

# Food allergy diagnosis today and in the future

By Pia Nørhede

*Self-diagnosis of food allergies is notoriously unreliable and highly over-reported. Unnecessary avoidance of certain foods may have adverse nutritional consequences. People with food allergies therefore rely on accurate diagnosis in order to manage their allergies, as they need to avoid foods to which they react, but also must not needlessly restrict their diet. Accurate food allergy diagnosis is a specialized procedure requiring considerable clinical expertise. Currently, there are a range of diagnostic tests and procedures available to clinicians. However, all have their advantages as well as shortcomings. Further research is required to develop more accurate, convenient, and inexpensive tests. EuroPrevall is a large European research project aimed at improving the quality of life for food allergic individuals. EuroPrevall will develop new food allergy diagnostic tests as one of the ways to attempt to meet this goal. New diagnostic tests will help people to more effectively manage their food allergies. The new tests will also provide a clearer picture of the number of people allergic to different foods across Europe.*

## **Why is it important to diagnose food allergy accurately?**

Individuals with food allergy develop symptoms by eating foods that for the vast majority of the population are part of a healthy diet. The only way for the allergic individual to manage food allergy is to avoid eating the food that causes the allergic reaction. In order to avoid unnecessary dietary restrictions it is important to have reliable methods to diagnose food allergy.

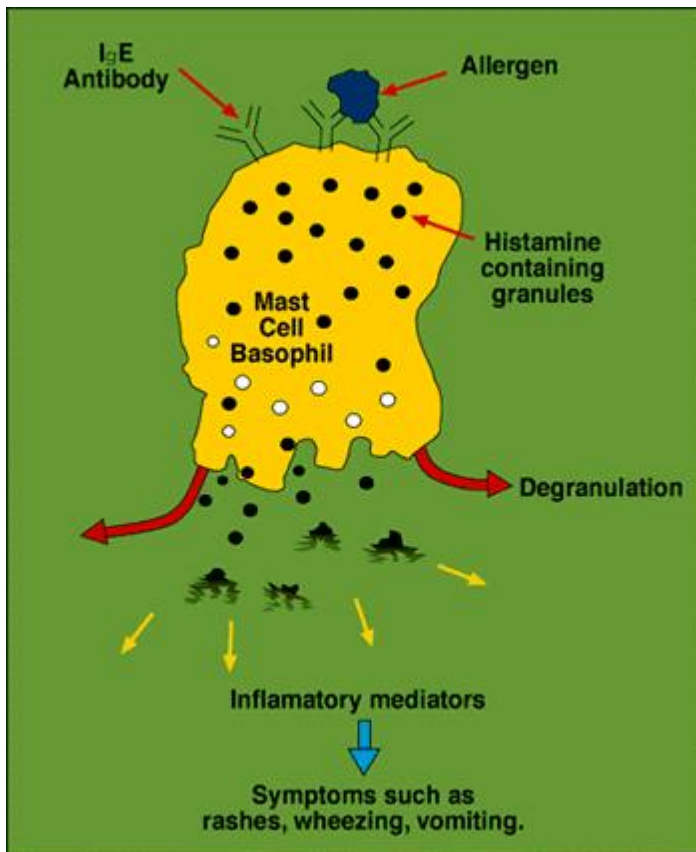
Unfortunately, the public generally overestimates the number of people with food allergy. As a result many people avoid certain foods unnecessarily. Researchers have roughly estimated that up to 8% for children and up to 4% for adults have a food allergy. However, even researchers have had difficulties estimating the true number of people with food allergies due to differences in the diagnostic procedures and tests used. It is therefore also important to develop reliable diagnostic methods in order to find out how big the problem of food allergy is.

