditional IgE antibody testing based on whole allergen sources are effected by cross-reactivity, making them difficult to interpret in terms of actual sensitization.

• Food allergen component tests help to determine whether a patient has been primarily sensitized to proteins that are cross-reactive with Fagales trees (such as peanut **Ara h 8**) or the food itself (peanut **Ara h 2** and **Ara h 6**) (see the peanut allergy section on page 49).

Storage proteins

• Three storage protein families in plants have been identified as significant from an allergy point of view. They are the 2S albumins (prolamins), 7S globulins (vicilins), and 11S globulins (legumins).

• The stable storage proteins of nuts, seeds and legumes are mostly specific to the allergen source, but may sometimes cross-react.

• Storage proteins are highly resistant to heating and digestion and often cause serious symptoms.

• See Table 4 on page 22.

Non-specific lipid transfer proteins (nsLTPs)

• Non-specific lipid transfer proteins (nsLTPs) are probably involved in the defensive mechanisms of plants. Such nsLTPs are found in pollens (olive tree **Ole e 7**), nuts (peanut **Ara h 9**), food (wheat **Tri a 14**), and many other plant products as well (Table 5 on page 26).

• Sensitization to nsLTPs varies geographically. In southern Europe, it is the most significant cause of plant food allergies. In line with the purpose of these proteins, they remain stable even under extreme conditions.

For example, peach **Pru p 3** binds to IgE even after being heated for 160 minutes at 100°C.

• Studies indicate that the peach nsLTP **Pru p 3** often acts as a primary sensitizer, possibly leading to cross-reactions with other nsLTP-containing foods. However, not all proteins in this family cross-react so strongly that a particular patient's detailed sensitization profile could be determined just by measuring IgE binding of a single nsLTP. For example, peach **Pru p 3** antibody levels do not correlate with those of wheat **Tri a 14** (as in baker's asthma).
• The severity of symptoms due to nsLTPs is difficult to predict. For example, **Pru p 3** can cause mild pollen food allergy syndrome, also known as OAS (oral allergy syndrome, redness and itching of the mouth area, swollen lips) or systemic symptoms (extensive urticaria, vomiting, diarrhea, anaphylaxis).

Profilins

• Profilins are panallergens found in nearly all eukaryotic cells (protozoa, fungi, plants, animals) (Table 6, page 32). The amino acid sequences of profilins are at least 75% identical even between distant relatives within the plant kingdom.
• Primary sensitization is most often due to pollen (e.g. birch **Bet v 2**, timothy grass **Phl p 12,** mugwort Art v 4). Nearly half of people with pollen allergies are sensitized to a profilin, and many of them also experience oropharyngeal symptoms from raw plant foods. Profilins have a tendency to cause test reactions for almost any product of plant origin that have nothing to do with the patient's symptoms. For example, a person sensitized to a profilin may have positive skin prick and serum sIgE results (based on extracts prepared from whole allergen sources) due to the unprocessed latex used in these tests, even in the absence of an actual latex allergy. True latex allergy involves sensitization to the stable allergens in latex.
• Profilins are labile proteins that bind considerably less to IgE after being heated. They rarely cause significant symptoms.
• Routine testing for profilin sensitization is unnecessary.

Table 2.

Recognized plant homologs of birch Bet v 1 in the PR-10 family

This table shows some examples of taxonomic relationships in the plant kingdom. Plants belonging to the same family are most likely to cross- react. It is impossible to predict who will experience cross-reactions or how pronounced they will be.

Protein family	Allergen source	Allergen
Nightshade	Tomato (*Solanum lycopersicum*)	Sola l 4
Birch *(Betulaceae)*	Hazelnut (*Corylus avellana*)	**Cor a 1.04**
Chinese gooseberry (*Actinidiaceae)*	Kiwi (*Actinidia deliciosa*)	**Act d 8**
Legume (*Fabaceae*)	Peanut (*Arachis hypogaea*) Soybean (*Glycine max*) Mung bean (*Vigna radiata*)	**Ara h 8** **Gly m 4** Vig r 1
Beech (*Fagaceae*)	Chestnut (*Castaea sativa*)	Cas s 1
Rose (*Rosaceae*)	Strawberry (*Fragaria ananassa*) Apple (*Malus domestica*) Apricot (*Prunus armeniaca*) Cherry (*Prunus avium*) Peach (*Prunus persica*) Pear (*Pyrus communis*) Raspberry (*Rubus idaeus*)	Fra a 1 **Mal d 1** Pru ar 1 Pru av 1 **Pru p 1** Pyr c 1 Rub i 1
Parsley (*Apiaceae*)	Celery (*Apium graveolens*) Carrot (*Daucus carota*)	**Api g 1** Dau c 1

The component IgE tests that are presently commercially available are indicated in bold text.

Table 3. PR-10 proteins of pollen

Protein family	Allergen source	Allergen
Birch (*Betulaceae*)	Birch (*Betula verrucosa*) Alder (*Alnus glutinosa*) Hazel (*Corylus avellana*)	**Bet v 1** **Aln g 1** **Cor a 1**
Beech (*Fagaceae*)	Beech (*Fagus silvatica*) White oak (*Quercus alba*) Chestnut (*Castanea sativa*)	Fag s 1 Que a 1 Cas s 1

The component IgE tests that are presently commercially available are indicated in bold text.

Cereal prolamins

• Cereal prolamins are also storage proteins, but only occur in cereal grains. See Table 1.
• Cereal prolamins do not cross-react with storage proteins of seeds, nuts or legumes.
• Wheat contains several prolamins, such as **Tri a 19** (ω-5-gliadin), **Tri a 21** (α/β-gliadin) and **Tri a 26** (glutenin).

Parvalbumins

β-parvalbumins are the most significant fish allergen and the highest concentrations of them are found in fish muscle. See Table 1 on page 14.
• Highly stable proteins that usually cause immediate symptoms.
• May also cause symptoms in aerosol form (e.g. when fish is fried).
• Parvalbumin concentrations vary considerably from one fish species to another.
• Parvalbumins of different fish orders easily cross-react, but not always.
• Not cross-reactive with the tropomyosin of crustaceans and mollusks.
• Not cross-reactive with fish egg (roe) proteins (vitellogenins and glycoproteins).
• α-parvalbumin is found in the muscles and organs of mammals and birds, and is not considered a major allergen. α-parvalbumin has not shown significant cross- reactivity with β-parvalbumins in fish.
• See the fish allergy section on page 44 for more details.

Tropomyosins

• A significant food allergen family. They usually cause immediate symptoms. See Table 1 on page 14.
• A major protein in crustaceans, mollusks, nematodes, mites and cockroaches.
• Found in muscle and other cells. Approximately 20% of a crustacean's protein mass consists of tropomyosin.

• Sensitization to tropomyosin can be demonstrated in approximately 60% of people allergic to crustaceans.
• Strong cross-reactivity between different crustaceans (more than 95% homology). Weaker cross-reactivity between crustaceans and mollusks (approximately 50% homology).
• Some of these are inhaled allergens (dust mites and other mites, cockroaches).
• See the crustaceans and mollusks section on page 46 for details.

Serum albumin

• Found in animal saliva, urine, dander, serum and meat.
• The majority of serum albumins are inhaled minor allergens.
• Heat-sensitive, i.e., denatured at 50–60 °C.
• Significant cross-allergen in animal allergy attributed to mammals. The serum albumins of different animals resemble each other, which can cause false positive results in skin prick tests and other tests. If necessary, the primary sensitizer can be established by component testing.
• Sensitization is most commonly seen to the proteins **Can f 3** of dog and **Fel d 2** of cat.
• Sensitization to the proteins **Bos d 6** of domestic cattle and **Sus s 1** of pig is rare. For example, Bos d 6 (bovine serum albumin) is found in domestic cattle dander, milk (only about 1% of milk protein) and meat. Bos d 6 mainly causes symptoms as an inhaled allergen. Heating milk for 10 minutes eliminates Bos d 6 allergenicity, and will also cause no symptoms if used in food. Bos d 6 is not a clinically significant meat allergen and cooked beef does not cause symptoms.
• Serum albumin has also been linked to pork-cat syndrome. Very rarely, cat **Fel d 2** protein cross-reacts with pig **Sus s 1** protein. In theory, someone who has a cat allergy could develop symptoms from undercooked pork. Cooked pork causes no symptoms.
• Serum albumin cross-reactivity between mammals and birds is about 60% due to Sus s 1.

Table 4. Nuts and seeds.

Allergen source	Plant family	Storage proteins			nsLTP	PR10	Profilin
		2S albumin	7S globulin	11S globulin			
Peanut (*Arachis hypogaea*)	Legume (*Fabaceae*)	**Ara h 2** **Ara h 6**	**Ara h 1**	**Ara h 3**	**Ara h 9**	**Ara h 8**	Ara h 5
Hazelnut (*Corylus avellana*)	Birch (*Betulaceae*)	**Cor a 14**	Cor a 11	**Cor a 9**	**Cor a 8**	**Cor a 1**	Cor a 2
Walnut (*Juglans regia*)	Beech (*Fagaceae*)	**Jug r 1**	**Jug r 2**	Jug r 4	**Jug r 3**		
Pecan (*Carya illinoinensis*)	Beech (*Fagaceae*)	Car i 1		Car i 2			
Chestnut	Beech (*Fagaceae*)						
Brazil nut (*Bertholletia excelsa*)	Brazil nut (*Lecythidaceae*)	**Ber e 1**		Ber e 2			
Cashew (*Anacardium occidentale*)	Sumac (*Anacardiaceae*)	**Ana o 3**	Ana o 1	**Ana o 2**			
Pistachio (*Pistacia vera*)	Sumac (*Anacardiaceae*)	Pis v 1	Pis v 3	Pis v 2			
Almond (*Prunus dulcis*)	Rose (*Rosaceae*)			Pru du 6	Pru du 3		Pru du 4
Pine nut (*Pinus pinea*)	Pine (*Pinaceae*)		Pin pi 1				
Coconut (*Cocos nucifera*)	Palm (*Arecaceae*)		Coc n 2	Coc n 4			Coc n 5
Mustard seed (*Sinapis alba*)	Mustard (*Brassicaceae*)	Sin a 1		Sin a 2	Sin a 3		
Sunflower seed (*Helianthus annuus*)	Aster (*Asteraceae*)	Hel a 2S			Hel a 3		Hel a 2
Sesame seed (*Sesamum indicum*)	Sesame (*Pedaliaceae*)	**Ses i 1**, Ses i 2	Ses i 3	Ses i 6 Ses i 7			
Poppy seed (*Papaverin somniferum*)	Poppy (*Papaveraceae*)					Pop s 1	Pop s 2
Buckwheat (*Fagopyrum esculentum*)	Buckwheat (*Polygonaceae*)	**Fag e 2**	Fag e 3				

The component IgE tests that are presently commercially available are indicated in bold text.

• A skin prick test with uncooked chicken can cause a wheal in some patients who are allergic to egg (due to **Gal d 5**), but cooked chicken causes no allergic symptoms.

Lipocalins

• Lipocalins constitute the majority of mammal allergens. They also occur in arthropods, plants and bacteria.
• The highest concentrations are found in mammal secretions (saliva, urine, serum) and dander.
• Mammal serum proteins such as cow **Bos d 5** are included in this family, along with many proteins present in animal dander, such as dog **Can f 1** and **Can f 2,** cat **Fel d 4**, cow **Bos d 2**, and horse **Equ c 1**.
• Primarily inhaled allergens, except for cow serum **Bos d 5** (β-lactoglobulin).
• Widespread in the environment, adhering to surfaces (clothing, carpets, wallpaper).
• Lipocalins are mostly species specific. Sequence homology between different species is usually only about 20% to 30%, but exceptions can be found. For example, cross-reactions may occur between cat Fel d 4, dog Can f 6 and horse Equ c 1. As a result, skin prick testing for an animal the patient was not primarily sensitized to could result in a wheal of more than 3 mm in diameter. If necessary, allergen component testing can be used to identify the primary sensitizing animal more specifically in order to plan desensitization therapy.
• See Figures 6/A and 6/B on pages 37-38

Bifunctional inhibitors

• Bifunctional inhibitors are only present in cereal grains. The most important components are wheat Tri a 29 and barley Hor v 15. See Table 1 on page 14.
• Sensitization takes place through the airways or the gastrointestinal tract.
• A significant cause of baker's asthma.

Polcalcins

• A pollen panallergen. See Table 1 on page 14.
• Calcium-binding proteins whose specific biologic function is unknown.
• They also cause significant cross-reactions in skin prick testing and blood tests based on extracts prepared from whole allergen sources.
• They do not cause clinically relevant symptoms.

The importance of allergy testing

• It is important to find out whether symptoms are due to an allergy or some other disease.
• Approximately 80% of atopic patients are sensitized to more than one allergen. An effort should be made to identify the allergens that have the most impact on a patient's symptoms and quality of life.
• The more precise the diagnosis, the easier it will be to avoid triggers and to treat symptoms correctly and effectively. This also precludes inappropriate medication. Unnecessary allergen avoidance can be averted with the help of testing.
• The potential for immediate or delayed symptoms can be investigated, as well as determining which allergens are causing persistent or episodic symptoms.
• The sensitization profile may change over time. This information can be updated if there was any change in the patient's symptoms or worsening of the condition.
• Characterizing the sensitization profile allows for more detailed prognosis, especially in the case of food allergy symptoms.
• The patient's risk of developing a severe, systemic allergic reaction can be assessed.
• The cause of anaphylaxis must always be investigated as thoroughly as possible.
• Prior to desensitization immunotherapy, it is necessary to confirm that the patient is sensitized to the allergens being used in the therapy.

The following information is needed for accurate diagnosis:

1. A description, in as much detail as possible, of:
    a. the exposure (what the patient was exposed to and by what route);
    b. the symptoms (nature, severity and speed of onset);
    c. other factors that aggravate the symptoms (medication, alcohol, physical exertion);
    d. attempted treatments.
2. Logical analysis, temporal relationship, dose-dependency, repeatability.
3. Have any allergies been diagnosed previously?
4. Other atopic diseases (eczema, asthma, allergic rhinitis).
5. Familiarity with the properties of various allergens.
6. Knowledge of what is measured with antibody tests and how: understanding the strengths and weaknesses of different methods.

What to test for and when?

• IgE-mediated sensitization is evaluated by measuring the specific IgE antibody level in the blood or by skin prick testing. These methods are not suitable for investigating non-IgE-mediated mechanisms.
• IgE-mediated reactions are usually immediate.

Table 5.

Non-specific lipid transfer proteins (allergens of the nsLTP family).
Plants belonging to the same family are most likely to cross-react.
Not all proteins belonging to the nsLTP family cross-react with each other.

Plant family	Allergen source	Allergen
Banana (*Musaceae*)	Banana (*Musa acuminate*)	Mus a 3
Grass (*Poaceae*)	Corn (*Zea mays*) Wheat (*Triticum aestivum*)	Zea m 14 **Tri a 14**
Legume (*Fabaceae*)	Peanut (*Arachis hypogea*)	**Ara h 9**
Nightshade (*Solanaceae*)	Tomato (*Solanum lycopersicum*)	Sola l 3
Birch (*Betulaceae*)	Hazelnut (*Corylus avellana*)	**Cor a 8**
Chinese gooseberry (*Actinidiaceae*)	Kiwi (*Actinidia deliciosa*)	Act d 19
Aster (*Asteraceae*)	Sunflower seed (*Helianthus annuus*)	Hel a 3
Beech (*Fagaceae*)	Walnut (*Juglans regia*)	**Jug r 3**
Mustard (*Brassicaceae*)	Mustard seed (*Sinapis alba*)	Sin a 3
Rose (*Rosaceae*)	Almond (*Prunus dulcis*) Apple (*Malus domestica*) Peach (*Prunus persica*) Cherry (*Prunus avium*) Plum (*Prunus domestica*)	Pru du 3 **Mal d 3** **Pru p 3** Pru av 3 Pru d 3
Citrus (*Rutaceae*)	Lemon (*Citrus limon*) Orange (*Citrus sinensis*)	Cit l 3 Cit s 3
Spurge (*Euphorbiaceae*)	Latex (*Hevea brasiliensis*)	Hev b 12
Grape (*Vitaceae*)	Grape (*Vitis vinifera*)	Vit v 1

The component IgE tests that are presently commercially available are indicated in bold text.

