NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

ImmunoCAP ISAC and Microtest for multiplex allergen testing

Final scope

April 2015

1 Introduction

The Medical Technologies Advisory Committee identified ImmunoCAP ISAC (and alternative technologies identified during scoping) for multiplex allergen testing in people with complex allergic disease as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note.

The revised scope was informed by discussions at the scoping workshop on 11 March 2015 and at the assessment subgroup meeting held on the 24 March 2015. The alternative technology, Microtest, was identified as similar to the Immunocap ISAC and has been included in the final scope.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE by manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

ImmunoCAP Immuno-Solid phase Allergy Chip (ISAC; Thermo Scientific) and Microtest (MicrotestDx) simultaneously measure sensitisation to multiple allergen components in a single blood test. The risk and severity of an allergic reaction to an allergen component varies from person to person. Using multiplex allergen testing may enable a person's individual sensitisation profile to be determined. The resulting profile may help clinicians to distinguish between genuine sensitisation to an allergen component and cross reactivity, assess the risk of a severe systemic allergic reaction and identify triggering allergen components prior to starting immunotherapy. Multiplex allergen tests

are indicated in more complex allergy cases such as those with inconsistent case histories, unsatisfactory response to treatment, those who are polysensitised and patients with idiopathic anaphylaxis. People with complex allergy are often those with multisystem allergic disease, that is, more than one system in the body has symptoms associated with allergy. It is claimed that using multiplex allergen testing could improve health outcomes by improving allergy management, more appropriately targeting specific immunotherapy, reducing the number of investigative diagnostic tests and hospital visits. These improvements could also lead to potential savings to the NHS from reducing the number of diagnostic tests and avoiding the use of unnecessary immunotherapy.

2.2 Product properties

2.2.1 ImmunoCAP ISAC

ImmunoCAP Immuno-Solid phase Allergy Chip (ISAC; Thermo Scientific) is a CE marked in vitro diagnostic test which uses microarray technology to simultaneously measure specific antibodies to multiple allergen components in a single blood test.

It is a miniaturised immunoassay platform comprising of the ImmunoCAP ISAC Chip and a microarray scanner. The ImmunoCAP ISAC chips are polymer coated slides on which multiple allergen components are immobilised covalently in triplicate. Each slide contains 4 microarrays allowing 4 samples per slide to be assayed. A 30 microlitre sample of serum, plasma or capillary blood is used for each microarray.

The ImmunoCAP Immuno-Solid phase Allergy Chip is a two-step reaction. The sample is incubated on the slide during which time the IgE antibodies from the sample bind to the immobilized allergen components. Fluorescently labelled anti-IgE antibodies are then incubated on the slide which bind and detect the allergen-bound IgE antibodies. The level of fluorescence is measured using a microarray scanner and analysed using proprietary software produced by the same company, Phadia Microarray Image Analysis software (MIA). The company recommends the CapitalBio LuxScan 10k microarray scanner for measuring fluorescence. The results are semi-quantitative and the levels of IgE antibodies are expressed in arbitrary ISAC Standardized Units for IgE (ISU-E) which are proportional to the concentration of specific antibodies detected in the sample. The units are reported in a continuous scale and the measuring range of ISAC is 0.3 to 100 ISU-E. This range approximately corresponds to a concentration range of 0.3 -100 kilo international units of allergen specific antibody per unit volume of sample (kUA/L) of IgE (1 kUA/L is equal to 2.4 nanogram per millilitre).

There is an association between the level of IgE antibodies and likelihood of allergic symptoms, the higher the IgE antibody levels the higher the probability of symptoms. There is no useful clinical correlation between allergen-specific IgE levels and type (severity) of symptoms experienced. There are a number of factors that influence the clinical reactivity at a certain IgE level, such as age, population, concomitant exposure to other allergens, other clinical conditions such as infections etc. Thus it is not possible to establish general cut off values valid for all people at all times. Together with clinical history, ISAC test results may aid the clinician in the diagnosis of allergy by giving information about which allergen components the person is sensitised to as well as indicating IgE antibody levels to each component.

The ISAC procedure including washing and incubation steps is reported to take less than 4 hours.