## **What is food allergy?**

Our immune system protects our bodies from infections. We produce molecules, called antibodies, which recognise germs that cause infections. We produce a number of different types of antibodies that differ in their specific roles in the immune system. The one, which may cause an allergic reaction, is called **IgE**. We produce IgE molecules to fight infections caused by parasites, like worms or those that cause malaria. We do not understand why, but the immune system of some people mistakenly makes IgE to harmless things like pollen or dust mites, giving rise to hay fever and asthma, and to some foods, giving rise to food allergies.

Food **allergens** (the parts of food responsible for an allergic reaction) are usually proteins, and there are generally several kinds of allergens in each food. It is not yet clear what makes some proteins food allergens, and not others.

When a person eats a food, the food may trigger immune cells to produce large amounts of IgE that recognises that food. Sometimes the immune cells can be triggered to produce IgE when a person breathe in tiny parts of a food e.g. sunflower seeds when they are used to feed birds. The IgE circulates in the blood and some of it attaches to the surface of specialized inflammatory cells called **mast cells**. These cells occur in all body tissues but are especially common in areas of the body that



Release of inflammatory mediators like histamine from a mast cell after allergens have interacted with IgE on its surface

are typical sites of allergic reactions. The person is then **sensitized** to the food and primed to produce an allergic reaction.

On any subsequent occasion when the person eats the same food, the food allergens interact with the specific IgE on the surface of the mast cells. In response, the activated mast cells rapidly release chemicals such as **histamine**. Depending upon the tissue in which they are released, these chemicals will cause a person to have various symptoms of food allergy. For some people it is enough to just breathe in a tiny part of the food to get an allergic reaction.

Some people have allergic reactions where IgE is not involved.

### Foods that may cause allergy

More than 120 foods have been described as causing food allergies. The foods most commonly causing serious allergic reactions on a worldwide basis are: Cereals containing gluten, milk, egg, tree nuts,

peanuts, soybeans, fish, and crustacean. Several studies indicate that most allergic reactions among children are due to a limited number of foods, namely egg, peanut, milk, fish and tree nuts. Egg and milk allergy are often outgrown during the first years of life. Fruits, vegetables, tree nuts and peanuts are responsible for most allergic reactions to foods among adults. Individuals with pollen or latex allergy often experience allergic symptoms when they eat certain fruits, vegetables or nuts. This “**cross-reactivity**” occurs because the body cannot distinguish between the allergens in pollen or latex and related proteins in food and may react to both. The foods, which are common causes of allergic reactions, differ between geographical areas, as a result of dietary preferences, for instance.

### The symptoms of food allergy

The symptoms of food allergies range from mild discomfort to severe, life-threatening reactions (**anaphylactic shock**), which require immediate medical treatment. Symptoms may be triggered in the skin (e.g. itching, redness, swelling), gastrointestinal tract (e.g. pain, nausea, vomiting, diarrhoea, itching and swelling of oral cavity), respiratory tract (e.g. itching and swelling of the nose and throat, asthma), eyes (e.g. itching and swelling), and/or cardiovascular system (e.g. chest pain, abnormal heart rhythm, very low blood pressure causing fainting, and even loss of consciousness). Fortunately anaphylactic shock is much less frequent than skin rashes or symptoms from the gastrointestinal tract.

Allergic reactions to foods may occur within a few minutes after eating the offending food, but rarely symptoms may also develop after hours, making the relationship with ingestion of food less clear. Symptoms can last for days. The specific symptoms and severity of an allergic reaction are affected by the type and amount of the allergen consumed, by the form in which the food containing the allergen was eaten, by the intake of alcohol, aspirin and other drugs such as beta-blockers and ACE inhibitors, by exercise or stress, and by the sensitivity of the allergic person.

The most frequent symptoms of food allergies are itching and/or swelling of the mouth. Oral itching (known as Oral Allergy Syndrome) can be an initial symptom in any kind of food allergy. Oral itching is, however, a well known symptom in food allergy induced by cross-reaction with pollen, such as for instance by apple, kiwi, hazelnuts, walnuts, celery, carrot, tomato, cherry, and melon. Most of the allergens in cross-reacting foods will be destroyed in the gastrointestinal tract. This explains why the symptoms are frequently mild and limited to the mouth. Most of the allergens in the cross-reactive foods will be destroyed if the food is cooked. This explains, for example, why many birch pollen allergic people cannot eat raw apples without experiencing symptoms but stewed apples and apple juice might not be a problem.