Symptoms develop within two hours of exposure and persist for as long as the exposure. No symptoms occur if the allergen is successfully avoided.

Measuring allergic sensitization by traditional methods

• Total serum IgE may be markedly elevated in allergies or in allergic diseases such as atopic eczema and asthma. In effect, elevated total IgE suggests an atopic tendency, but it is non-specific in the same way as fever is an indicator of infection. Elevated values provide no detailed information about the cause, and low values do not rule out disease.

Symptoms that may indicate IgE-mediated sensitization	Symptoms that usually indicate a non-IgE-mediated mechanism
• Anaphylaxis • Immediate urticaria or edema (duration usually less than 24 h) • Allergic rhinitis • Hoarse voice, dyspnea, exacerbation of asthma • Itchy, red and watery eyes • Severe atopic dermatitis in an infant • Immediate gastrointestinal symptoms (itchy mouth, vomiting)	• Atopic dermatitis starting at preschool age or later. • Mild atopic dermatitis that worsens occasionally • Delayed gastrointestinal symptoms • Restlessness or tearfulness at night • Food intolerance • Chronic urticaria (persisting for days) • Airway irritation from chemicals (smoke, perfumes)

• Allergic sensitization has traditionally been investigated with skin prick tests or by measuring specific IgE antibody levels. These methods actually measure sensitization to an allergen source, and are unable to discern which proteins of the whole allergen source a patient has been sensitized to.

• In general, traditional methods are sufficiently accurate for inhaled allergens. If a skin prick test for timothy grass results in a wheal more than 3 mm in diameter, there is no need to further investigate sensitization to grasses.

In the case of foods, these methods cannot determine whether a positive sensitization test is clinically relevant for the patient or results from a cross-reaction with other allergen sources. A reaction to a peanut skin prick test or an elevated level of specific IgE to peanut may be caused by either specific or cross-reactive proteins.

• Measuring sensitization to particular allergen components for a patient's sensitization profile provides clinically meaningful results.

• **Patients who are sensitized to labile, cross-reactive components usually experience only mild, local symptoms. On the other hand, those who are sensitized to stable, specific components are at high risk of developing severe, systemic reactions.**

• Specific IgE antibody assays use reference values to indicate a threshold of observable sensitization. The sensitivity of the allergen-specific serum IgE antibody assay has been increased by providing numeric results even for very low IgE antibody concentrations of 0.1–0.35 kU/l.
The clinical threshold is still considered to be 0.35 kU/l, however. Above 0.1 (there is no upper limit), the patient's antibody levels are quantifiable for the allergen under investigation. However, this does not necessarily mean that the patient has symptoms (he or she is allergic to the allergen source in question).

• Absolute clinically significant cutoff values cannot be provided for particular allergens, but the higher the antibody level, the greater the likelihood that sensitization will be associated with symptoms as well. **The clinical relevance of results must always be considered on a case-by-case basis according to the patient's symptoms and the allergen involved.**

• Patients who suffer from atopic eczema may have elevated levels of antibodies to numerous allergens, only some of which might cause symptoms. **In other words, sensitization is not the same thing as allergy** (Figure 2, page 9).

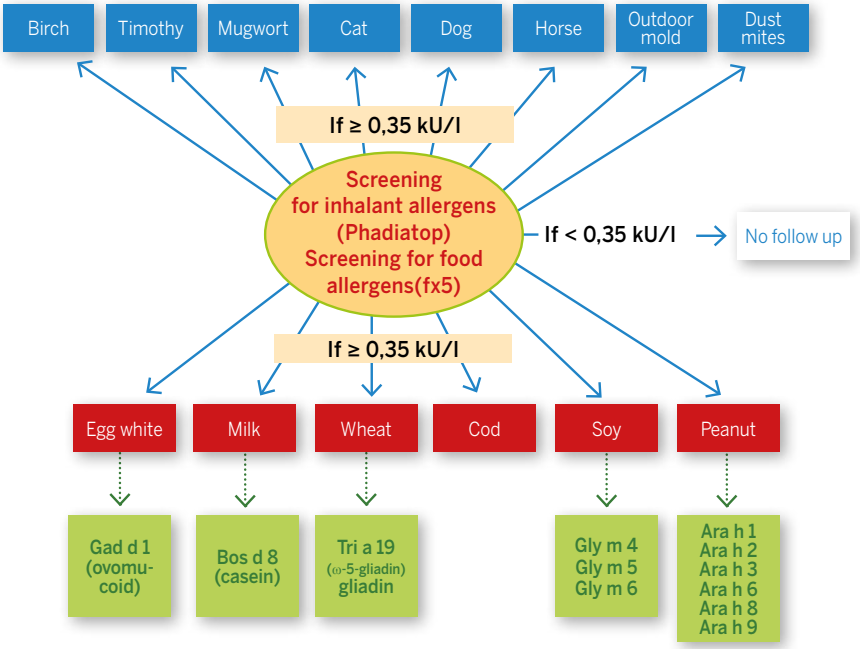
• **Sensitization reflects exposure, but the nature of symptoms cannot be predicted directly based on antibody levels.** This means there is no certain way to tell whether a patient will develop rhinitis, itchy eyes or breathing difficulties, or which organs will be most affected by the symptoms.
• An individual's sensitization profile may change over time, usually expanding to include new sensitizations. Someone who has low levels of pollen antibodies at 2 years of age may be sensitized to numerous pollens by adulthood.
• The use of a broad range of single specific IgE tests is analytically more sensitive than using only one screening test but, by using a screening test like Phadiatop or food screening with fx5, the analytical sensitivity compared to single allergens is very high. Antibody levels may be measured repeatedly as needed.
• Basic IgE screening with automatic follow-up (Figure 4 on page 30) includes ImmunoCAP Phadiatop (a mixture of common inhalant allergens) and ImmunoCAP fx5 (a food mixture of egg white, milk, fish, wheat, peanut and soybean). If the mixture yields a positive result, a quantitative measurement of the individual whole allergens included in the allergen mix would be automatically performed to identify the allergen specific IgE. The specificity of the basic IgE screening is considerably enhanced, particularly for foods, if the positive whole allergens are further analyzed by component testing.

Allergen component testing, or molecular allergology

• Allergen skin prick tests and serum IgE antibody tests have traditionally used extracts prepared from whole allergen sources. An extract contains thousands of water-soluble substances found in the source, such as proteins, carbohydrates and low-weight molecules. IgE antibodies recognize less than 10% of the substances in an extract, and the rest are not relevant to allergic sensitization.
A single allergen source contains dozens of individual proteins called allergen components (Figure 3 on page 11). See also the "What is an allergen?" section on page 8.

Figure 4.

Basic IgE screening with automatic follow-up covers both inhaled allergens as well as food allergens to the component level.



• Sensitization to a particular allergen component can be evaluated using the **ImmunoCAP®** method, either one component at a time or in panels (e.g. of peanut components) depending on the laboratory. The required specimen volume is 1-2 mL of serum (0.04 mL/allergen component). The results are quantitative (as kU/L) (Figure 5).

• **ImmunoCAP® ISAC microarray testing** may be considered when the cause of a severe allergic reaction has not been determined by other methods or in order to save the serum specimen for a polysensitized patient. The test uses a microchip to measure IgE antibody responses to 112 allergen components from more than 50 different allergen sources simultaneously. The results are semiquantitative and are reported as ISU units (ImmunoCAP® ISAC Standardized Unit). See also Table 12 on page 68.

Examples where allergen component testing can significantly enhance clinical practices

• Evaluating the risk of a severe, systemic allergic reaction (sensitization to high-risk proteins).
• Specifying a diet: which foods can be consumed and which should be avoided.
• Identifying cross-reactions.
• Recognizing genuine and primary sensitization (e.g. when considering immunotherapy).
• Investigating labile proteins.
• Investigating sensitization to an allergen source for which the concentration of a particular component is very low.

Figure 5.

Compared to traditional methods, component tests yield more precise information about a patient's sensitization to key allergens linked to symptoms, as opposed to just cross-reactive allergens.
Allergen source A contains proteins that are specific for the source itself (A1 and A2) and a protein resembling that of another source (A3).

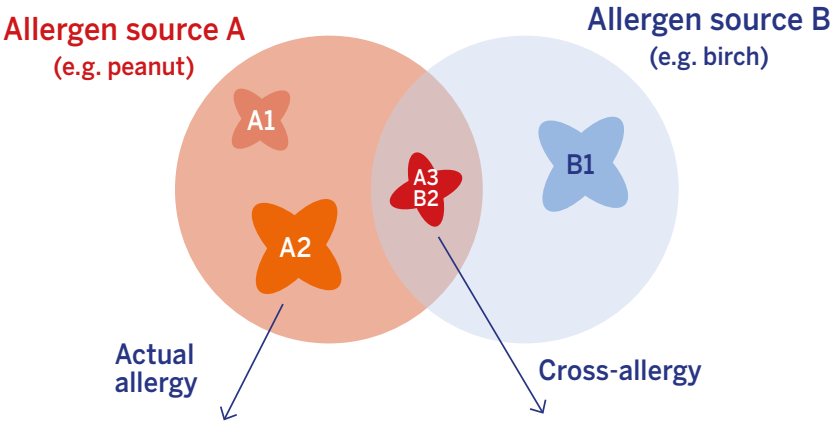


Table 6. Profilins.

Profilins are panallergens found in nearly all eukaryotic cells. Profilins cross-react with each other extensively, but rarely cause significant symptoms.

Plant family	Allergen source	Allergen
Bromeliad (*Bromeliaceae*)	Pineapple (*Ananas comosus*)	Ana c 1
Banana (*Musaceae*)	Banana (*Musa acuminata*)	Mus a 1
Nightshade (*Solanaceae*)	Tomato (*Solanum lycopersicum*)	Sola l 1
Grass (*Poaceae*)	Timothy grass (*Phleum pratense*)	**Phl p 12**
Birch (*Betulaceae*)	Birch (*Betula verrucosa*) Hazelnut (*Corylus avellana*)	**Bet v 2** Cor a 2
Gourd (*Cucurbitaceae*)	Melon (*Cucumis melo*)	Cuc m 2
Chinese gooseberry (*Actinidiaceae*)	Kiwi (*Actinidia deliciosa*)	Act d 9
Mulberry (*Moraceae*)	Fig (*Ficus carina*)	Fic c 4
Aster (*Asteraceae*)	Sunflower seed (*Helianthus annuus*)	Hel a 2
Olive (*Oleaceae*)	Olive tree (*Olea europaea*)	Ole e 2
Legume (*Fabaceae*)	Peanut (*Arachis hypogaea*) Soy (*Glycine maxima*)	Ara h 5 Gly m 3
Mustard (*Brassicaceae*)	Mustard seed (*Sinapis alba*)	Sin a 4
Rose (*Rosaceae*)	Apple (*Malus domestica*) Peach (*Prunus persica*) Pear (*Pyrus communis*)	Mal d 4 **Pru p 4** Pyr p 4
Citrus (*Rutaceae*)	Orange (*Citrus sinensis*)	Cit s 2
Parsley (*Apiaceae*)	Carrot (*Daucus carota*) Celery (*Apium graveolens*)	Dau c 4 Api g 4

The component IgE tests that are presently commercially available are indicated in bold text.

Interpreting results

• Allergy tests are intended to assess whether the allergen being tested is a likely cause of the symptoms.
• Interpreting the results of sensitization and allergy tests requires knowledge of allergens and local conditions.
• The clinical relevance of IgE antibody levels varies according to the allergen, population and geographic location.
• Elevated antibody levels indicate sensitization, but the diagnosis is confirmed by follow-up observation of allergy symptoms worsening with renewed allergen contact and improving with allergen avoidance or desensitization. Food challenge testing is important in confirming the diagnosis when a food allergy is suspected.
• Even if a test is technically positive, symptoms may be entirely absent, or the test may not explain the exact symptoms for which the patient sought medical attention.
• The severity of symptoms should be considered rather than focusing too much on absolute values. A positive allergy test says nothing about what symptoms a patient will have or how severe they will be.
• See the interpretation diagrams in the various allergen sections for more details.
• See Appendix 1 on page 76 for suggested allergen component interpretations.

Tests that should not be used when allergy is suspected

• Specific blood IgA or IgG antibodies are not helpful in investigating allergic sensitization as these antibodies are normally found in the body. The body develops IgG antibodies to any new substances it encounters. This is a normal response.

Pollen allergy

Trees

• In Nordic countries allergic rhinitis is most commonly caused by pollen from plants of the birch and beech families in the order Fagales. These include birch, alder, hazel, beech, oak, chestnut, and others. Approximately 20% of Finland's population is sensitized to birch, and other Fagales trees also trigger symptoms in many of those who are sensitized.

• The major proteins belong to the PR-10 family (see Table 1 on page 14).

• Sensitization to the birch **Bet v 1** protein suggests Fagales allergy with its typical pollen allergy symptoms.

• Fagales trees also contain profilin (e.g. birch **Bet v 2**, hazel Cor a 2) and polcalcins (birch **Bet v 4**, alder Aln g 4), as do other plants.

• Sensitization to the pollen of other Fagales trees may also occur with repeated exposure. The major protein in olive trees is **Ole e 1**; Ole e 2 is a profilin and Ole e 3 is a polcalcin. The major protein in plane trees is **Pla a 1**, and Pla a 8 is a profilin. The major protein of cypress is **Cup a 1**.

• Basic IgE screening and specific follow-up with complete allergen IgE tests, or a skin prick test is usually sufficient for investigating tree pollen allergy. Even a birch-specific IgE antibody assay may suffice, since someone who is sensitized to birch is also likely to have symptoms due to other Fagales pollens (Table 3, page 19).

• Since many foods contain proteins in the PR-10 family (Table 2, page 19), the symptoms of someone with a Fagales allergy may need to be characterized in more detail. Food allergen component tests help to determine whether a patient has been primarily sensitized to proteins that are cross-reactive with Fagales trees (such as peanut **Ara h 8**) or the food itself (peanut **Ara h 2**).

Grasses

• This family (*Poaceae*) includes common grasses and tufted grasses (*Phleum*), and cultivated grains such as wheat (*Triticum*), barley (*Hordeum*) and rye (*Secale*).
• The most significant grass allergens are **Phl p 1** and **Phl p 5b** of timothy grass. Most patients with grass allergy are sensitized to these proteins. Cross-reactions with other grasses are very common. It is usually sufficient to test for sensitization to a single grass using traditional methods.
• Cross-reactions also occur between tufted grass and wheat pollens. A skin prick test or specific IgE antibody response to wheat is usually a sign of a grass allergy, and more rarely a food allergy. When investigating a cereal allergy, allergen component testing is recommended (e.g. **Tri a 19** and **gliadin**) because it is considerably more specific and less likely to cause a false positive result (see the cereal allergy section).
• Sensitization to other grass proteins (e.g. timothy **Phl p 4** or **Phl p 7**) is also possible, but is not clinically relevant and there is usually no need to test for these components.

Other pollens

• Any plant pollen can cause allergic symptoms. The geographical location and pollination periods effect the rate of sensitization and occurrence of symptoms.
• Allergic symptoms due to mugwort (*Artemisia*: **Art v 1, Art v 3,** Art v 6), ragweed (*Ambrosia*: **Amb a 1**), pellitory (*Parietaria*: **Par j 2**), and plantain weed (*Plantago*: **Pla l 1**) are similar to other tree and grass allergy.
• Weed allergens cross-react. For example, ragweed sensitized patients with elevated **Amb a 1** component shows cross-reactivity with mugwort (Art v 6). In the same way **Art v 1** from mugwort show cross-reactivity with ragweed's Amb a 4.
• Weed pollen LTP allergens (like **Art v 3**) show a significant degree of cross-reactivity with other LTPs especially in Mediterranean countries.