2.2.2 MicroTest.

Microtest is a CE marked in vitro diagnostic test, which uses microarray technology to simultaneously measure specific antibodies to multiple allergen extracts and components in a single blood test.

It is a miniaturised immunoassay platform comprising of the Microtest biochip, reagents, platform and software. Multiple allergen extracts and components are immobilised covalently in triplicate or quadruplicate onto a precoated slide in the form of a matrix. Each slide contains one matrix microarray. Up to 5 microarrays can be assayed at the same time on the platform. A single 100 microlitre sample of serum sample (venous or capillary blood sample) is required per slide.

Microtest is fully automated and includes a three-step reaction. The sample is incubated on the slide during which time the IgE antibodies from the sample bind to the immobilized allergens. The bound IgE antibodies from the serum sample are then detected using an anti-human IgE that is subsequently bound to by an enzyme-labelled antibody. When a chemical detection solution is added, the enzyme speeds up a reaction which causes light to be emitted. Once the chips have been washed and dried, the signal is read and analysed by the platform automatically. The Microtest platform can simultaneously process up to five samples in each run. The Microtest procedure is fully automated, and reported to take about 4.5 hours.

The results are semi-quantitative and the levels of IgE antibodies are expressed in class scores (negative, low, medium and high) which are derived from the concentration of specific antibodies detected in the sample. The measuring range of Microtest is 0.35 to 100 kU/l.

There is an association between the level of IgE antibodies and likelihood of allergic symptoms, the higher the IgE antibody levels the higher the probability of symptoms. However, there is no such clear association between allergen-specific IgE levels and the type (severity) of symptoms experienced. There are a number of factors that influence the clinical reactivity at a certain IgE level, such as age, population, concomitant exposure to other allergens, other clinical conditions such as infections etc. Thus it is not possible to establish general cut off values valid for all people at all times. Together with clinical history, Microtest results may aid the clinician in the diagnosis of allergy by giving information about which allergen sources and allergen components the person is sensitised to as well as indicating the IgE antibody levels.

3 Target conditions

3.1 Allergy

Background

Allergy is a form of exaggerated sensitivity (hypersensitivity) to a substance which is either inhaled, swallowed, injected, or comes into contact with the skin, eye or mucosa. The term ‘allergy’ is used for situations where hypersensitivity results from heightened (or ‘altered’) reactivity of the immune system in response to external or ‘foreign’ substances. Foreign substances that provoke allergies are called allergens. Examples include grass, weed and tree pollens, substances present in house dust (particularly the house dust mite), fungal spores, animal products, certain foods, and various chemical agents found in the home and at work.

Hypersensitivity reactions are divided into two categories; Immunoglobulin E (IgE) mediated reactions and non-IgE mediated reactions. IgE is a type of antibody that is normally present in very small amounts in the body but has increased levels in allergic disease. The IgE-mediated reactions are typically rapid onset reactions and can sometimes involve prolonged symptoms such as urticaria or eczema. Non-IgE-mediated reactions are less well understood and are mediated by other components of the immune system. They are typically delayed in onset, and occur 4 to 28 hours after exposure.

IgE-mediated reactions are called type I hypersensitivity reactions. During an allergic response, the allergen stimulates the production of the corresponding allergen-specific IgE antibodies which then enter the circulation. The IgE antibodies then bind to receptors on the surface of immune system cells which causes the release of inflammatory chemical substances in the body. This results in vasodilation (widening of blood vessels), increased capillary permeability, mucus hypersecretion, smooth muscle contraction, and tissue

infiltration with various inflammatory mediators. Type I reactions underlie atopic disorders. An atopic disorder is a genetic tendency to develop allergic disease – for example eczema, hay fever and allergic asthma. Anaphylaxis, some cases of angioedema (swelling of the deeper layers of the skin, caused by a build-up of fluid), urticaria (raised, itchy rash that appears on the skin), and latex and many food allergies are also type 1 reactions.