In Europe and the US, peanut and tree nuts are the foods most commonly reported to cause life-threatening reactions.

### **Food allergy diagnosis today**

The first step in the diagnosis of a food allergy involves a medical specialist taking a full clinical history, and performing a clinical examination. The clinical history is a detailed record of past allergic reactions and other allergic conditions, such as asthma, eczema and hay fever, and consideration of any seasonal or environmental symptoms. The clinical examination consists of a close look to see if there are allergic symptoms in the skin, eyes and nose. If the patient is asthmatic, the clinician may assess this by measuring measure peak flow. This information will help the specialist decide which tests are appropriate.

The first test is usually a test for the detection of food-specific IgE antibodies. **Skin prick testing** and **blood tests** are the main tests used for this purpose. However, the presence of specific IgE does not necessarily mean that a person will experience symptoms. Therefore, it is normally necessary to perform a provocation or **challenge test** with the suspect food, which involves introducing the food to the patient in gradually increasing amounts in very controlled conditions. Challenge tests must be performed in a hospital or clinic, where any serious reactions can be safely managed. Before the challenge test is performed the patient needs to avoid the suspected food(s) for a period in order to be free of symptoms.

The specialist needs to consider the clinical history, the suspected food, the severity of the symptoms, and the availability of diagnostic reagents before choosing the diagnostic test(s). It is important that the specialist has access to well-documented tests. The specialist will interpret any test result in combination with findings from the clinical examination and the patient's clinical history. For that reason it remains the case that accurate food allergy diagnosis is a specialized procedure requiring considerable clinical expertise. If a food allergy is suspected, diagnosis by a qualified medical practitioner who specializes in allergy is required. Self-diagnosis of food allergy is notoriously unreliable and highly over-reported, while the missed diagnosis of a serious food

allergy could be potentially life threatening. Therefore, people who suspect that they have a food allergy should seek specialist medical advice.

### ***Skin prick testing***

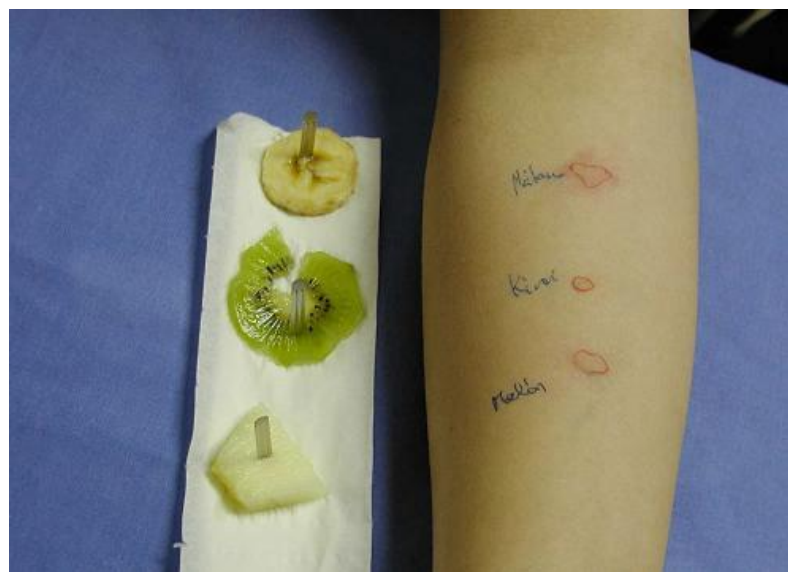
Skin prick tests are frequently used to screen for food-specific IgE as they can be performed at the first visit and the results are ready available. Furthermore, skin prick testing is cheap. The test is usually safe even in case of severe nut allergy as the method introduces a very small amount of allergen just under the outer layer of the skin.