• Weed pollen allergy is less frequent in Nordic countries compared to warmer climates.

Animal allergy

• The highest concentrations of animal allergens are found in dander, saliva and urine.
• Animal allergens are widely distributed and adhere to fur, skin, fabrics and other surfaces.
• They mostly cause respiratory symptoms, but direct contact with secretions can also cause skin symptoms (from licking) or even anaphylaxis (from biting).
• Animal allergens represent several protein families.
• Lipocalins from secretions are usually major animal allergens (dog **Can f 1** and **Can f 2**, cat **Fel d 4**, rabbit Ory c 1, hamster Mes a 1, cow Bos d 2, and horse **Equ c 1**). These allergens spread into the environment through saliva and dander.
• Serum albumins originate from saliva and dander (dog **Can f 3**, cat **Fel d 2**, horse **Equ c 3**).
• **Fel d 1** from cat saliva and skin is referred to as a uteroglobin and is a major allergen specific to cats.
• **Can f 5** is a prostate-related protein excreted into the urine of male dogs.
• The proteins of different types of animals, particularly serum albumins, can cross-react. This can cause a false-positive wheal in skin prick testing, for example.
• For the most part, traditional methods such as skin prick testing or specific serum antibody assays are sufficient for investigating animal allergen sensitization.
• In cases of uncertainty (e.g. a test result that might have been caused

by a cross-reaction), allergen components offer a means to investigate animal allergy more precisely. If a patient's sIgE antibodies to both dog and cat are elevated, it is possible to find out whether both animals are relevant to the patient's symptoms. More detailed profile mapping is necessary when considering desensitization therapy, for example. Which animal should the patient be desensitized to? Patient A is found to have elevated antibodies to Can f 1, Can f 2 and Fel d 2, thus a dog was probably the primary sensitizer and a cat might not cause any symptoms. Patient B has a result profile of Fel d 1, Fel d 2, Fel d 4 and Can f 3, indicating a primary cat allergy (Figures 6/A and6/B).

Food allergy

• In the case of food allergies, it is particularly important to bear in mind that sensitization to an allergen source is not the same thing as allergy. No exact IgE antibody cutoff or reference value can be given to reliably express how likely a patient is to develop symptoms or how severe those symptoms might be. Food allergy should always be confirmed by challenge testing.

Figure 6/A. The patient has elevated antibodies to Can f 1, Can f 2 and Fel 2, so a dog was probably the primary sensitizer and a cat might not cause any symptoms.

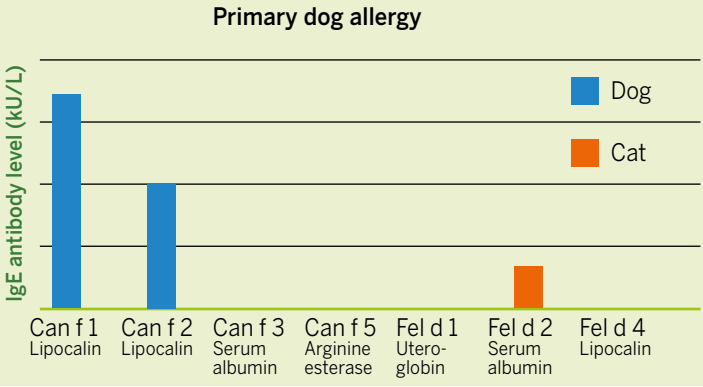
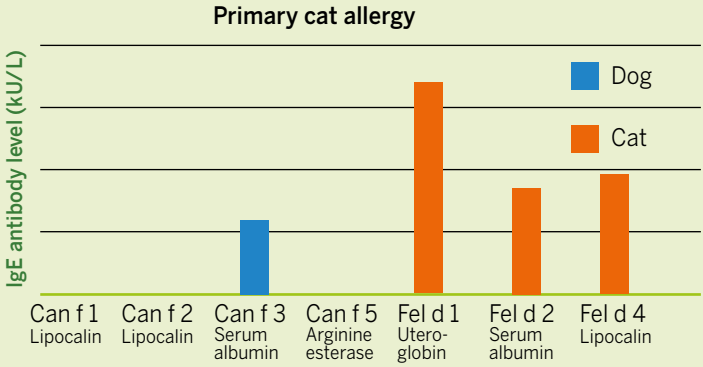


Figure 6/B. The patient's result profile is Fel d 1, Fel d 2, Fel d 4 and Can f 3, indicating a primary cat allergy.



- A false positive result could lead to
  - unnecessary avoidance that has an impact on nutrition, growth, and the natural development and maintenance of tolerance; and
  - needless fear and restrictions on everyday life.
- A false negative result could lead to unexpected allergic reactions due to not knowing which foods to avoid.
- Together with traditional methods, allergen component testing significantly enhances the sensitivity and accuracy of food allergy diagnostics. Traditional methods consider sensitization to whole allergen sources. Allergen components, in turn, can narrow down which proteins within an allergen source are meaningful for a particular individual, since only some proteins of an allergen source are associated with the risk of a clinically significant allergic reaction.
- Allergen component tests provide valuable additional information especially when
  - investigating labile allergens;
  - evaluating the significance of cross-reactions between different allergen sources and the potential for them to occur;
  - assessing which allergen a patient was primarily sensitized to; and
  - assessing a patient's risk of experiencing a severe, systemic allergic reaction.

• Wide-ranging panels of multiple tests should generally be avoided. The patient's medical history should be reviewed to establish whether the symptoms are consistent with IgE- mediated allergy (see the table of IgE-mediated symptoms on page 27). Sensitization tests should be focused on the suspected allergens.

Milk allergy

• Approximately 80% of the proteins in cow's milk are caseins (such as **Bos d 8**), and the rest are serum proteins (α-lactalbumin **Bos d 4**, ß-lactoglobulin **Bos d 5** and serum albumin **Bos d 6**). Casein is quite resistant to heating and remains allergenic even if milk is heated for 90 minutes at 90°C. Serum proteins are labile and heat-sensitive. Sensitization to one or more milk proteins may occur.
• Approximately two-thirds of children with milk allergy, who cannot drink milk as is, can tolerate extensively heated milk (cooked in an oven at ≥ 175°C for at least 30 minutes) as an ingredient in foods and baked goods.
• The amino acid sequences of cow's milk proteins are more than 80% identical to those of sheep's milk and goat milk. More than 90% cross-reactivity between these has been observed clinically. Most people who are allergic to cow's milk will also get symptoms from sheep's milk and goat milk. However, there is very little cross-reactivity (< 5%) with horse, donkey, buffalo or camel milk.
• Allergen component studies can help establish whether milk products can be used if cooked.

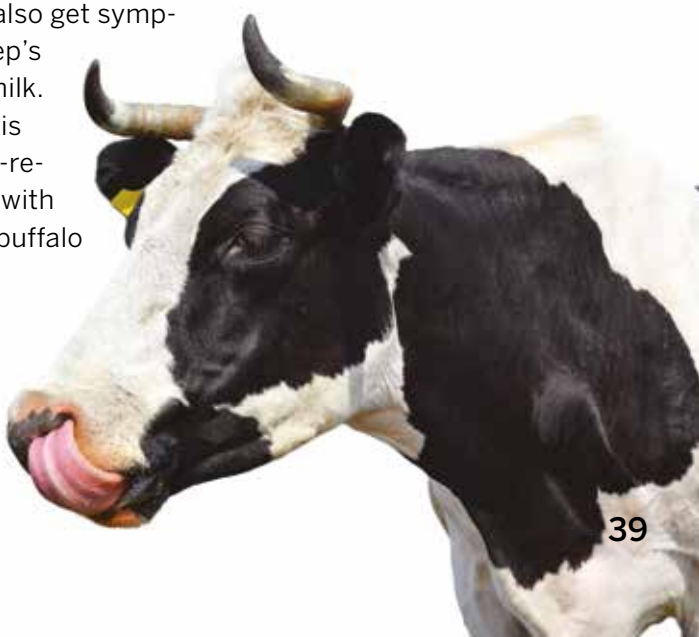
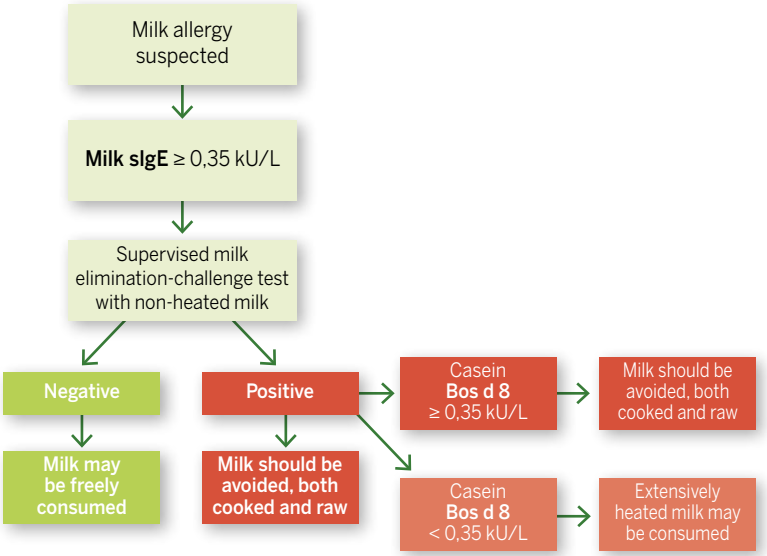


Figure 7. Investigating IgE-mediated milk allergy.



If casein antibody levels are low, heated milk products can usually be consumed. This also helps with maintaining and developing tolerance. (See Figure 7.)

• Milk allergy usually disappears by four years of age. Children of school age who still experience symptoms due to milk are usually sensitized to casein (**Bos d 8**).

• Elevated levels of antibodies to milk proteins indicate IgE-mediated sensitization, but not necessarily allergy. If an IgE-mediated mechanism is suspected, milk allergy should be investigated further (see Figure 7).

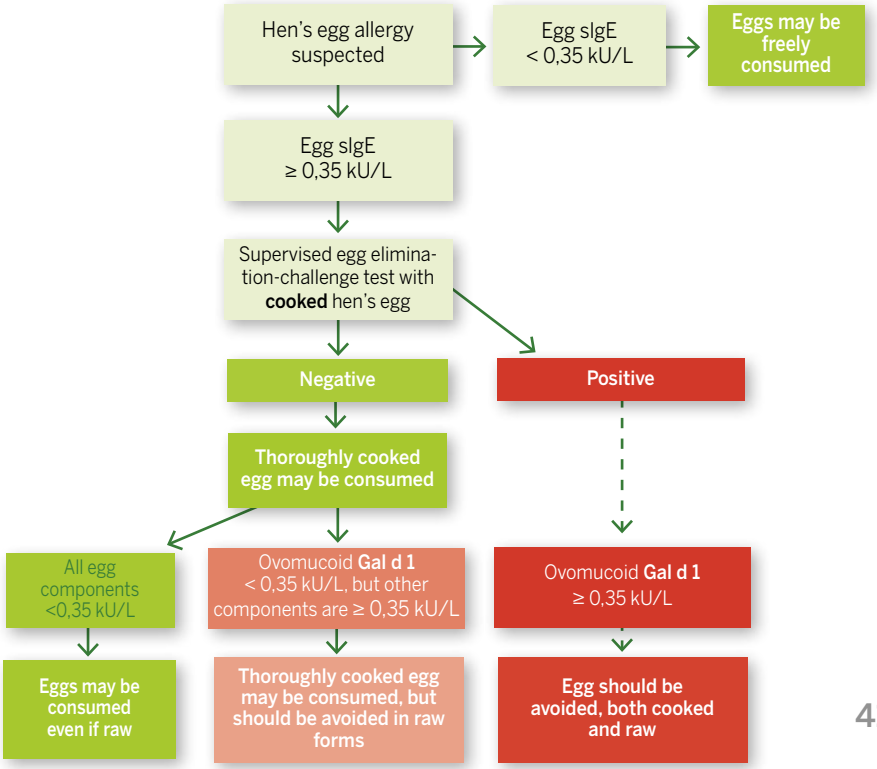
• If a non-IgE-mediated milk allergy is suspected, proceed directly to supervised elimination- challenge testing, double-blind if necessary.

Hen's egg allergy

• Atopic children often have elevated IgE antibody levels or positive skin prick tests in response to hen's egg. However, only two-thirds of those who are sensitized exhibit symptoms.

• An assay of antibodies to egg allergen components can help establish clinical relevance and support challenge testing.
• Ovomucoid (**Gal d 1**) is the most clinically significant hen's egg component and remains allergenic even when heated.
• Other egg allergens, such as ovalbumin (**Gal d 2**), conalbumin (**Gal d 3**) and lysozyme (**Gal d 4**), are heat-labile. Their allergenicity is significantly reduced by extensive heating. Lysozyme (E1105) is often used as a food additive, as well as in some toothpastes and oral care products.
• Some patients with hen's egg allergy will tolerate extensively heated products. Supervised elimination-challenge testing is recommended to confirm an egg allergy. Cooked egg white is the most commonly used ingredient for the test. Some children whose challenge test is negative for

Figure 8. Investigating hen's egg allergy.



cooked egg, but who have an elevated egg-specific IgE antibody level, may experience symptoms from raw egg (the challenge with cooked egg does not address this). The extent of tolerance can be further characterized by component testing. If no sensitization to ovomucoid is found, but other components are elevated, the patient is likely to tolerate cooked egg, but should avoid it in raw forms (see Figure 8, page 41).

Wheat allergy

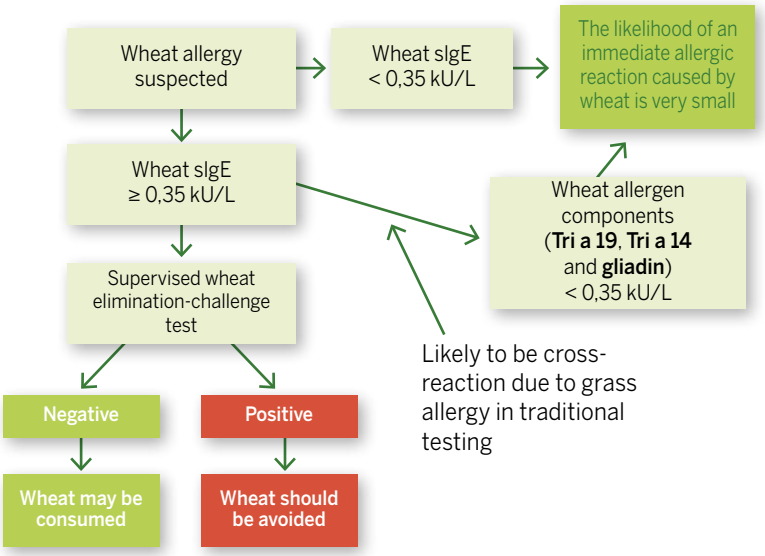
• Wheat is a grass and thus cross-reacts with other members of the same family, such as timothy grass and meadow grass.

• Cereal allergy often involves cross-reactions between wheat, barley and rye, whereas no clinically relevant cross-reaction is seen between wheat and oat. The effect of processing and heating on wheat allergenicity is not yet understood.

• The most important wheat-specific allergens are albumins, globulins and glutenins (including gliadins). Gliadins and glutenins are storage proteins of wheat. Omega-5-gliadin (**Tri a 19**) is probably the most significant allergen in immediate cereal allergy. Other proteins that cause clinically relevant symptoms include Tri a 15 (an alpha-amylase inhibitor), **Tri a 14** (a lipid transfer protein), Tri a 26, and Tri a 36. Sensitization profiles vary, and the significance of each major allergen for a particular patient is difficult to predict.

• Traditional methods (skin prick testing or wheat IgE) based on a whole-allergen extract offer adequate

Figure 9. Investigating wheat allergy in IgE-mediated wheat allergy.



sensitivity, but only about 40% specificity. **An antibody assay performed with whole-allergen extract will give false positive results for as many as 60% of patients with grass allergy.**

• Component tests can give a clearer picture of genuine sensitization, particularly in grass-allergic patients. For example, gliadin testing has approximately 94% sensitivity and 96% specificity.