Prevalence

In the UK, it is reported that there are approximately 21 million adults with at least one allergy and 10 million of those have 2 or more allergies. Multiple and complex allergies are becoming more common (Allergy UK). It was estimated that 16% of children had two diagnosed allergies and 2.5% had 3 diagnosed allergies; eczema, asthma and rhinitis (Punekar and Sheikhm 2009). The younger the child is when the first allergic condition appears, the more likely it is that he or she will develop multiple allergy conditions (Childhood allergies - Parliamentary briefing 467 July 2014). Gupta et al. (2004) state that "39 per cent of children and 30 per cent of adults have one or more of asthma, eczema and hay fever; and 38 per cent of children and 45 per cent of adults had experienced symptoms of these disorders"

Food allergy is among the most common of all allergic disorders and has been recognised as a major paediatric health problem in western countries. Only 25–40% of self-reported food allergy is confirmed as true clinical food allergy by an oral food challenge. (NICE Clinical Guideline 116: Food allergy in children and young people [February 2011]). A European study by Rona et al. (2007) reported that 1-11% of self-reported food allergy is confirmed by challenge testing. Recent evidence suggests that the prevalence of self-reported food allergy differs for individual foods and ranges from 3% to 35% (NICE Clinical Guideline 116: Food allergy in children and young people [February 2011]).

3.1.1 Complex allergy

Complex allergy is difficult to define but in general, it is used when allergy is difficult to manage and it often includes the following types of allergy:

3.1.1.1 Multi-system allergic disease

People with multi-system allergic disease have symptoms throughout the body, that is, people with a combination of at least 2 of the following types of allergy: allergic rhinitis, asthma, IgE-mediated and non-IgE-mediated food allergy and other food allergic syndromes such as eosinophilic oesophagitis.

3.1.1.2 Polysensitisation

Monosensitisation is sensitisation to one allergen source or to a closely related taxonomical family or group of allergen sources. Polysensitisation usually refers to sensitisation to two or more allergen sources, and the term paucisensitisation has been used to describe sensitisation to between two and four allergens. Polysensitised people can be particularly difficult to diagnose because of problems distinguishing between true sensitisation and cross-reactivity. Cross-reactivity occurs when an IgE antibody recognises two different antigens as the same antigen; for example, an IgE antibody that recognises and causes an allergic reaction to bet v 1 in birch pollen can also trigger an allergic response to cor a 1 in hazelnut. The structural similarity of bet v 1 and cor a 1 means that the IgE antibody cannot distinguish between them. Cross-reactive molecules can be responsible for multiple positive results from skin prick tests and specific IgE tests. These positive results may or may not correlate to clinical symptoms, depending on host factors, allergen and the nature of the exposure.

3.1.1.3 Idiopathic anaphylaxis

Anaphylaxis is an acute, potentially fatal, multi-organ system, allergic reaction. It is characterised by rapidly developing life-threatening airway, breathing and/or circulation problems, usually associated with skin and mucosal changes (Ewan, 2006). In most cases, anaphylaxis is caused by an allergic reaction. Anaphylaxis is considered idiopathic if it occurs without a known cause or event. Anaphylaxis may be an allergic response that is IgE mediated or non-IgE mediated response. Certain foods, insect venoms, some drugs and latex are common causes of IgE-mediated allergic anaphylaxis. Co-factors such as exercise can contribute to triggering an anaphylactic episode. A significant proportion of anaphylaxis is classified as idiopathic. Food is a particularly common trigger in children, while medicinal products are much more common triggers in older people.

There is no estimate for the frequency of anaphylaxis from all causes in the UK. As anaphylaxis presents mainly in accident and emergency departments and outpatient settings, few estimates of prevalence are available from NHS sources. Anaphylaxis may not be recorded, or may be misdiagnosed as another condition, for example, asthma. It may also be recorded by cause, such as food allergy, rather than as an anaphylactic reaction (NICE clinical guideline 134: Anaphylaxis (December 2011). One study in the UK suggested that approximately 1 in 1333 of the population of England has experienced anaphylaxis at some point in their lives (Stewart and Ewan 1996). There are an estimated 20 deaths from anaphylaxis reported each year in the UK (Pumphrey 2000).