A tiny prick is made with a 1mm lancet through a drop of allergen extract placed on the skin, usually on the forearm. The drops are then wiped away carefully. The site where the allergen was introduced may then become red and swollen with a raised weal in the centre that looks like a nettle sting (= positive response). The weal may enlarge and reaches its maximum size within 15-20 minutes, after which the diameter of the weal is recorded. The reaction fades within an hour.

A negative response usually means the patient is not sensitised to that allergen. But skin prick testing for food allergens may be unreliable and "false negatives" can occur:

- a. Where the reaction to food is not immediate.
- b. If the patient is taking drugs containing antihistamines. These should be stopped five days before testing. Drugs containing antihistamines prevent histamines from attaching to your cells and causing symptoms.
- c. If the allergens in the extracts are unstable as is often the case for fruits and vegetables. In these cases, skin testing with native foods by the prick-prick technique is much better, but not standardized and possibly less safe. In this test, the lancet is plunged several times into the food immediately before pricking the patient's skin.

A positive response usually means the patient has IgE antibodies to that allergen. However, a patient may have a positive skin test but suffer no symptoms when coming into contact with the allergen. Positive skin tests may e.g. occur after sensitisation but before an individual has experienced allergic symptoms to a food. People may also still have positive skin tests to foods and inhalants, even when they have grown out their allergy and no longer have an allergic reaction when they eat a previously offending food.



**A skin prick test with fresh food carried out by the prick-prick technique**

The skin prick test is a good method to rule out a food allergy to egg, milk, peanuts and fish in children. But a positive result may need to be confirmed with a challenge test. A positive result in skin prick tests with fruits and vegetables also may need to be confirmed with a challenge test.

### ***Blood tests***

Several types of blood tests are available to test for food allergies. A blood sample has to be taken from the patient and analysed in a well-equipped laboratory. Therefore the results of the blood tests are not available immediately. Unlike for skin prick tests, antihistamines do not interfere with blood tests, which means that the blood tests can be used in patients with severe allergic symptoms from e.g. the skin without stopping the intake of antihistamines.

The idea with most of the available tests is to measure the amount of IgE in the blood that can bind to specific food allergens. As mentioned earlier, IgE is an antibody involved in allergic reactions. What the different blood tests have in common is that IgE in the blood will be brought in contact with different food allergens extracted from the suspected foods. If the patients are allergic to the suspected food they will have specific IgE antibodies in their blood that will bind to the food allergens. In different blood tests the amount of specific IgE bound to food allergens is measured in different ways.

In some cases the blood test is negative, but an individual may still experience symptoms on consuming a food. As with skin prick testing the reliability of the results of blood tests are dependent on the quality and stability of the food allergen extracts used. Clearly, if some allergens are lost or degraded during the preparation of the food allergen extracts, the blood test may not be able to detect a specific food allergy. Allergens can be lost during the extraction if they are unstable or only present in small amounts. Apple, cherry, soybean and peanut are examples of foods where some allergens may be lost during the extraction. In practice, this means that the blood test may not pick up a food allergy towards these foods. However, the different blood tests currently available are in general better at ruling out than at predicting food allergies.

As for skin prick testing, a patient may have a positive blood test but suffer no symptoms when coming into contact with the allergen. One explanation for this is that it is the IgE bound to mast cells that matters as far as reactivity is concerned, not the IgE in the blood. Another explanation is that the presence of structurally similar allergens in different foods and pollens may in some cases cause IgE to bind to foods against which the patient does not react or has never even consumed.

The results of the blood tests can be graded. Several allergy specialists are investigating whether particular concentrations of specific IgE can predict whether a patient will react to a food challenge, but this work is at an early stage, even with milk, peanut, egg, and fish. There is often not a clear relationship between the amount of specific IgE and the severity of the symptoms. In pollen-related allergies, the amount of specific IgE is generally not strongly related to allergic symptoms.