• The symptoms of IgE-mediated wheat allergy depend on the exposure route. Orally ingested wheat may cause urticaria, severe gastrointestinal symptoms, breathing difficulties, or anaphylaxis. Airway exposure through baking, for example, may cause respiratory symptoms. Skin contact with wheat protein in cosmetic products may lead to anaphylaxis as well as skin symptoms.

• Cereal allergy should always be confirmed through supervised wheat challenge testing (Figure 9). Children usually outgrow cereal allergy, but challenge testing should be repeated to confirm tolerance.

Fish

• The most important fish allergen is parvalbumin, which can be found in the muscle tissue. Most people who are allergic to fish are sensitized to this protein. Heating does not significantly affect its allergenicity. Parvalbumin concentration varies from one type of fish to another.

• For example, the parvalbumin concentration in herring is a hundred times that of tuna. The higher the allergen concentration, the greater the likelihood that the fish will cause notable symptoms.

• Most people with fish allergy get symptoms from all types of fish, but some only react to fish from a certain order (Table 7). Some fish-allergics may be sensitized not to parvalbumin, but to proteins such as enolase and aldolase, which are characteristic of particular fish orders.

• Someone who is allergic to fish will not necessarily get symptoms from crustaceans or mollusks, since fish parvalbumin does not significantly cross-react with the tropomyosin.

• People with fish allergy may tolerate fish roe (eggs), and people with fish roe allergy may likewise tolerate fish. Vitellogenin is the most important protein in fish roe, which contain no parvalbumin at all.

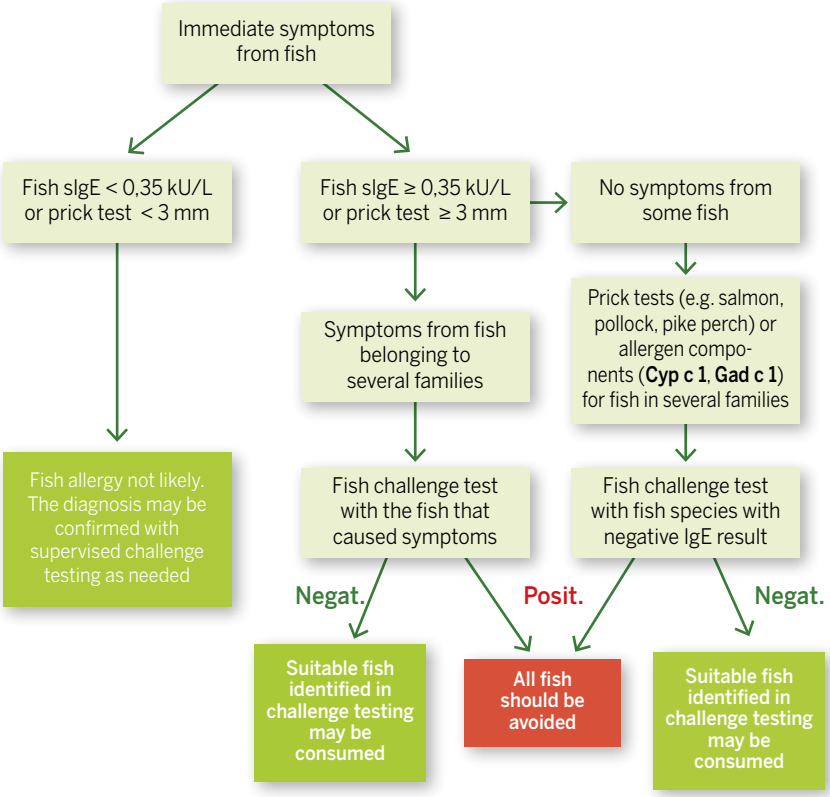
• See the diagram for diagnosing fish allergy (Figure 10 on page 46).

Table 7.

Fish orders and taxonomic relationships.

Order	Fish
Salmon and trout (*Salmoniformes*)	Salmon, trout, arctic char, vendace, whitefish, grayling, smelt
Cod (*Gadiformes*)	Burbot, cod, pollock
Perch-like (*Perciformes*)	Pikeperch, ruffe, perch, tuna, mackerel
Herring (*Clupeiformes*)	Herring, Baltic herring, anchovy, sprat
Carp (*Cypriniformes*)	Common roach, ide, carp, dace, chub, minnow, rudd, asp, tench, gudgeon, bleak, bream, silver bream, blue bream, vimba, crucian carp
Catfish (*Siluriformes*)	Sheat-fish, pangasius
Flatfish (*Pleuronectiformes*)	Flounder, sole
Lampreys (*Petromyzontiformes*)	River lamprey
Eels and morays (*Anguilliformes*)	Eel
Pikes and mudminnows (*Esociformes*)	Pike

Figure 10. Investigating fish allergy.



Crustaceans and mollusks

• Seafood can cause severe, systemic allergic reactions.

• Crustaceans include shrimps, crabs and lobsters. Mollusks include clams, oysters, snails and squid.

• The major allergens, such as tropomyosin, are stable and heat-resistant. Approximately 60% of seafood-allergic patients are sensitized to tropomyosin (**Pen a 1** of fish). Other allergens found in marine organisms include Hom a 1 of lobster, Cha f 1 of crab, Per v 1 of clam, Hel as 1 of snail, and Top p 1 of squid.

• Cross-reactions occur easily between different types of crustaceans. A patient whose symptoms are triggered by crab is likely to get them from other crustaceans as well.

However, some people who are allergic to crustaceans will tolerate mollusks, and mollusk-allergics may tolerate crustaceans.

• These sea creatures are more closely related to arachnids than to fish. Cross-reactions with dust mites, for example, may occur in traditional tests.

• An allergic reaction may be caused by a parasitic nematode (*Anisakis*) found in marine mammals and fish.

• Skin prick testing with a commercial seafood extract may produce a false negative result. A negative result should be confirmed with prick-prick testing using the food that has caused symptoms. In a prick-prick test, the substance being tested is pricked with a lancet that is then used to prick the patient's skin.

• The serum level of specific IgE antibody to tropomyosin (**Pen a 1**) predicts the potential for an allergic reaction more accurately than a shrimp skin prick test with a commercial extract or the shrimp sIgE level. The diagnosis may be confirmed with supervised challenge testing as needed.

Soy

• Soy belongs to the legume family (*Fabaceae*). This family includes more than 10,000 species of plants including herbs, shrubs and trees. Some soy proteins are cross-reactive, especially with other legumes (e.g. peas, beans, lentils, peanut, lupin, clover). Soy contains a multitude of proteins with a variety of functions, and the allergenicity of many of these has not yet been established.

• Patients sensitized to soy can be divided into roughly two groups:

1. Sensitized to stable and specific soy proteins (**Glym 5, 6** and 8). These allergens are highly heat-resistant, so patients in this group have an elevated risk of immediate and severe reactions.

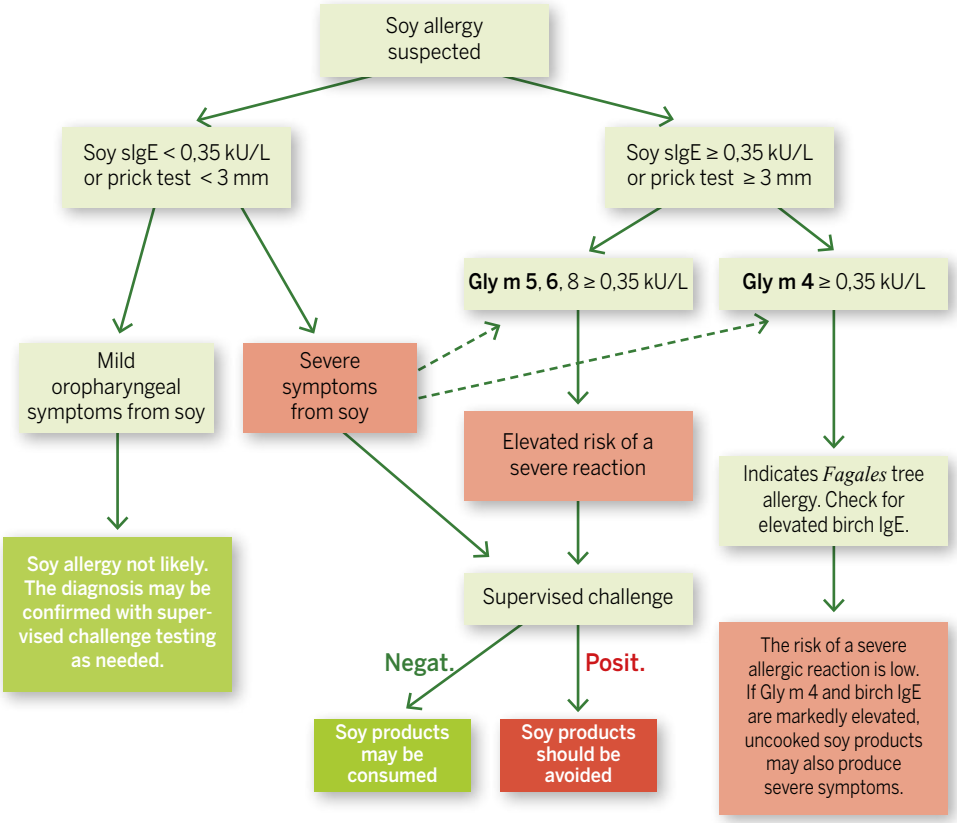
2. Sensitized primarily to pollen PR-10 proteins (the soy protein in the same group is **Gly m 4**) or profilins (Gly m 3 in soy). Heating reduces the allergenicity of these proteins and they usually cause only mild symptoms. More than 70% of patients who are sensitized to *Fagales* trees are also found to have antibodies to soy PR-10 protein (**Gly m 4**). This category includes most patients in Nordic countries who are sensitized to soy. In other words, the allergy is really to *Fagales* trees.

• Skin prick testing with soybean or a commercial soy extract has very low sensitivity and specificity, so it is not clinically helpful.

• If soy sIgE is less than 0.35 kU/L, an immediate allergic reaction is very unlikely but cannot be completely ruled out. If necessary, the result should be checked by component testing and soy tolerance should be confirmed with a supervised challenge test.

• Elevated soy sIgE is not always related to a true soy allergy. Soy IgE associated with a whole allergen source does not indicate which allergen component the patient is sensitized to. In many patients sensitized to *Fagales* trees, elevated soy IgE is an unexpected or incidental finding. Approximately 10% of these patients may experience severe oropharyngeal symptoms from completely uncooked soy products (such as soy beverages). Their birch antibody level is usually notably elevated.

Figure 11. Investigating soy allergy.



• Allergen component testing provides a broader picture of the sensitization profile and the risk of severe reactions. See the soy allergy investigation diagram (Figure 11).

Peanut

• Peanut belongs to the legume family (*Fabaceae*). This family includes more than 10,000 species of herbs, shrubs and trees. Some peanut allergens are cross-reactive with other plants, including other legumes (e.g. peas, beans, lentils, soy, lupin, clover).

• Peanut has a high concentration of proteins, about 25%. More than 30 proteins with different functions have been identified so far.

Cooking peanuts decreases the allergenicity of some of these proteins, but roasting them increases the allergenicity of others.

• Patients sensitized to peanut can be divided into roughly three groups:

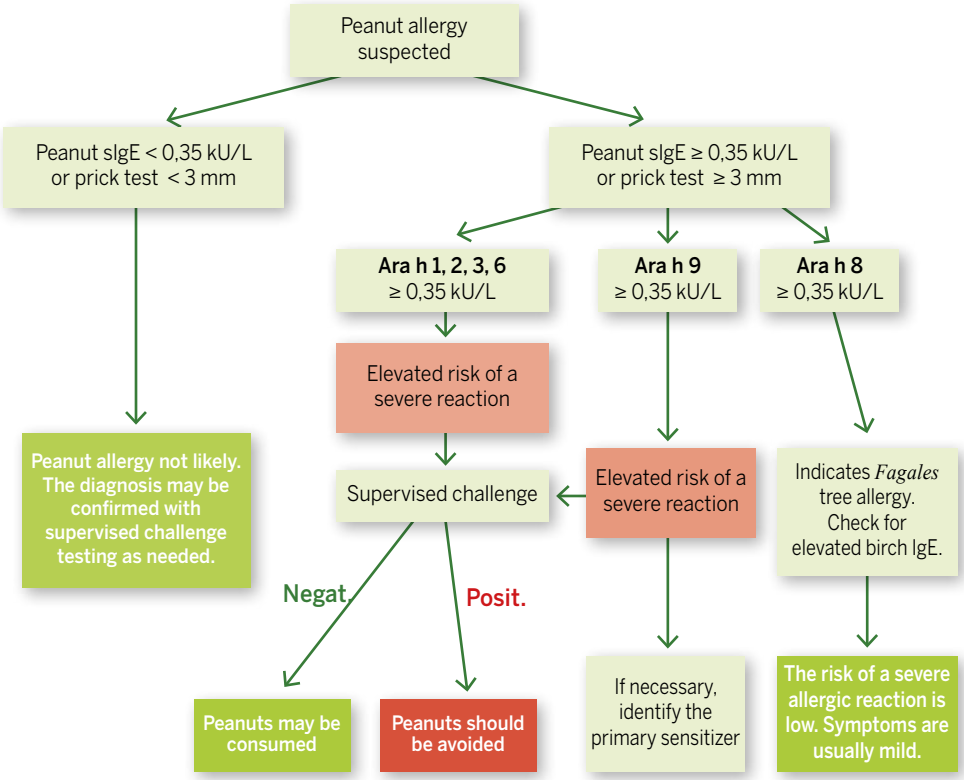
1. Sensitized to stable and specific peanut proteins (**Ara h 1, 2, 3, 6**, 7). These patients have an elevated risk of immediate and severe reactions.
2. Sensitized primarily to pollen PR-10 proteins (**Ara h 8** in peanut) or profilins (Ara h 5 in peanut). Heating reduces the allergenicity of these proteins and they usually cause only mild symptoms. In Nordic countries this group includes a significant proportion of patients sensitized to peanut.
3. Sensitized primarily to non-specific lipid transfer proteins (nsLTPs) from other plants (**Ara h 9** in peanut). Since nsLTPs are stable, these patients may experience severe symptoms. This type of sensitization profile is typically seen in southern Europe.

• If peanut IgE is less than 0.35 kU/l, an allergic reaction is unlikely.

• Elevated peanut sIgE is not always related to a true peanut allergy. Commercial skin prick test extracts and peanut IgE associated with a whole allergen source do not indicate which allergen component the patient is sensitized to. In many patients sensitized to *Fagales* trees, a positive skin prick test or elevated IgE to peanut is an unexpected or incidental finding.

• Allergen component testing provides a wider picture of the sensitization profile and the risk of severe reactions.

Figure 12. Investigating peanut allergy.



See the peanut allergy investigation illustrations (Figure 12 and Table 8).

Tree nuts and seeds

• In addition to the plants generally thought of as seeds, tree nuts and legumes are seeds as well. Their most important allergens are storage proteins (7S, 9S, 11S globulins and 2S albumins) and non-specific lipid transfer proteins (nsLTPs). The allergens of all nuts and seeds have not yet been identified.

• The likelihood of nut and seed cross-reactions depends on the protein families and taxonomic relationships involved. Visualizing which nuts are closely related may

therefore be useful (Table 4, page 22). It is important to bear in mind that peanuts are in the legume family.

• Some patients are only sensitized to the seeds of a particular plant family. For example, if walnut and pecan components are elevated but antibodies against other nuts are low, the patient should avoid nuts from the beech family (and possibly also from the birch family). The patient may tolerate other nuts, however. If sensitization is only found to cashews and pistachios, nuts from outside the sumac family may be acceptable.