3.1.2 Atopic Eczema

Atopic eczema, also known as atopic dermatitis, is the most common form of eczema. It mainly affects children, but can also affect adults. Eczema is a condition that causes the skin to become itchy, red, dry and cracked. It is a chronic condition in most people, although it can improve over time, especially in children. Atopic eczema can affect any part of the body, but the most common areas to be affected are the backs or fronts of the knees, the outside or inside of the elbows, around the neck, the hands, cheeks and scalp.

People with atopic eczema usually have periods when symptoms are less noticeable, as well as periods when symptoms become more severe (flare-ups).

As atopic eczema can cause the skin to become cracked and broken, there is a risk of the skin becoming infected. This may result in the need for treatment with antibiotics.

It is often difficult to identify the source of the allergy in people with atopic eczema as it may not be feasible for people to stop taking anti-histamines to allow skin prick testing to be done. High total IgE levels mean that false positives can occur on specific IgE tests.

3.2 Patient issues and preferences

Allergic reactions have a daily impact on the quality of life of the individual, and can affect their ability to participate in everyday and social activities, perform work related duties, undertake examinations and pursue their career of choice. The effect of allergies is described in two reports produced by Allergy UK. Stolen Lives found that for 28.4% of respondents allergies had a serious effect on how they planned important life events, and for 26% their allergy severely affected their everyday life. The impact of skin allergy and sensitivity in the UK revealed that 78% of respondents suffered from reactions to their skin allergy all year round, and for 62% their condition had stopped them from going out socially and carrying out day to day activities.

Implementing special diets for children can also be difficult for families to manage because allergies are often atopic so can lead to multiple dietary requirements in one family. Cummings et al. 2010 reported that non allergic siblings often adopted the restricted diet that the allergic child followed.

Sleep disturbance affects up to 60% of children with eczema, increasing to 83% during a flare up which has an effect on behaviour and also performance in school (Camfferman et al. 2010). Educational attainment can also be affected by poor attendance caused by flare ups and by the need for the child

to attend medical appointments. Patients with eczema can also have self-esteem and self-image issues caused by its effect on their appearance. They can also be affected by bullying.

A review (Cummings et al. 2010) highlighted the effect of allergy on the quality of life of patients and care givers. It reported that allergy heightened patients' and care givers' anxiety because of the need for constant vigilance, particularly in new situations. It also showed that parents tended to be overprotective of children with allergy, particularly those who have had anaphylaxis. There can also be anxiety for a parent or care giver associated with administering an epinephrine injection.

3.3 Diagnostic and care pathway

The diagnosis and management of allergy is described in several guidelines:

- NICE Clinical Guideline 116: Food allergy in children and young people (February 2011)
- NICE Clinical Guideline 57: Atopic eczema in children (December 2007)
- NICE Quality Standard 44: Atopic eczema in children quality standard (September 2013)
- NICE clinical guideline 134: Anaphylaxis (December 2011)
- The Royal College of Paediatrics and Child Health (RCPCH): RCPCH Allergy Care Pathways Project: Taking an allergy focused clinical history (2009)
- The World Allergy Organization consensus document: A WAO - ARIA - GA²LEN consensus document on molecular-based allergy diagnostics (2013)

According to NICE clinical guidelines on children with food allergy and eczema, most allergy diagnosis and management takes place in primary care. People with a clear diagnosis, and mild but persistent symptoms, are usually managed in general practice without referral to a specialist service. In cases where there is diagnostic doubt or symptoms of more severe disease, GPs are recommended to refer for a specialist opinion. However, it also highlighted that there is considerable variation in current practice for allergy care, with no agreed treatment pathways, referral criteria or service models.

Currently there are no guidelines for managing allergy in adults unless there is anaphylaxis

3.3.1 Diagnosis

Allergy focused clinical history

The first step if an allergy is suspected should be an allergy focused clinical history.