Another kind of blood test is the cellular allergy test, which measures mast cell reactivity. Several types of cellular allergy tests exist. The different tests measure activation of the mast cells in different ways. Some of the tests for instance measure the release of histamine from the mast cells.

Mast cells are activated when specific IgE has attached to their surface and food allergens interact with the specific IgE. Researchers and clinicians have started using this kind of test because they hope that it could be more accurate in diagnosing allergy than the skin prick testing and blood tests measuring IgE. At present the cellular allergy tests are as good as the skin prick tests. But they cannot replace challenge testing.

### ***Challenge testing***

A positive challenge test provides strong evidence of a food allergy. The test is, however, time consuming and expensive in clinical resources. It is also more stressful for the patient than the skin prick test or blood test, as the patient has to eat the suspected offending food risking an allergic reaction.

A challenge test involves giving a patient increasing doses of the suspected allergenic food, allowing ample time between doses for a response to occur. A medical specialist with a high degree of knowledge about food allergy must always supervise the performance of the challenge test. The challenge must be conducted within a medical facility with equipment and staff to deal with possible life-threatening reactions. A patient who has had a genuinely life-threatening allergic reaction, like anaphylaxis, should not be challenged with the food that caused it unless the challenge start with extremely low doses.

Before oral food challenges, patients must avoid the suspected food(s) for at least 2 weeks. Regular antihistamine medication is also withdrawn. When performing the test the doses should be increased very gradually. In 2004 Europe published guidelines giving advice on how to perform a food challenge test. Despite the guidelines, handling of food challenges differs a lot in different clinics. For example, in a peanut challenge, the doctor or nurse might choose to start with a small piece of peanut (or peanut butter) rubbed on the lip. If there is no reaction after 15 to 60 minutes, they can proceed cautiously to the next stage. The next stage might be allowing the patient to eat, for example, a tiny smear of peanut butter spread thinly on a small piece of bread. The dose should be gradually increased until a normal serving of the foods has been eaten, for example, 8-16 peanuts. A negative challenge is valid only if no symptoms are observed following exposure to the problem food in a dose equivalent to a normal serving. The medical team will observe the patient for symptoms for up to several hours after the challenge. For infants/small children an open challenge as described above is the standard procedure.

For older children and adults, challenges are normally conducted in a double-blind manner with a placebo control. This is when neither the patient, nor the investigator knows whether or not the food preparation being given contains the specific allergen under investigation hidden in it. The suspected allergenic food will be hidden in a food matrix (recipe) consisting of foods normally tolerated by the patient. Pancakes, meat recipes or cookies are examples of suitable food matrices. Unstable allergens such as the many food allergens, which cross-react with birch pollen, may lose their ability to cause allergy when they are hidden in a food matrix. If that is the case they can be delivered in capsule form.

Even though the double-blind placebo-controlled challenge test is the gold standard in food allergy diagnosis, the test may produce false negative results. The challenge procedure usually cannot reproduce the circumstances under which the patient experienced the adverse reaction. For instance, exercise can be a co-factor. Some patients only experience an allergic reaction when eating an offending food either closely before or after exercise. As exercise is normally not included in the challenge test it will not take that into account. The food matrix used to hide the challenge food may influence how much of the food allergen that enters the body. This may differ from what happens when the patient normally eats the food. A virus infection in the gastrointestinal tract or the intake of alcohol or medicine such as aspirin may also change how much of the allergen enters the body and thus how severe the reaction might be. Obviously the challenge test cannot detect delayed reactions occurring after the observation period.

### ***Unproven diagnostic methods***

Different Internet pages advertise many alternative diagnostic methods, e.g. measurement of food specific IgG antibodies, hair-analysis, cytotoxic tests, kinesiology, iridology, and electrodermal testing. The usefulness of these methods for food allergy diagnosis has not been proven by properly performed scientific studies. Hence, scientist cannot recommend the use of these methods in the diagnosis of food allergy.