• However, clinically significant cross-reactions may occur more extensively within protein families. A patient who is strongly sensitized to a nut 2S albumin, for example, has a higher risk of allergic reactions to other nuts and seeds. The risk of a clinically significant cross-reaction is even higher if elevated component levels are seen for nuts or seeds belonging to several different plant families. In other words, if a common denominator in a patient's sensitization profile is a 2S albumin, for example, and sensitization is observed to the components **Cor a 14, Jugr r 1, Ber e 1** and **Ses i 1**, it is possible that the patient will have symptoms due to many other nuts and seeds as well.

• Patients sensitized to tree nuts can be divided into roughly two groups:

1. Sensitized to stable and specific storage proteins of nuts. These allergens are highly heat-resistant, so a patient in this group has an elevated risk of immediate and severe reactions.
2. Sensitized primarily to pollen PR-10 proteins (e.g. hazelnut **Cor a 1**) or profilins (e.g. almond Pru du 4). Heating reduces the allergenicity of these proteins slightly and they usually only cause mild reactions. In Nordic countries, for example, most patients who are sensitized to hazelnut belong in this category.

• Allergen component testing clarifies which protein family the patient's sensitizing allergen belongs to.

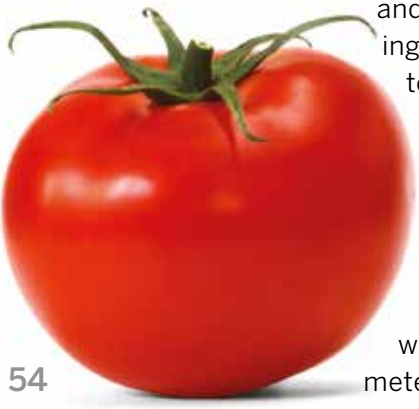
Table 8. Using traditional methods, the results do not differ significantly for patients Mary and Sophie. Allergen components can be used to assess their sensitization profiles and risk of severe reactions in more detail.

	Mary	Sophie
Atopic eczema	Yes	Yes
Allergic rhinitis	Yes	Yes
Asthma	No	Yes
Vegetables/ root vegetables	Itchy mouth	Itchy mouth
Symptoms from "nuts"	Itchy mouth, irritated throat, swollen lips	Hives, difficulty breathing, nausea
Skin prick tests (mm)	Birch 5, timothy 0, dog 10, cat 9, peanut 5, hazelnut 3	Birch 8, timothy 5, dog 5, cat 7, peanut 10, hazelnut 5
sIgE (kU/L)	Peanut 26, hazelnut 3.8	Peanut 35, hazelnut 7.3
Peanut allergen components (kU/L)	Ara h 1 < 0.10 Ara h 2 0.28 Ara h 3 < 0.10 Ara h 6 < 0.10 Arah 8 (PR-10) 7.01 Arah 9 < 0.10 →Challenge negative	Ara h 1 2.12 Ara h 2 18.53 Ara h 3 < 0.10 Ara h 6 9.60 Ara h 8 5.31 Ara h 9 1.10 →Challenge positive
Hazelnut allergen components (kU/L)	Cor a 1 (PR-10) 1.98 Cor a 14 0.44 Cor a 9 0.57 →Challenge negative	Cor a 1 5.32 Cor a 14 < 0.10 Cor a 9 < 0.10 →Challenge negative
What should I advise?	The patient may eat both nuts. Mild symptoms such as mouth itching may occur, but severe symptoms are unlikely.	Peanuts must be avoided completely; risk of anaphylaxis. Hazelnuts may be consumed in moderation.

Finding the common denominator can be very helpful for patient counseling and planning food challenge tests.
• See example cases (Table 8 on page 53).

Fruits

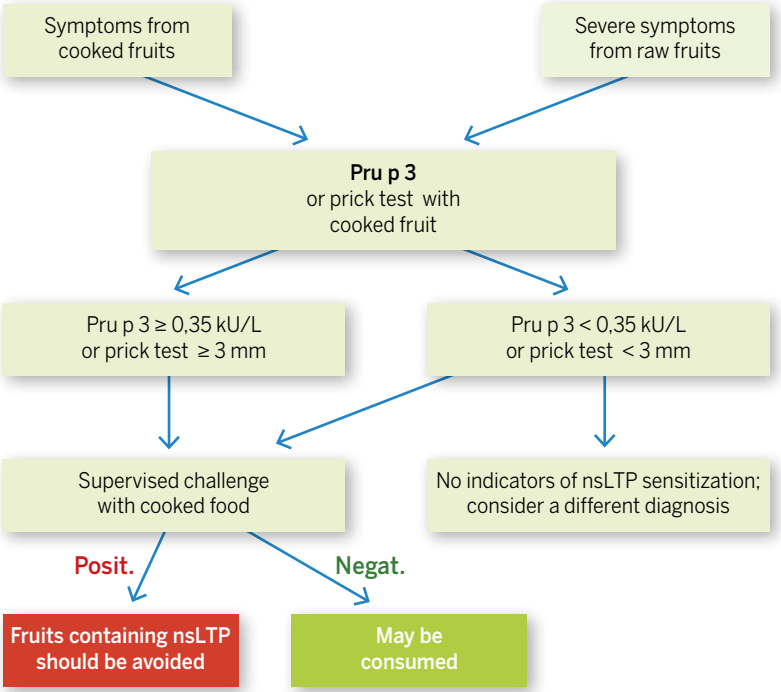
• In the case of fruits, it is always advisable to establish whether the patient has a food allergy or a cross-reaction to pollens.
• The fruits that most commonly cause symptoms belong to the rose family (e.g. stone fruits). See Table 9, page 58.
• In Nordic countries the majority of symptoms caused by fruits are due to cross-reaction with pollens in the PR-10 family and with profilins (see the protein families section for more details). Since heating reduces the allergenicity of these labile proteins, someone with a pollen allergy can usually eat cooked fruits without developing significant symptoms. Even if uncooked, they usually cause symptoms limited to the mouth, lips and pharynx. Allergen amounts may vary among different cultivars of a fruit. For example, the PR-10 protein concentrations of some apple varieties differ several-fold.
• If a patient has very severe symptoms triggered by uncooked fruit or is getting symptoms even from cooked fruit, it is advisable to investigate whether this is really a food allergy and which protein the patient is sensitized to. See Figure 14, page 57.
• Traditional commercial whole-allergen extracts of fruits and vegetables for skin prick testing have rather low sensitivity due to PR-10 and profilin lability.
• Skin prick tests with raw ingredients (prick-prick tests) are not recommended for investigating fruit allergy. If the patient has a pollen allergy, cross-reactions could cause wheals more than 3 mm in diameter from numerous fruits, even



if the patient would not get symptoms from them. **The result of a skin prick test with raw ingredients most often indicates a pollen allergy rather than an actual food allergy**, so it is not useful for patient counseling. When a true food allergy is suspected, a prick-prick test should use well-cooked (more than 10 min) products. If the skin prick test is positive with cooked food, diagnosis can be confirmed by supervised challenge testing with cooked fruit (Figure 14).

• Allergen component testing can clarify whether a patient is sensitized to proteins that cross-react with pollens, such as PR-10 proteins (birch **Bet v 1**, apple **Mal d 1**, peach **Pru p 1**) and profilins (apple Mal d 4, peach **Pru p 4**), or to stable food proteins (e.g. peach **Pru p 3**).

Figure 13. Significance and investigation of nsLTP (Pru p 3) sensitization.



• Sensitization to stable nsLTPs is relatively rare in Nordic countries. Symptoms associated with nsLTP sensitization are more prevalent in southern Europe, where the primary sensitization typically occurs through stone fruits, such as peach. In theory, due to cross-reactivity, affected patients could experience symptoms from several fruits that contain nsLTPs. One way to investigate the primary sensitization is to measure peach nsLTP (**Pru p 3**).
• Lipid transfer proteins are found in both the skin and pulp of fruits. For example, the skin layers of a peach contain 200 times more nsLTPs (**Pru p 3**) than the pulp. Peeling a fruit may reduce the risk and severity of symptoms. See Figure 13.
• The most important kiwi allergen is actinidin (**Act d 1**). Sensitization to Act d 1 can cause severe, systemic allergic reactions. The nsLTP of kiwi (Act d 10) has not been shown to cross-react significantly with nsLTPs in stone fruits. The heat-sensitive kiwi allergens **Act d 8** (PR-10) and Act d 9 (profilin) usually cause only mild symptoms.
• One function of thaumatin-like proteins (TLPs) is to play a role in fruit defenses. Their significance as allergens is probably low.

Figure 14.

Significance and investigation of PR-10 (Bet v 1) sensitization.

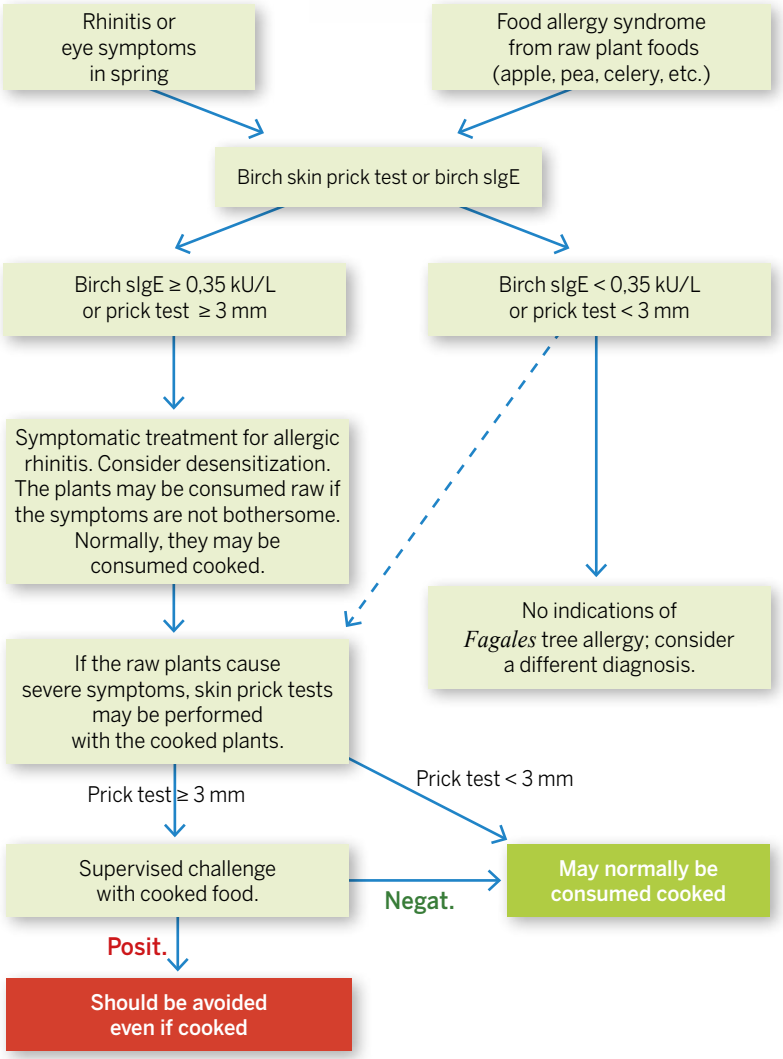


Table 9. Fruits.

Plant family	PR-10	Profilin	nsLTP	Thaumatin-like protein	Other proteins
Rose (*Rosaceae*)	**Mal d 1** (apple) **Pru p 1** (peach) Pru ar 1 (apricot) Pru av 1 (cherry) Pru d 1 (plum) Pyr c 1 (pear) Rub i 1 (raspberry) Fra a 1 (strawberry)	Mal d 4 (apple) Pru p 4 (peach) Pru av 4 (cherry) Pru d 4 (plum) Pyr c 4 (pear)	**Mal d 3** (apple) **Pru p 3** (peach) Pru ar 3 (apricot) Pru av 3 (cherry) Pru d 3 (plum) Pyr c 3 (pear) Rub i 3 (raspberry) Fra a 3 (strawberry)	Mal d 2 (apple) Pru d 2 (plum) Pru p 2 (peach) Pru ar 2 (apricot)	**Pru p 7** gibberellin regulated protein (peach)
Banana (*Musaceae*)		Mus a 1 (banana)	Mus a 3 (banana)	Mus a 4 (banana)	Mus a 2 hevein (banana)
Citrus (*Rutaceae*)		Cit s 2 (orange)	Cit l 3 (lemon) Cit s 3 (orange)		Cit s 1 (orange germin- like protein)
Gourd (*Cucurbitaceae*)		Cuc m 2 (melon) Cit la 2 (water-melon)			
Grape (*Vitaceae*)		Vit v 4 (grape)	Vit v 1 (grape)		
Chinese gooseberry (*Actinidiaceae*)	**Act d 8** (kiwi)	Act d 9 (kiwi)	Act d 10 (kiwi)	**Act d 2** (kiwi)	**Act d 1** actinidin (kiwi) **Act d 5** kiwellin (kiwi)

The component IgE tests that are presently commercially available are indicated in bold text.

Vegetables

• The vegetables that most commonly cause symptoms (e.g. celery and carrot) belong to the parsley family. See Table 10 on page 60.

• In Nordic countries most symptoms attributed to vegetables are due to cross-reactivity with the pollen of Fagales trees, grasses, and mugwort. Since heating reduces the allergenicity of heat-labile proteins that cause cross-reactions (PR-10 and profilin), someone with a pollen allergy can usually eat cooked vegetables without developing significant symptoms. Even if uncooked, they usually cause symptoms limited to the mouth, lips and pharynx. Primary sensitization can be investigated by testing which pollens the patient is sensitized to. See Figure 14 on page 57.

• Plants in the nightshade family (e.g. tomato, bell pepper) may cause mild symptoms if eaten raw, most commonly due to profilins. They usually cause no symptoms if cooked, however. The profilin in nightshades may result in false positive prick-prick test results with raw products.

• Proteins in potato cross-react with other nightshades and pollens. Peeling a potato may irritate the skin or eyes, for example. Similarly, a skin prick test with raw potato may be positive, but allergic reactions from cooked potato are extremely rare. Protective gloves may be worn for peeling and the cooked potatoes can then be eaten normally.

• Celery nsLTP can cause symptoms even after heating, and theoretically it could cross-react with nsLTPs in other plants. All the allergens responsible for cross-reactions have not yet been identified. Anaphylaxis caused by vegetable allergy is very rare. See Figure 13 on page 55.

Table 10. Vegetables.

Plant family	PR-10	Profilin	nsLTP	Thaumatin-like protein	Other proteins
Parsley (*Apiaceae*)	Api g 1 (celery) Dau c 1 (carrot)	Api g 4 (celery) Dau c 4 (carrot)	Api g 2 and 6 (celery)		
Nightshade (*Solanaceae*)		Cap a 2 (bell pepper) Sola l 1 (tomato) Sol t 8 (potato)	Sola l 3 (tomato)	Cap a 1 (bell pepper)	
Gourd (*Cucurbitaceae*)		Cuc s 2 (cucumber)			
Laurel (*Lauraceae*)		Pers a 4 (avocado)			Pers a hevein (avocado)
Legume (*Fabaceae*)	**Gly m 4** (soy)	Gly m 3 (soy)			**Gly m 5, 6** and 8 (soy)

The component IgE tests that are presently commercially available are indicated in bold text.

Meat allergy

• Allergy to products derived from mammals – such as meat, organs, fat, tendons or gelatin – is extremely rare in Nordic countries. Isolated cases described in the literature involve IgE-mediated binding to serum albumin, myoglobin and actin, for example.

• Various figures have been published estimating the risk that milk-allergics will develop symptoms from beef or that egg-allergics will have reactions to chicken. No precise figures for such cross-reactions are available because there have been very few cases.

• Some allergic reactions have been described involving a cross-reaction between cat and pork albumins.

Albumins are heat-labile, so well-cooked meat rarely causes symptoms.