Obtaining a clinical history and asking specific allergy focused questions is extremely important during diagnosis. NICE Clinical Guideline 116: Food allergy in children and young people states that this can be done by GPs or other primary healthcare professionals with the appropriate competencies. According to the guidelines, the following should be included when taking a clinical history:

- Any personal history of atopic disease (asthma, eczema or allergic rhinitis)
- Any individual and family history of atopic disease (such as asthma, eczema or allergic rhinitis) or food allergy in parents or siblings
- Details of any foods that are avoided and the reasons why
- An assessment of presenting symptoms and other symptoms that may be associated with food allergy including questions about:
  - the age of the child or young person when symptoms first started
  - speed of onset of symptoms following food contact
  - duration of symptoms
  - severity of reaction
  - frequency of occurrence
  - setting of reaction (for example, at school or home)
  - reproducibility of symptoms on repeated exposure
  - what food and how much exposure to it causes a reaction
- Cultural and religious factors that affect the foods they eat
- Who has raised the concern and suspects the food allergy
- What the suspected allergen is
- The child or young person's feeding history, including the age at which they were weaned and whether they were breastfed or formula-fed – if the child is currently being breastfed, consider the mother's diet
- Details of any previous treatment, including medication, for the presenting symptoms and the response to this
- Any response to the elimination and reintroduction of foods.

In addition, the Royal College of Paediatrics and Child Health (RCPCH): RPCH Allergy Care Pathways Project: taking an allergy focused clinical history includes a set of specific allergy focused questions for use when taking an allergy focused clinical history. They recommend a number of questions grouped into themes. The first set contains 3 screening questions for identifying allergy in the community and are used to identify a person who might require more detailed allergy questioning. Following on from these, if allergy is suspected, a further set of questions is recommended. Also, if the expertise is not available in the primary care setting to take an allergy focused clinical history, a referral to secondary care is recommended. The further history taking is presented across six areas. The questioning will partly depend on the child, young person or parent/carer responses. There are:

- Two general history questions asking about general health, current medications, previous allergy testing, lifestyle and general home conditions.
- Nine general allergy history questions
- Eight food-related questions
- Seven respiratory-related questions
- Five Ear, Nose and Throat (ENT)-related questions
- Five skin-related questions.

NICE Clinical Guideline 57: Atopic eczema in children recommends that, healthcare professionals should seek to identify potential trigger factors during clinical assessment including:

- Irritants
- Skin infections
- Contact allergens
- Food allergens
- Inhalant allergens.

A food allergy should be considered in children with atopic eczema who have reacted previously to a food with immediate symptoms, or in infants and young children with moderate or severe atopic eczema that has not been controlled by optimum management, particularly if associated with gut dysmotility (colic, vomiting, altered bowel habit) or failure to thrive.

A diagnosis of inhalant allergy should be considered in children with seasonal flares of atopic eczema, children with atopic eczema associated with asthma or allergic rhinitis, and children aged 3 years or over with atopic eczema on

the face, particularly around the eyes. A diagnosis of allergic contact dermatitis should be considered in children with an exacerbation of previously controlled atopic eczema or with reactions to topical treatments. Children with moderate or severe atopic eczema and suspected food allergy should be referred for specialist investigation and management of the atopic eczema and allergy.

Based on the results of the allergy-focused clinical history, if IgE-mediated allergy is suspected, NICE Clinical Guideline 116: Food allergy in children and young people recommends that the child or young person should be offered a skin prick test and/or blood tests for specific IgE antibodies to the suspected foods and likely coallergens. It recommends that these tests should only be undertaken by healthcare professionals with the appropriate competencies to select, perform and interpret them and should only be undertaken where there are facilities to deal with an anaphylactic reaction. The choice between a skin prick test and a specific IgE antibody blood test should be based on:

- The results of the allergy-focused clinical history and
- Whether the test is suitable for, safe for and acceptable to the child or young person and
- The available competencies of the healthcare professional to undertake the test and interpret the results.

It is recommended that the results of tests are interpreted in the context of information from the allergy-focused clinical history.

Skin prick test

The British Society for Allergy and Clinical Immunology (BSACI) provide guidelines on skin prick testing (BSCAI Paediatric skin prick testing guideline (2010)). Skin prick testing (SPT) is a method to diagnose IgE-mediated allergic disease in people with rhinoconjunctivitis, asthma, urticaria, anaphylaxis, atopic eczema and suspected food and drug allergy. It provides evidence for sensitization and can help to confirm the diagnosis of a suspected type I allergy. It is minimally invasive, inexpensive and results are immediately available. It is indicated if a type I (immediate type) allergy is suspected, based on the clinical history and clinical symptoms.