### **Food allergy diagnosis in the future**

Today double-blind placebo-controlled food challenges remain the "gold standard" for diagnosis, except where the patient has suffered an anaphylactic shock. This is because both the skin prick tests and blood tests, although indicative, are not reliable enough on their own to diagnose food allergy in all cases. The food challenge test is, however, time consuming and more stressful for the patient than the other tests. In the future researchers hope to have developed easy, safe and cheap diagnostic methods that are as reliable as the food challenge tests.

To improve current diagnostic tests, researchers are trying to use pure allergens instead of food allergen extracts for the skin prick tests and blood tests. With pure allergens it is possible to overcome the problem that unstable allergens and allergens present in small amounts may be lost when making a food allergen extract.

Another area in which researchers have started to work is the use of new technologies to measure many different IgE antibodies at the same time. These new technologies, combined with the use of pure allergens, will enable clinicians to obtain a complete picture of which allergens a patient reacts towards in several foods using just one test that requires only a small amount of blood. This will be particularly useful for younger children from whom only small amounts of blood may be taken for testing.

However, all allergic patients may benefit from these new techniques as their clinician can better advise them about the best way to manage their food allergy when it is known to which specific allergens they react and not just to which foods. The explanation for this is that some foods contain a number of allergens that may differ in their stability and, hence, in their ability to induce mild or severe symptoms. Different patients may react to different allergens in the same food and hence experience different symptoms or severity of symptoms. An example is apple allergy. IgE from

patients with birch pollen allergy typically cross-reacts with one particular allergen in apples. Usually the symptoms are mild and limited to the mouth as this allergen is unstable. Other patients may have a type of apple allergy where another more stable allergen is involved. These patients are likely to experience more severe symptoms.

A third area of research is to improve the cellular allergy tests, which use mast cell activity as a measure of allergic responsiveness. These tests have the potential to improve the accuracy of food allergy diagnosis over the currently used skin prick and serum IgE tests, and reduce the need for challenge testing.

### **New diagnostic tools within EuroPrevall**

EuroPrevall is a large European research project aimed at improving the quality of life for food allergic individuals. EuroPrevall will develop new food allergy diagnostic tests as one of the ways to attempt to meet this goal. When the EuroPrevall studies are completed in 2009 we aim to have new diagnostic methods that are just as reliable as challenge testing but that are safer and cheaper. The project will also foster greater standardization of diagnostic procedures, allowing improved comparability of data collected across Europe and providing a clearer picture of the number of people with food allergy.

The above writing is based on the paper:

R. Asero, B.K. Ballmer-Weber, K. Beyer, A. Conti, R. Dubakiene, M. Fernandez-Rivas, K. Hoffmann-Sommergruber, J. Lidholm, T. Mustakov, J.N.G. Oude Elberink, R.S.H. Pumphrey, P.S. Skov, R. van Ree, B.J. Vlieg-Boerstra, R. Hiller, J.O. Hourihane, M. Kowalski, N.G. Papadopoulos, J.-M. Wal, E.N.C. Mills, Stefan Vieths (2007). IgE-Mediated food allergy diagnosis: Current status and new perspectives. *Mol Nutr Food Res* 51, 135-147.

See the InformAll database at <http://foodallergens.ifr.ac.uk> for detailed information on the foods, which may cause allergic reactions.

*EuroPrevall is an EU-funded project about food allergy. The primary objective of EuroPrevall is to improve the quality of life for all food allergic consumers. To meet that objective EuroPrevall will conduct research to obtain information that we currently lack. EuroPrevall will also develop the tools necessary to manage food allergies more effectively. The 56 partners from 21 different countries include some of the leading allergy research organisations in Europe as well as clinical, patient, and industrial organisations. Visit [www.euoprevall.org](http://www.euoprevall.org) for more information on the project.*