• An oligosaccharide (not a protein) called **alpha-gal**, found in meat, organs and gelatin, can also cause allergic symptoms. This involves a peculiar cross-reaction with the saliva of some tick species. The first cases were observed in southeastern USA in recent years, and there have also been a few cases in Europe. Affected patients experience a delayed allergic reaction (even anaphylaxis) 2 to 6 hours after eating meat. Primary sensitization is associated with three particular tick species: *Amblyomma americanum, Ixodes holocyclus* and *Ixodes ricinus*. Patients sensitized to alpha-gal usually get no symptoms from small amounts of meat, and more than 80% of them tolerate dairy products.

Hymenoptera venom allergy

• Wasp and honeybee venoms differ from each other considerably and are not usually cross-reactive. A person who is allergic to one will not necessarily react to the other. Bumblebees only rarely cause allergic reactions. See Table 11 on page 63 for distinctions between hymenoptera.

• The venoms of various wasp species are very similar to each other, as are the venoms of various honeybee species.

• Hymenoptera stings always cause a toxic reaction (pain, swelling and redness), but allergic reactions rarely occur.

• The prevalence of systemic reactions due to hymenoptera allergy varies from 0.4% to 3% in most countries but in some areas it can be as high as 7%. An allergic reaction differs from a toxic one. Urticaria may develop around the sting site or all over the body. More severe, systemic reactions are also possible. Fatal reactions occur in less than one case per million.

Wasp

• Desensitization therapy is recommended for patients who have had a severe reaction to a sting. **When considering desensitization, identifying which hymenoptera the patient was sensitized to is especially important because the therapy will be specific for either wasps or bees.**

• Traditional tests, such as a skin prick test or hymenoptera sIgE response, are not specific enough. Cross-reactive carbohydrate determinant (CCD) in both bee and wasp venoms can cause a false positive test result for either one, even though CCD is not the cause of the allergic reactions. Component diagnostics are helpful in identifying which of the hymenoptera the patient was sensitized to.

Honeybee

• Components specific to wasp venom are **Ves v 1** and **Ves v 5**. A positive result for these components confirms the diagnosis and a negative result rules out wasp allergy with 95% certainty.

• Components specific to honeybee venom are **Api m 1, 2, 3, 5** and **10**. A positive result for these components confirms the diagnosis and a negative result rules out honeybee allergy with approximately 90% certainty.

• An antibody assay is recommended within 1 to 4 weeks of the sting as the tests become less accurate with the passing of time.

Bumblebee

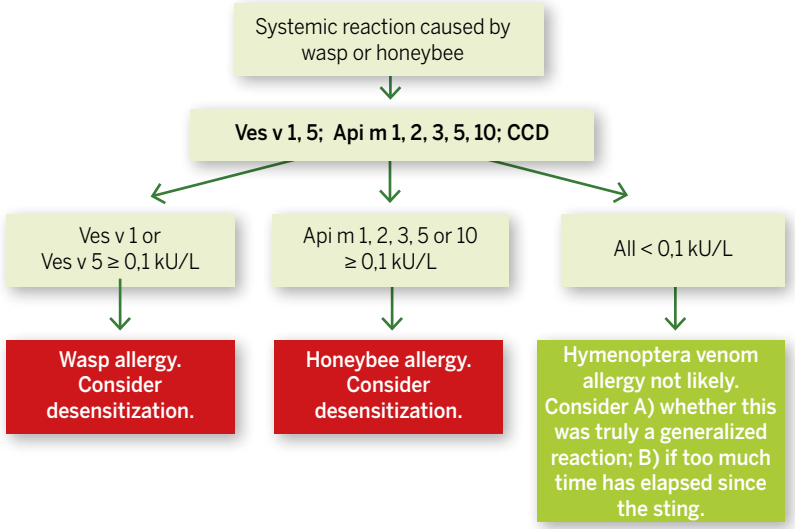
Table 11. Hymenoptera identification.

Source: Lapsiperheen allergiaopas (Pediatric allergology –a parental guide), Péter Csonka and Päivi Junttila, 2013 (WSOY).

Type	Size	Appearance	Stinger	Behavior	Other
Wasps	10–15 mm	Yellow-black striped abdomen	Not barbed; does not detach; can sting many times	Sting in self-defense or to paralyze their prey; very aggressive defenders of their nest; idle workers are irritable in the autumn	Only the queen hibernates
Honeybees	11–20 mm	Somewhat hairy; various color patterns	Barbed; detaches after stinging and the insect dies	Sting only in self-defense	Hibernate
Bumblebees	15–25 mm	Hairy; various color patterns	Not barbed; the insect does not die after stinging	Sting very rarely	Only the queen hibernates

Figure 15.

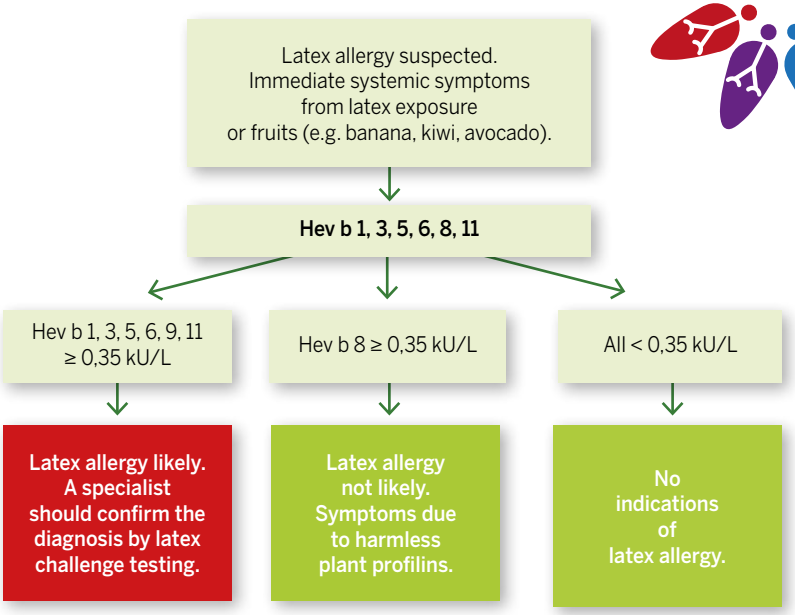
Investigating hymenoptera venom allergy. A reference value of < 0.1 kU/L is used in hymenoptera venom allergy.



Latex allergy

• Latex can cause both immediate (type I) and delayed (type IV) symptoms. Only immediate IgE-mediated mechanisms are discussed here.
• True latex allergy is rare. The latex allergens **Hev b 1** and **3** are specific to latex and are the most important allergens in patients who have undergone multiple surgeries. **Hev b 5, 6** and **11** sensitization can lead to symptoms not only from latex, but also from certain fruits (including banana, kiwi, avocado, pineapple, chestnut, mango, melon, fig, passion fruit) due to cross-reactivity.
• Latex **Hev b 8** is a profilin, a panallergen of the plant kingdom, that cross-reacts with profilin in pollen and other plant sources. Pollen-allergic patients should not be screened for latex allergy using whole-allergen extract (for skin prick tests or conventional blood tests) as this will often give a false positive result.

Figure 16. Investigating latex allergy.

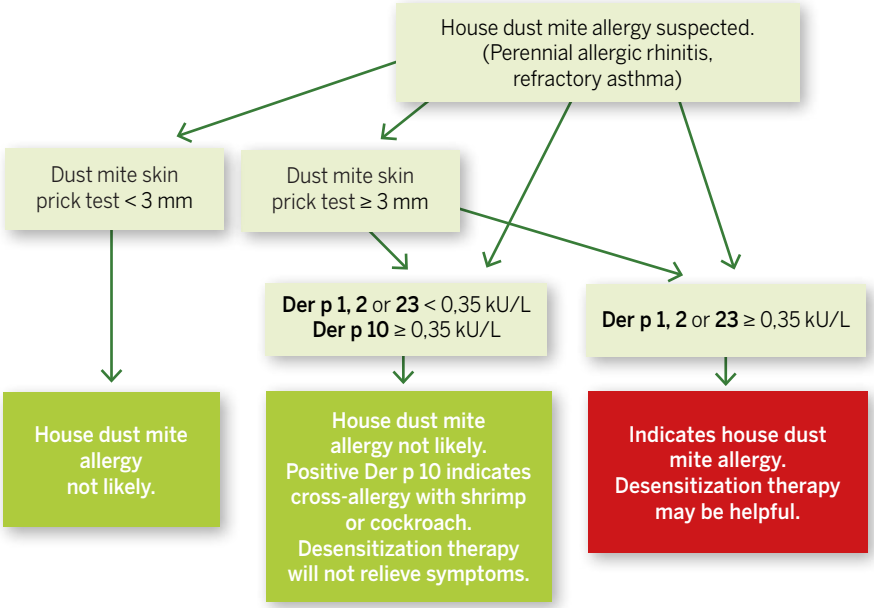


• Conventional blood tests may also give false negative results because they do not necessarily recognize all the essential latex allergens.
• Allergen component tests (Figure 16) and latex challenge testing if necessary (using a latex glove) are recommended for investigating latex allergy.

House dust mite allergy

• House dust mite allergy is a risk factor for asthma and can cause allergic rhinitis.
• Skin prick tests are usually sufficient for investigating dust mite sensitization, but could give false positive results in some patients due to dust mite tropomyosin (**Der p 10**). Der p 10 cross-reacts with the tropomyosin of shrimp and cockroach, for example.
• When considering desensitization, component testing can be useful in confirming that the patient is sensitized to specific dust mite allergens (**Der p 1, Der p 2** and **Der p 23**), not just to non-specific tropomyosin (Der p 10).

Figure 17. Investigating allergy to house dust mites.



Tryptase as a diagnostic tool

• In a systemic and severe allergic reaction, anaphylaxis, mast cells release tryptase and other substances.
• The blood tryptase concentration is normally quite stable, in the range of 1 to 8 µg/l.
• An individual's tryptase level is influenced by the number of mast cells. Mastocytosis patients, for example, often have elevated tryptase levels (above 20 µg/l).
• A high baseline tryptase level increases a person's risk of anaphylaxis.
• Blood tryptase concentration increasing from its normal baseline level indicates mast cell activation.
• After anaphylaxis, the tryptase concentration rises within minutes and falls to the individual's regular baseline level within about two days (Figure 19, page 67).
• Tryptase measurement helps to
    1. distinguish between a severe allergic reaction (no significant change in the tryptase level) and anaphylaxis (significant, transient increase in the tryptase level);
    2. identify patients at risk of anaphylaxis (tryptase baseline level above 10 µg/l); and
    3. identify mastocytosis patients (tryptase baseline level above 20 µg/l).
• When anaphylaxis is suspected, the tryptase concentration should be measured from about 15 minutes to a maximum of three hours after symptom onset. Another sample representing the baseline level should be taken more than two days after the symptoms subside. The difference between the peak and baseline tryptase concentrations is expressed by a delta value (Δ-tryptase). Basophil activation that indicates anaphylaxis is likely if Δ-tryptase is ≥ 20% of an individual's personal baseline level + 2 µg/l.

Figure 18. Tryptase as a diagnostic tool.

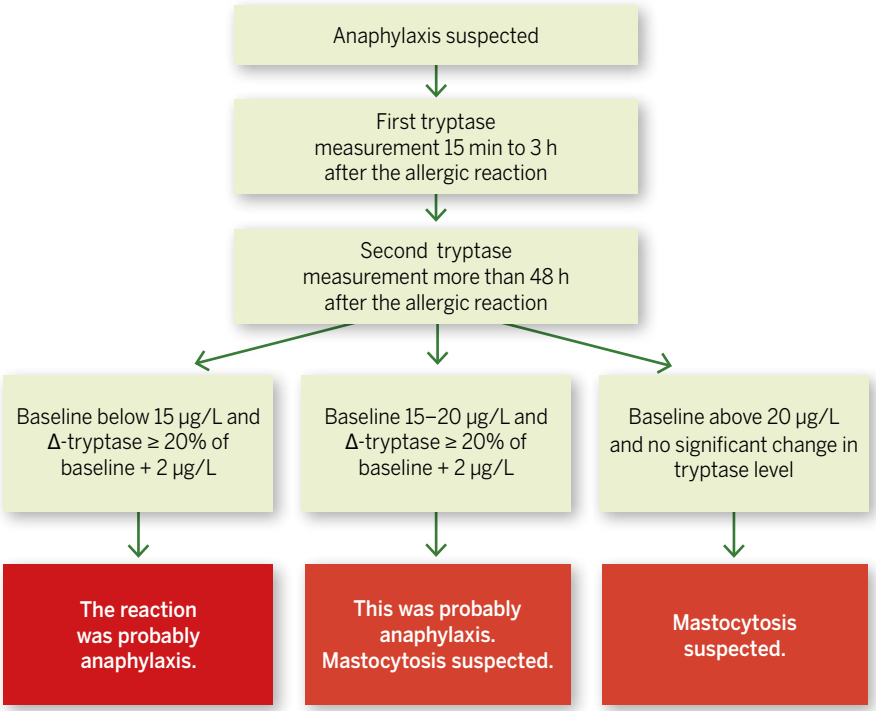
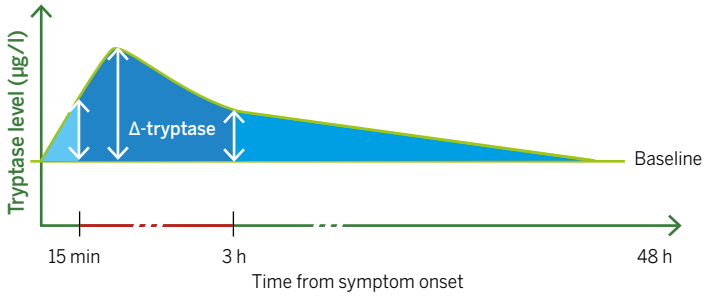


Figure 19. Transient tryptase elevation is measured 15 min to 3 h after symptom onset. Baseline measurement is performed 48 h after clinical symptoms have subsided. Each patient acts as his or her own control.