The test involves putting a drop of liquid allergen onto the skin, followed by a gentle pin prick through the drop. SPT interpretation utilises the presence and degree of skin reactivity as a surrogate marker for sensitisation. When relevant allergens are introduced into the skin, specific IgE product and IgE mediated immune response. This produces a wheal and flare response which

can be quantitated. Many different allergens can be tested simultaneously because the resultant reaction to a specific allergen is localized to the immediate area of the SPT.

The chief advantage of SPT compared to an in vitro measurement of specific IgE antibodies is that the test can be interpreted within 15 to 20 minutes after the reagent is applied to the skin. SPT can also be utilised to test less common allergens, such as certain medications, and fresh fruits and vegetables where no specific IgE antibody measurements are available. The SPT confirms sensitization to a specific allergen, but its results and clinical relevance must be interpreted based on the medical history, clinical symptoms, and, where necessary any other test results in order to assess possible allergy to a specific allergen.

Skin testing is rapid and inexpensive but, has the following limitations:

- Skin reactivity might be affected by previous ingestion of antihistamines or other drugs
- Children often do not tolerate multiple skin needle pricks
- Prior or coexisting dermatologic conditions, such as eczema may preclude the performance of skin tests
- The potency of antigen extracts needs to be maintained
- Potential systemic reactions may occur.

Specific IgE testing

Allergen-specific IgE antibody assays are designed to detect and measure circulating IgE antibodies that can bind to specific allergens. This involves testing a single allergenic molecule at one time and allows the clinician to select the individual allergenic molecules to be tested based on the clinical history. A blood sample is incubated on a slide on which the whole allergen (or component) is immobilised. Allergen-specific IgE in the blood sample binds to the allergen. Unbound antibodies and excess sample are removed by washing. A fluorescently labelled anti-IgE antibody is then added. The amount of bound allergen-specific IgE is calculated via a standard calibration curve, which is linked to the World Health Organization IgE standard and reported in arbitrary mass units (kilo international units of allergen specific antibody per unit volume of sample [kUA/L]).

The allergen-specific IgE antibody test may be done when skin prick tests are not possible or in addition to skin prick tests. If the person has significant

dermatitis or eczema or is taking anti-histamines, skin prick tests are difficult to perform and/or interpret.

Higher levels of IgE are indicative of an allergy but not all people with a positive specific IgE test will have an allergic reaction when exposed to that allergen. The amount of specific IgE present is not predictive of the severity of a reaction; although the higher the level the more likely a reaction to the allergen will occur. Specific IgE test results should be interpreted in the context of clinical history and other allergy test results if available.

Allergen challenge tests

An allergen challenge or provocation test is done by challenging a person directly with the suspected allergen. This is considered the gold standard in allergy diagnosis because it demonstrates a clinical response to the allergen. This is only practical in a controlled hospital environment as it can be dangerous and trigger a severe allergic reaction. Challenge tests include lung, conjunctiva and nasal challenges with the suspected allergen (for example pollen and mould spores) and food challenge tests for suspected food allergy.

Oral food challenges (OFCs) are performed either because the food allergy is not supported by history or because there is a discrepancy between history and test results. NICE Clinical Guideline 116: Food allergy in children and young people states that information on when, where and how an oral food challenge or food reintroduction procedure may be undertaken should be given. However they should not be performed in primary care. Oral food challenges can be useful in establishing the identity of specific food triggers. The most rigorous method is double-blinded and placebo controlled (DBPC), but single blind and open challenges can be performed. An open challenge refers to an oral food challenge in which the person can recognize the target food without blinding. This is the least time intensive food challenge. The general methodology of an oral food challenge is to administer the suspected food in gradually increasing doses under a medical setting. Oral food challenges should be performed in a setting that is fully equipped for emergency treatment if an episode of anaphylaxis occurs.

3.3.1.1 Management

The management of allergy is dependent on the type and severity of the allergy. Mild allergies can be managed and treated in primary care. More severe allergies and people with more complex allergies may require additional management and referral on to specialist services.

NICE Clinical Guideline 116: Food allergy in children and young people recommends referral to secondary or specialist care in any of the following circumstances.