Mast cell activation if:
Δ-tryptase ≥ 20% above personal baseline + 2 µg/L

Table 12 A. Commercially available allergen component tests

ImmunoCAP Allergen Component test for individual IgE measurements

Allergen component	Allergen source		Code
Grass pollens			
Cyn d 1	Bermuda grass	*Cynodon dactylon*	g216
rPhl p 1	Timothy	*Phleum pratense*	g205
rPhl p 2	Timothy	*Phleum pratense*	g206
nPhl p 4	Timothy	*Phleum pratense*	g208
rPhl p 6	Timothy	*Phleum pratense*	g209
rPhl p 7	Timothy	*Phleum pratense*	g210
rPhl p 11	Timothy	*Phleum pratense*	g211
rPhl p 12 Profilin	Timothy,	*Phleum pratense*	g212
rPhl p 1, rPhl p 5b	Timothy	*Phleum pratense*	g213
rPhl p 7, rPhl p 12	Timothy	*Phleum pratense*	g214
rPhl p 5b	Timothy	*Phleum pratense*	g215
Weed pollens			
nAmb a 1	Ragweed	*Ambrosia artemisiifolia* (A. elatior)	w230
nArt v 1	Mugwort	*Artemisia vulgaris*	w231
nArt v 3 LTP,	Mugwort	*Artemisia vulgaris*	w233
rPar j 2 LPT,	Wall pellitory	*Parietaria judaica*	w211
rPla l 1	Plantain	*Plantago lanceolata*	w234
nSal k 1	Saltwort	*Salsola kali*	w232
Tree pollens			
rBet v 1 PR-10,	Birch	*Betula verrucosa*	t215
rBet v 2 Profilin,	Birch	*Betula verrucosa*	t216
rBet v 4	Birch	*Betula verrucosa*	t220
rBet v 6	Birch	*Betula verrucosa*	t225
rBet v 2, rBet v 4	Birch	*Betula verrucosa*	t221
nCup a 1	Cypress	*Cupressus arizonica*	t226
rOle e 1	Olive	*Olea europaea*	t224
nOle e 7 LTP,	Olive	*Olea europeae*	t227
rOle e 9,	Olive	*Olea europeae*	t240
rPla a 1	Maple leaf sycamore, London plane	*Platanus acerifolia*	t241
Microorganisms			
rAlt a 1		*Alternaria alternata*	m229
rAsp f 1		*Aspergillus fumigatus*	m218
rAsp f 2		*Aspergillus fumigatus*	m219
rAsp f 3		*Aspergillus fumigatus*	m220
rAsp f 4		*Aspergillus fumigatus*	m221
rAsp f 6		*Aspergillus fumigatus*	m222

Allergen component	Allergen source		Code
Epidermals and animal proteins			
nBos d 6	Cow BSA	Bos spp.	e204
rCan f 1	Dog	*Canis familiaris*	e101
rCan f 2	Dog	*Canis familiaris*	e102
nCan f 3	Dog serum albumin	*Canis familiaris*	e221
rCan f 4	Dog	*Canis familiaris*	e229
rCan f 5	Dog	*Canis familiaris*	e226
rCan f 6	Dog	*Canis familiaris*	e230
rFel d 1	Cat	*Felis domesticus*	e94
rFel d 4	Cat	*Felis domesticus*	e228
rFed d7	Cat	*Felis domesticus*	e231
rEqu c 1	Horse	*Equus caballus*	e227
rFel d 2	Cat serum albumin	*Felis domesticus*	e220
nSus s	Pig serum albumin, Swine	*Sus scrofa*	e222
Mites			
rDer p 1	House dust mite	*Dermatophagoides Pteronyssinus*	d202
rDer p 2	House dust mite	*Dermatophagoides Pteronyssinus*	d203
rDer p 10	Tropomyosin, House dust mite	*Dermatophagoides Pteronyssinus*	d205
rDer p 23	House dust mite	*Dermatophagoides Pteronyssinus*	d209
Venoms			
rApi m 1	Honey bee Phospholipase A2	*Apis mellifera*	i208
rApi m 2	Honey bee Hyaluronidase	*Apis mellifera*	i214
rApi m 3	Honey bee, Acid phosphatase	*Apis mellifera*	i215
rApi m 5	Honey bee Dipeptidyl peptidase	*Apis mellifera*	i216
rApi m 10	Honey bee Icarapin	*Apis mellifera*	i217
rVes v 1	Common wasp Phospholipase A1	*Vespula vulgaris*	i211
rVes v 5	Common wasp	*Vespula vulgaris*	i209
rPol d 5	Paper wasp	*Polistes dominulus*	i210

Allergen component	Allergen source		Code
Latex			
rHev b 1	Latex	*Hevea brasiliensis*	k215
rHev b 3	Latex	*Hevea brasiliensis*	k217
rHev b 5	Latex	*Hevea brasiliensis*	k218
rHev b 6.02	Latex	*Hevea brasiliensis*	k220
rHev b 8 Profilin	Latex,	*Hevea brasiliensis*	k221
rHev b 11	Latex	*Hevea brasiliensis*	k224
Occupational / Enzymes			
nAna c 2 Bromelain	Pineapple,	*Ananas comosus*	k202
nAsp o 21	alpha-amylase	*Aspergillus oryzae*	k87
nCar p 1	Papain, Papaya	*Carica papaya*	k201
nGal d 4	Lysozyme, Egg	*Gallus spp.*	k208
	Maxatase	*Bacillus licheniformis*	k204
	Savinase	*Bacillus spp.*	k206
nSus s	Pepsin, Swine	*Sus scrofa*	k213
Foods			
rAct d 8 PR-10	Kiwi	*Actinidia deliciosa*	f430
rAna o 3	Cashew nut	*Anacardium occidentale*	f443
rApi g 1.01 PR-10	Celery	*Apium graveolens*	f417
rAra h 1	Peanut	*Arachis hypogaea*	f422
rAra h 2	Peanut	*Arachis hypogaea*	f423
rAra h 3	Peanut	*Arachis hypogaea*	f424
rAra h 6	Peanut	*Arachis hypogaea*	f447
rAra h 8 PR-10	Peanut	*Arachis hypogaea*	f352
rAra h 9 LTP	Peanut	*Arachis hypogaea*	f427
rBer e 1	Brazil nut	*Bertholletia excelsa*	f354
nBos d 4 alpha-lactalbumin	Milk	Bos spp.	f76
nBos d 5 beta-lactoglobulin	Milk	Bos spp.	f77
nBos d 8 Casein	Milk	Bos spp.	f78
rCor a 1 PR-10	Hazel nut	*Corylus avellana*	f428
rCor a 8 LTP	Hazel nut	*Corylus avellana*	f425
nCor a 9	Hazel nut	*Corylus avellana*	f440
rCor a 14	Hazel nut	*Corylus avellana*	f439
rCyp c 1	Carp	*Cyprinus carpio*	f355
rGad c 1	Cod	*Gadus morhua*	f426

Allergen component	Allergen source		Code
nGal d 1 Ovomucoid	Egg	*Gallus spp.*	f233
nGal d 2 Ovalbumin	Egg	*Gallus spp.*	f232
nGal d 3 Conalbumin	Egg	*Gallus spp.*	f323
rGly m 4 PR-10	Soy	*Glycine max*	f353
nGly m 5 beta-conglycinin	Soy	*Glycine max*	f431
nGly m 6	Glycinin	*Glycine max*	f432
rJug r 1	Walnut	*Juglans regia*	f441
rJug r 3 LTP	Walnut	*Juglans regia*	f442
rMal d 1 PR-10	Apple	*Malus domestica*	f434
rMal d 3 LTP	Apple	*Malus domestica*	f435
rPen a 1 Tropomyosin	Shrimp	*Penaeus aztecus*	f351
rPru p 1 PR-10	Peach	*Prunus persica*	f419
rPru p 3 LTP	Peach	*Prunus persica*	f420
rPru p 4 Profilin	Peach	*Prunus persica*	f421
rTri a 14 LTP	Wheat	*Triticum aestivum*	f433
rTri a 19 Omega-5 Gliadin	Wheat	*Triticum aestivum*	f416
Gliadin			f98
Miscellaneous			
nGal-alpha-1,3-Gal (alpha-Gal) Thyroglobulin, bovine			o215
MUXF3 CCD, Bromelain			o214

Table 12 B. ImmunoCAP ISAC

ImmunoCAP ISAC is a miniaturized immunoassay platform that allows for simultaneous measurement of specific IgE antibodies to 112 different allergen components using only 30 µl of serum or plasma.

Allergen component	Allergen source		Protein group
Food Allergens			
nGal d 1	Egg white	*Gallus domesticus*	Ovomucoid
nGal d 2	Egg white	*Gallus domesticus*	Ovalbumin
nGal d 3	Egg white	*Gallus domesticus*	Conalbumin/Ovotransferrin
nGal d 5	Egg yolk/chicken meat	*Gallus domesticus*	Livetin/Serum albumin
nBos d 4	Cow's milk	*Bos domesticus*	Alpha-lactalbumin
nBos d 5	Cow's milk	*Bos domesticus*	Beta-lactoglobulin
nBos d 6	Cow's milk and meat	*Bos domesticus*	Serum albumin
nBos d 8	Cow's milk	*Bos domesticus*	Casein
nBos d lactoferrin	Cow's milk	*Bos domesticus*	Transferrin
rGad c 1	Cod	*Gadus callarias*	Parvalbumin
nPen m 1	Shrimp	*Penaeus monodon*	Tropomyosin
nPen m 2	Shrimp	*Penaeus monodon*	Arginine kinase
nPen m 4	Shrimp	*Penaeus monodon*	Sarcoplasmic Ca-binding protein
rAna o 2	Cashew nut	*Anacardium occidentale*	Storage protein, 11S globulin
rBer e 1	Brazil nut	*Bertholletia excelsa*	Storage protein, 2S albumin
rCor a 1.0401	Hazelnut	*Corylus avellana*	PR-10 protein
rCor a 8	Hazelnut	*Corylus avellana*	Lipid transfer protein (nsLTP)
nCor a 9	Hazelnut	*Corylus avellana*	Storage protein, 11S globulin
rJug r 1	Walnut	*Juglans regia*	Storage protein, 2S albumin
nJug r 2	Walnut	*Juglans regia*	Storage protein, 7S globulin
nJug r 3	Walnut	*Juglans regia*	Lipid transfer protein (nsLTP)
rSes i 1	Sesame seed	*Sesamum indicum*	Storage protein, 2S albumin
rAra h 1	Peanut	*Arachis hypogaea*	Storage protein, 7S globulin
rAra h 2	Peanut	*Arachis hypogaea*	Storage protein, 2S albumin
rAra h 3	Peanut	*Arachis hypogaea*	Storage protein, 11S globulin
nAra h 6	Peanut	*Arachis hypogaea*	Storage protein, 2S albumin
rAra h 8	Peanut	*Arachis hypogaea*	PR-10 protein
rAra h 9	Peanut	*Arachis hypogaea*	Lipid transfer protein (nsLTP)

Allergen component	Allergen source		Protein group
Food Allergens			
rGly m 4	Soybean	*Glycine max*	PR-10 protein
nGly m 5	Soybean	*Glycine max*	Storage protein, Beta-conglycinin
nGly m 6	Soybean	*Glycine max*	Storage protein, Glycinin
nFag e 2	Buckwheat	*Fagopyrum esculentum*	Storage protein, 2S albumin
rTri a 14	Wheat	*Triticum aestivum*	Lipid transfer protein (nsLTP)
rTri a 19.0101	Wheat	*Triticum aestivum*	Omega-5 gliadin
nTri a aA_TI	Wheat	*Triticum aestivum*	Alpha-amylase/Trypsin inhibitor
nAct d 1	Kiwi	*Actinidia deliciosa*	
nAct d 2	Kiwi	*Actinidia deliciosa*	Thaumatin-like protein
nAct d 5	Kiwi	*Actinidia deliciosa*	
rAct d 8	Kiwi	*Actinidia deliciosa*	PR-10 protein
rApi g 1	Celery	*Apium graveolens*	PR-10 protein
rMal d 1	Apple	*Malus domestica*	PR-10 protein
rPru p 1	Peach	*Prunus persica*	PR-10 protein
rPru p 3	Peach	*Prunus persica*	Lipid transfer protein (nsLTP)
rPru 7	Peach	*Prunus persica*	Gibberelin regulated protein (GRP)
Aeroallergens			
nCyn d 1	Bermuda grass	*Cynodon dactylon*	Grass group 1
rPhl p 1	Timothy	*Phleum pratense*	Grass group 1
rPhl p 2	Timothy	*Phleum pratense*	Grass group 2
nPhl p 4	Timothy	*Phleum pratense*	
rPhl p 5b	Timothy	*Phleum pratense*	Grass group 5
rPhl p 6	Timothy	*Phleum pratense*	
rPhl p 7	Timothy	*Phleum pratense*	Polcalcin
rPhl p 11	Timothy	*Phleum pratense*	
rPhl p 12	Timothy	*Phleum pratense*	Profilin
rAln g 1	Alder	*Alnus glutinosa*	PR-10 protein
rBet v 1	Birch	*Betula verrucosa*	PR-10 protein
rBet v 2	Birch	*Betula verrucosa*	Profilin
rBet v 4	Birch	*Betula verrucosa*	Polcalcin
rCor a 1.0101	Hazel pollen	*Corylus avellana*	PR-10 protein

Allergen component	Allergen source		Protein group
Aeroallergens			
nCry j 1	Japanese ceder	*Cryptomeria japonica*	
nCup a 1	Cypress	*Cupressus arizonica*	
rOle e 1	Olive	*Olea europaea*	
nOle e 7	Olive	*Olea europaea*	Lipid transfer protein (nsLTP)
rOle e 9	Olive	*Olea europaea*	
rPla a 1	Plane tree	*Platanus acerifolia*	
nPla a 2	Plane tree	*Platanus acerifolia*	
rPla a 3	Plane tree	*Platanus acerifolia*	Lipid transfer protein (nsLTP)
nAmb a 1	Ragweed	*Ambrosia artemisiifolia*	
nArt v 1	Mugwort	*Artemisia vulgaris*	
nArt v 3	Mugwort	*Artemisia vulgaris*	Lipid transfer protein (nsLTP)
rChe a 1	Goosefoot	*Chenopodium album*	
rMer a 1	Annual mercury	*Mercurialis annua*	Profilin
rPar j 2	Wall pellitory	*Parietaria judaica*	Lipid transfer protein (nsLTP)
rPla l 1	Plantain (English)	*Plantago lanceolata*	
nSal k 1	Saltwort	*Salsola kali*	
rCan f 1	Dog	*Canis familiaris*	Lipocalin
rCan f 2	Dog	*Canis familiaris*	Lipocalin
nCan f 3	Dog	*Canis familiaris*	Serum albumin
rCan f 5	Dog	*Canis familiaris*	Arginine esterase
rEqu c 1	Horse	*Equus caballus*	Lipocalin
nEqu c 3	Horse	*Equus caballus*	Serum albumin
rFel d 1	Cat	*Felis domesticus*	Uteroglobin
rFel d 2	Cat	*Felis domesticus*	Serum albumin
rFel d 4	Cat	*Felis domesticus*	Lipocalin
nMus m 1	Mouse	*Mus musculus*	Lipocalin
rAlt a 1	Alternaria	*Alternaria alternata*	
rAlt a 6	Alternaria	*Alternaria alternata*	Enolase
rAsp f 1	Aspergillus	*Aspergillus fumigatus*	
rAsp f 3	Aspergillus	*Aspergillus fumigatus*	
rAsp f 6	Aspergillus	*Aspergillus fumigatus*	Mn superoxide dismutase
rCla h 8	Cladosporium	*Cladosporium herbarum*	

Allergen component	Allergen source		Protein group
Aeroallergens			
rBlo t 5	House dust mite	*Blomia tropicalis*	
nDer f 1	House dust mite	*Dermatophagoides farinae*	
rDer f 2	House dust mite	*Dermatophagoides farinae*	
nDer p 1	House dust mite	*Dermatophagoides pteronyssinus*	
rDer p 2	House dust mite	*Dermatophagoides pteronyssinus*	
rDer p 10	House dust mite	*Dermatophagoides pteronyssinus*	Tropomyosin
rLep d 2	Storage mite	*Lepidoglyphus destructor*	
rBla g 1	Cockroach	*Blattella germanica*	
rBla g 2	Cockroach	*Blattella germanica*	
rBla g 5	Cockroach	*Blattella germanica*	
nBla g 7	Cockroach	*Blattella germanica*	Tropomyosin
Other			
rApi m 1	Honey bee venom	*Apis mellifera*	Phospholipase A2
nApi m 4	Honey bee venom	*Apis mellifera*	Melittin
rPol d 5	Paper wasp venom	*Polistes dominulus*	Venom, Antigen 5
rVes v 5	Common wasp venom	*Vespula vulgaris*	Venom, Antigen 5
rAni s 1	Anisakis	*Anisakis simplex*	Serine protease inhibitor
rAni s 3	Anisakis	*Anisakis simplex*	Tropomyosin
rHev b 1	Latex	*Hevea brasiliensis*	
rHev b 3	Latex	*Hevea brasiliensis*	
rHev b 5	Latex	*Hevea brasiliensis*	
rHev b 6.01	Latex	*Hevea brasiliensis*	
rHev b 8	Latex	*Hevea brasiliensis*	Profilin
nMUXF3	Sugar epitope from Bromelain		CCD-marker

Appendix 1.
Allergen component IgE tests and suggested clinical interpretations

Cow's milk

If sIgE to milk is below 0.35 kU/L, report:

Negative. Sensitization to milk is unlikely, but cannot be ruled out entirely.

If sIgE to milk is ≥ 0.35 kU/L, report:

Antibodies to milk are elevated indicating possible milk allergy. Approximately 80% of the proteins in cow's milk are caseins (such as Bos d 8), and the rest are serum proteins (ß-lactalbumin Bos d 4, ß-lactoglobulin Bos d 5 and serum albumin Bos d 6). Casein is quite resistant to heating and remains allergenic even if milk is heated for 90 minutes at 90°C. Approximately two-thirds of children with milk allergy, who cannot drink milk as is, can tolerate extensively heated milk (cooked in an oven at ≥ 175°C for at least 30 minutes) as an ingredient in foods and baked goods. Consider using allergen component tests (f76 nBos d 4, f77 nBos d 5, e204 nBos d 6, f78 nBos d 8) to clarify the sensitization profile more precisely. Supervised elimination-challenge testing is recommended to confirm milk allergy.