The child or young person has:

- Faltering growth in combination with one or more gastrointestinal symptoms
- Not responded to a single-allergen elimination diet
- Had one or more acute systemic reactions
- Had one or more severe delayed reactions
- Confirmed IgE-mediated food allergy and concurrent asthma
- Significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer.
- There is:
  - persisting parental suspicion of food allergy (especially in
  - children or young people with difficult or perplexing
  - symptoms) despite a lack of supporting history
  - strong clinical suspicion of IgE-mediated food allergy but
  - allergy test results are negative
  - clinical suspicion of multiple food allergies

NICE clinical guideline 134: Anaphylaxis recommends that prior to discharge a healthcare professional with the appropriate skills and competencies should offer the following:

- Information about anaphylaxis, including the signs and symptoms of an anaphylactic reaction
- Information about the risk of a biphasic reaction
- Information on what to do if an anaphylactic reaction occurs (use the adrenaline injector and call emergency services)
- A demonstration of the correct use of the adrenaline injector and when to use it
- Advice about how to avoid the suspected trigger (if known)
- Information about the need for referral to a specialist allergy service and the referral process

- Information about patient support groups

NICE Clinical Guideline 57: Atopic eczema in children and NICE quality standard 44 Atopic eczema in children recommend that children with a suspected food allergy should be referred for specialist investigation and management by paediatric allergist or paediatric dermatologist.

3.3.2 Treatment

Mild allergies can be treated using over the counter medications such as antihistamines and simple avoidance of the allergen.

NICE Clinical Guideline 116: Food allergy in children and young people recommends that once an allergy is suspected based on clinical history, information should be provided about:

- Type of allergy suspected
- Risk of severe allergic reaction
- Potential impact of the suspected allergy on other healthcare issues, including vaccination.

If a food elimination diet is advised information should be provided on:

- What foods and drinks to avoid
- How to interpret food labels
- Alternative sources of nutrition to ensure adequate nutritional intake
- The safety and limitations of an elimination diet
- The proposed duration of the elimination diet
- When, where and how an oral food challenge or food reintroduction procedure may be undertaken

Anaphylaxis (NICE clinical guideline 134) recommends that after emergency treatment for suspected anaphylaxis patients should be offered an appropriate adrenaline injector as an interim measure before the specialist allergy service appointment. An epinephrine autoinjector (EAI) is a medical device for injecting a measured dose or doses of epinephrine (adrenaline), by means of autoinjector technology. It is most often used for the treatment of anaphylaxis. Most individuals with a severe IgE-mediated food allergy are advised to carry an autoinjector in case of accidental exposure. There are many barriers to the successful use of an autoinjector, including the ability to recognize the

symptoms of anaphylaxis, the availability and, understanding of how to use the autoinjector, and anxiety associated with its use.

NICE Clinical Guideline 57: Atopic eczema in children recommends that healthcare professionals should use a stepped approach for managing atopic eczema in children and should tailor the treatment step to the severity of the atopic eczema. Emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments such as mild potency topical corticosteroids (for mild eczema), moderate potency topical corticosteroids (for moderate eczema), tacrolimus, bandages (for moderate or severe eczema), potent topical corticosteroids, phototherapy and systemic therapy (for severe eczema only). Very potent topical corticosteroids should not be used without specialist dermatological advice.

In selected people allergen immunotherapy may be appropriate. It involves the repeated administration, either subcutaneously or sublingually, of allergen extracts. The potential outcomes of immunotherapy are

- Reducing allergy symptoms on subsequent allergen exposure
- Improving quality of life
- Inducing long-term tolerance.

Immunotherapy is time-consuming, expensive and there is a risk of a severe allergic reaction or anaphylaxis during administration. According to the British Society for Allergy and Clinical Immunology (BSCAI) guidelines: Immunotherapy for allergic rhinitis (Walker et al. 2011), the main indications for immunotherapy in the United Kingdom are:

1. IgE-mediated seasonal pollen induced rhinitis, if symptoms have not responded adequately to optimal pharmacotherapy
2. Systemic reactions caused by hymenoptera venom allergy
3. Selected people with animal dander or house dust mite (HDM) allergy in whom rigorous allergen avoidance and reasonable pharmacotherapy fail to control symptoms.