Cow's milk allergen component IgE testing

Allergen component	**Interpretation** If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to cow´s milk is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpretation below:
f76 nBos d 4 α-lactalbumin	Sensitization indicates milk allergy. Extensive heating may reduce alpha-lactalbumin allergenicity.
f77 nBos d 5 ß-lactoglobulin	Sensitization indicates milk allergy. Extensive heating may reduce beta-lactoglobulin allergenicity.
e204 nBos d 6 serum albumin, BSA	Less than 1% of cow's milk consists of serum albumin. Sensitization indicates milk allergy. Very highly sensitized individuals may react to raw beef as well, but this is extremely rare. Extensive heating reduces allergenicity.
f78 nBos d 8 casein (heat-stable)	Sensitization indicates milk allergy. Casein is the most important cow's milk component and remains allergenic even when heated. Supervised elimination-challenge testing is recommended to confirm milk allergy.

Hen's egg

If sIgE to hen's egg is below 0.35 kU/L, report:

Negative. Sensitization to hen's egg is unlikely, but cannot be ruled out entirely.

If sIgE to hen's egg is ≥ 0.35 kU/L, report:

Antibodies to hen's egg are elevated indicating possible egg allergy. Ovomucoid (Gal d 1) is the most clinically significant hen's egg protein component and remains allergenic even when heated. Other egg allergens, such as ovalbumin (Gal d 2), conalbumin (Gal d 3) and lysozyme (Gal d 4), are heat labile. Their allergenic properties are significantly reduced by extensive heating. Some patients with hen's egg allergy will tolerate extensively heated products. Consider using allergen component tests (f233 nGal d 1, f232 nGal d 2, f323 nGal d 3 and k208 nGal d 4) to clarify the sensitization profile more precisely. Supervised elimination-challenge testing is recommended to confirm egg allergy.

Hen's egg allergen component IgE testing

Allergen component	**Interpretation** If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to egg is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpretation below:
f233 nGal d 1 ovomucoid (heat-stable)	Ovomucoid is the most clinically significant hen's egg component and remains allergenic even when heated. Supervised elimination- challenge testing is recommended to confirm an egg allergy.
f232 nGal d 2 ovalbumin	Ovalbumin is a heat-labile egg protein mostly found in the egg white. Sensitization is associated with an elevated risk of symptoms from raw egg or egg cooked at a low temperature. Allergenicity is reduced after extensive heating.
f323 nGal d 3 conalbumin	Conalbumin is a heat-labile egg protein. Sensitization is associated with an elevated risk of symptoms from raw egg or egg cooked at a low temperature. Allergenicity is reduced after extensive heating.
k208 nGal d 4 lysozyme	Lysozyme is a heat-labile egg protein. Sensitization is associated with an elevated risk of symptoms from raw egg or egg cooked at a low temperature. Allergenicity is reduced after extensive heating. Lysozyme (E1105) is often used as a food additive, as well as in some toothpastes and oral care products.

Wheat

If sIgE to wheat is below 0.35 kU/L, report:

Negative. Sensitization to wheat is unlikely, but cannot be ruled out entirely.

If sIgE to wheat is ≥ 0.35 kU/L, report:

Antibodies to wheat proteins are elevated indicating possible wheat allergy. Wheat sIgE testing based on whole-allergen extract offer adequate sensitivity, but only about 40% specificity. An antibody assay performed with whole-allergen extract might give false positive results for as many as 60% of patients with grass allergy. Consider using allergen component tests (f416 rTri a 19, f433 rTri a 14 and f98 Gliadin) to clarify the sensitization profile more precisely. Supervised elimination-challenge testing is recommended to confirm a wheat allergy.

Wheat allergen component IgE testing

Allergen component	**Interpretation** If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to wheat is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpretation below for each component:
f416 rTri a 19 (omega-5-gliadin)	Omega-5-gliadin of wheat. Sensitization is associated with an elevated risk of a systemic allergic reaction.
f433 rTri a 14 (LTP)	Tri a 14 of wheat is a lipid transfer protein. Sensitization is associated with an elevated risk of allergic reaction.
f98 Gliadin	The test includes α-, β-, γ- and ω-gliadins. Sensitization is associated with an elevated risk of a systemic allergic reaction to wheat.

Fish and crustacean allergen component IgE testing

Allergen component	Interpretation If the result is above 0.35 kU/L, use the interpretations below:	Interpretation If the result of the particular component is below 0.35 kU/L, use the interpretations below:
f355 rCyp c 1 carp, parvalbumin	A heat-stable carp protein that remains allergenic with digestion. Allergic reactions to both raw and cooked fish are possible. Other fish besides carp may also cause symptoms.	Negative. Sensitization to rCyp c 1 carp, parvalbumin is unlikely.
f426 rGad c 1 cod, parvalbumin	A heat-stable cod protein that remains allergenic with digestion. Allergic reactions to both raw and cooked fish are possible. Other fish besides cod may also cause symptoms.	Negative. Sensitization to f426 rGad c 1 cod, parvalbumin is unlikely.
f351 rPen a 1 shrimp, tropomyosin	Sensitization to the rPen a 1 protein indicates allergy to crustaceans (shrimp, lobsters). Also, cross-reactions may occur with other organisms that contain tropomyosin (squid, dust mites, cockroaches).	Negative. Sensitization to frPen a 1 shrimp, tropomyosin is unlikely.

Walnut

If sIgE to walnut is below 0.35 kU/L, report:

Negative. Sensitization to walnut is unlikely, but cannot be ruled out entirely.

If sIgE to walnut is ≥ 0.35 kU/L, report:

Antibodies to walnut are elevated indicating sensitization to walnut. Consider using allergen component tests (f441 rJug r 1, f442 rJug r 3) to clarify the sensitization profile more precisely.

Walnut allergen component IgE testing

Allergen component	Interpretation If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to walnut is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpretations below for each component:
f441 rJug r 1 (storage protein 2S)	Jug r 1 of walnut may cause symptoms even after heating. Sensitization indicates an increased risk of a systemic allergic reaction.
f442 rJug r 3 (LTP)	Jug r 3 of walnut may cause mild symptoms as well as severe reactions, even after heating.

Soy

If sIgE to soy is below 0.35 kU/L, report:

Negative. Sensitization to soy is unlikely, but cannot be ruled out entirely.

If sIgE to soy is ≥ 0.35 kU/L, report:

Antibodies to soy are elevated indicating sensitization to soy. The positive test result can be either due to true soy allergy or due to cross-reactivity with pollens. Consider using allergen component tests (f431 nGly m 5, f432 nGly m 6 and f353 nGly m 4) to clarify the sensitization profile more precisely.

Soy allergen component IgE testing

Allergen component	**Interpretation** If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to soy is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpretations below for each component:
f431 nGly m 5 (storage protein 7S)	Gly m 5 of soy may cause symptoms even after heating. Sensitization indicates an increased risk of a systemic allergic reaction.
f432 nGly m 6 (storage protein 11S)	Gly m 6 of soy may cause symptoms even after heating. Sensitization indicates an increased risk of a systemic allergic reaction.
f353 nGly m 4 (PR-10 protein, Bet v 1 birch homolog)	Gly m 4 of soy is a heat-labile protein that becomes less allergenic when heated. Sensitization usually causes only mild oral symptoms. Birch allergy patients who drink a large amount of soy beverages, especially in connection with physical excercise, may experience a generalized allergic reaction.

Cashew allergen component IgE testing

Allergen component	Report If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to cashew is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpreations below:
f443 rAna o 3 (storage protein 2S)	Ana o 3 of cashew may cause symptoms even after heating. Sensitization indicates an increased risk of a systemic allergic reaction.

Brazil nut allergen component IgE testing

Allergen component	Interpretation If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to brazil nut is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpretations below for each component:
f354 rBer e 1 (storage protein 2S)	Ber e 1 of brazil nut may cause symptoms even after heating. Sensitization indicates an increased risk of a systemic allergic reaction.

Peanut

If sIgE to peanut is below 0.35 kU/L, report:

Negative. Sensitization to peanut is unlikely, but cannot be ruled out entirely.

If sIgE to peanut is ≥ 0.35 kU/L, report:

Antibodies to peanut are elevated indicating sensitization to peanut. The positive test result can be either due to true peanut allergy or due to cross-reactivity with pollens. Consider using allergen component tests (f422 rAra h 1, f423 rAra h 2, f424 rAra h 3, f447 rAra g 6, f352 rAra h 8 and f427 rAra h 9) to clarify the sensitization profile more precisely.

Peanut allergen component IgE testing

Allergen component	**Interpretation** If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to peanut is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the reports below for each component:
f422 rAra h 1 (storage protein 7S)	Ara h 1 of peanut may cause symptoms even after heating. Sensitization indicates an increased risk of a generalized allergic reaction.
f423 rAra h 2 (storage protein 2S)	Ara h 2 of peanut may cause symptoms even after heating. Sensitization indicates an increased risk of a generalized allergic reaction.
f424 rAra h 3 (storage protein 11S)	Ara h 3 of peanut may cause symptoms even after heating. Sensitization indicates an increased risk of a generalized allergic reaction.
f447 rAra h 6 (storage protein 2S)	Ara h 6 of peanut may cause symptoms even after heating. Sensitization indicates an increased risk of getting a systemic allergic reaction.
f352 rAra h 8 (PR-10 protein, Bet v 1 birch homolog)	Ara h 8 of peanut is a heat-labile protein that becomes less allergenic when heated. Sensitization usually causes only local oral symptoms.
f427 rAra h 9 (LTP)	Ara h 9 of peanut may cause mild symptoms as well as severe reactions, even after heating.

Hazelnut

If sIgE to hazelnut is below 0.35 kU/L, report:

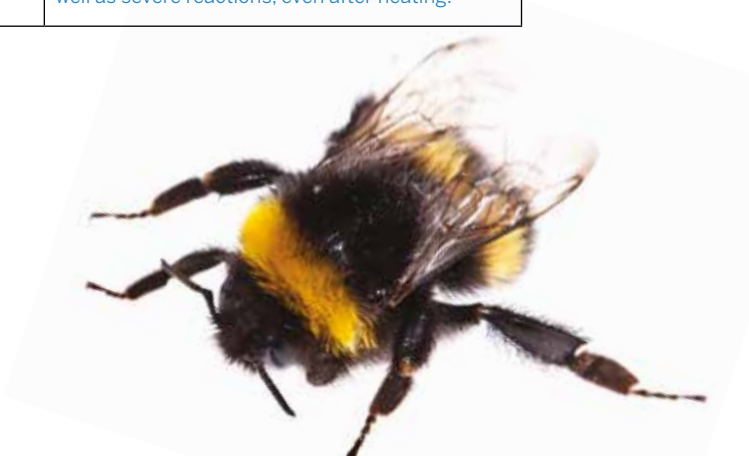
Negative. Sensitization to hazelnut is unlikely, but cannot be ruled out entirely.

If sIgE to hazelnut is ≥ 0.35 kU/L, report:

Antibodies to hazelnut are elevated indicating sensitization to hazelnut. The positive test result can be either due to true hazelnut allergy or due to cross-reactivity with pollens. Consider using allergen component tests (f440 rCor a 9, f439 rCor a 14, f428 rCor a 1 and f425 rCor a 8) to clarify the sensitization profile more precisely.

Hazelnut allergen component IgE testing

Allergen component	**Interpretation** If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization to hazelnut is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.35 kU/L, use the interpretations below for each component:
f440 rCor a 9 (storage protein 11S)	Cor a 9 of hazelnut may cause symptoms even after heating. Sensitization indicates an increased risk of a systemic allergic reaction.
f439 rCor a 14 (storage protein 2S)	Cor a 14 of hazelnut may cause symptoms even after heating. Sensitization indicates an increased risk of a systemic allergic reaction.
f428 rCor a 1 (PR-10 protein, Bet v 1 birch homolog)	Cor a 1 of hazelnut is a heat-labile protein that becomes less allergenic when heated. Sensitization usually causes only local oral symptoms.
f425 rCor a 8 (LTP)	Cor a 8 of hazelnut may cause mild symptoms as well as severe reactions, even after heating.



Hymenoptera venom

If sIgE to wasp is below 0.10 kU/L, report:

Negative. Sensitization to wasp is unlikely, but cannot be ruled out entirely. An antibody assay is recommended within 1 to 4 weeks of the sting as the tests become less accurate with the passing of time.

If sIgE to wasp is ≥ 0.10 kU/L, report:

Antibodies to wasp are elevated. Cross-reactive carbohydrate determinant (CCD) in both wasp and honeybee venoms can cause a false positive test result for either one, even though CCD is not the cause of allergic reactions. Consider using allergen component tests (i 211 rVes v 1, i209 rVes v 5) to identifying which of the hymenoptera (wasp or honeybee) the patient was sensitized to.

If sIgE to honeybee is below 0.10 kU/L, report:

Negative. Sensitization to honeybee is unlikely, but cannot be ruled out entirely. An antibody assay is recommended within 1 to 4 weeks of the sting as the tests become less accurate with the passing of time.

If sIgE to honeybee is ≥ 0.10 kU/L, report:

Antibodies to honeybee are elevated. Cross-reactive carbohydrate determinant (CCD) in both honeybee and wasp venoms can cause a false positive test result for either one, even though CCD is not the cause of allergic reactions. Consider using allergen component tests (i208 rApi m 1, i214 rApi m 2, i215 rApi m 3, i216 rApi m 5, i217 rApi m 10) to identifying which of the hymenoptera (wasp or honeybee) the patient was sensitized to.

Hymenoptera venom allergen component IgE testing

Components specific to wasp venom are rVes v 1 and rVes v 5. Components specific to honeybee venom are rArpi m 1, 2, 3, 5 and 10. An antibody assay is recommended within 1 to 4 weeks of the sting because the tests become less accurate with the passing of time.

Allergen component	**Interpretation** If the result of the particular component is below 0.35 kU/L, report: Negative. Sensitization is unlikely, but cannot be ruled out entirely. In case, not all available components of the particular allergen source are tested the likelihood of false negative result increases. If the result is above 0.10 kU/L, use the interpretations below for each component:
rVes v 1 or 5	Indicates wasp allergy.
rApi m 1, 2, 3, 5 or 10	Indicates honeybee allergy.
MUXF3 (CCD, Bromelain)	People who are sensitized to CCD, Bromelain (cross-reacting carbohydrate determinant) rarely experience clinically significant symptoms from insect venoms. CCD positivity can also reflect cross- reaction with plant products.

Allergen categories

sIgE antibody level (kU/L)	Suggested report
Below 0.35	Negative. Sensitization is unlikely, but not ruled out.
0.35–0.69	Positive. Mild sensitization. Few people experience symptoms.
0.70 or above	Positive. Many people experience symptoms. The higher the antibody level, the more likely clinically significant symptoms are to occur.

When interpreting results, even levels below 0.35 kU/L should be taken into account for the following allergen sources: hymenoptera, stable proteins, storage proteins, latex, and drugs.

References

• EAACI, Molecular Allergology, User's Guide, Pediatr Allergy Immunol 2016;27:1-250.

• Ansotegui et al. , A WAO — ARIA — GA2LEN consensus document on molecular-based allergy diagnosis (PAMD@): Update 2020, World Allergy Organization Journal (2020) 13:100091.

• Allergen Encyclopedia ww.allergyai.com

• Kukkonen AK, Pelkonen A, Mäkinen-Kiljunen S and Mäkelä M, Komponenttitutkimukset parantavat allergioiden diagnostiikkaa (Component tests improve allergy diagnostics). Finnish Medical Journal 2015;7:407-411.

• Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157:215-25.