The selection, initiation and monitoring of all people for immunotherapy should be supervised by specialists in allergy. Immunotherapy should only be administered by physicians and nurses with specialist knowledge of allergy and specific immunotherapy. Immunotherapy is an attractive option for the treatment of food allergies, as its goal is to induce tolerance in the person.

With desensitisation, the treated person manifests a decreased response to the allergen.

4 Scope of the evaluation

Table 1: Scope of the evaluation

Decision questions	1. What is the clinical and cost effectiveness of using ImmunoCAP ISAC or Microtest as an adjunct to current clinical assessment in aiding allergy diagnosis and in predicting the grade of allergic reaction?
Populations	• People with allergy that is difficult to manage
Interventions	• Clinical assessment and ImmunoCAP ISAC • Clinical assessment and Microtest
Comparator	Clinical assessment comprising: • Clinical history • Skin prick testing • Singleplex specific IgE
Healthcare setting	Secondary/tertiary care
Outcomes	Intermediate measures for consideration may include: • Diagnostic accuracy • Discordant results • Test failure rate • Number of specific IgE tests • Number of specific immunotherapies • Number of healthcare attendances and admissions • Use of corticosteroids • Prescription of rescue medicines in anaphylaxis • Number of allergy diagnoses • Number of challenge tests • Change in patient management
	Clinical outcomes for consideration may include: • Allergy symptoms • Incidence of acute exacerbations • Adverse effects of testing and treatment • Morbidity and mortality • Health-related quality of life including patient anxiety
	Costs will be considered from an NHS and Personal Social

	Services perspective. Costs for consideration may include: • Cost of equipment, reagents and consumables • Cost of staff and associated training • Medical costs arising from testing, treatment and care • Medical costs arising from adverse events including those associated with false test results and inappropriate treatment
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

5 Modelling approach

The aim and structure of the economic model will depend upon the final scope.

5.1 Existing models

During scoping searches, 2 abstracts reporting the results of economic analyses relating to the use of molecular allergy tests were found.

Glaumann et al. (2013) report cost effectiveness analysis of using molecular allerology versus double blind placebo controlled food challenge (DBPCFC) testing to confirm peanut allergy diagnosis. Three Markov models over a 5 year time horizon were constructed. The models included 200 children with suspected peanut allergy presenting to primary care. The three models compare DBPCFC, SPT and molecular allerology and the analysis was repeated for 5 different countries. They concluded that molecular allerology dominates DBPCFC and SPT. Molecular allerology is associated with a QALY gain of 3.97 compared to 2.54 (DBPCFC) and 3.86 (SPT).

Mascialino et al (2013) report the cost effectiveness of the ImmunoCAP ISAC and SPT versus SPT in identifying patients for SIT over a one year time horizon. The study included 141 patients with rhino-conjunctivitis and/or asthma. ICERS and outcomes were not reported. They conclude that ImmunoCAP and SPT are cost saving as it reduces SIT prescription.

In addition, both NICE clinical guideline 116 and NICE clinical guideline 134 include cost effectiveness models. NICE clinical guideline 116 includes an economic model which was designed to assess the cost effectiveness of

various strategies for the diagnosis of IgE mediated food allergy in children presenting to primary care. The model included both a decision tree for diagnostic test outcomes and a Markov model for longer term health outcomes which included the following health states: minor reaction, major reaction and death. The population included in the model was limited to children with a suspected peanut allergy on the assumption that this is the most common food allergy in children, and is also thought to be associated with the risk of severe allergic reaction.

NICE clinical guideline 134 includes an economic model which was designed to assess both the cost effectiveness of referring people who had experienced anaphylaxis to a specialist allergy service and of prescribing adrenaline injectors for people who had received emergency treatment. A Markov model was constructed to assess the recurrence of anaphylaxis in a population who had previously attended an Emergency Department for anaphylaxis and included the following health states: at risk, recurrence, remission and death. The population included subgroups which were defined by the cause of anaphylaxis; insect, food, drug or idiopathic. The population included in the model were assumed to have a diagnosis of anaphylaxis and the impact of misdiagnosis was not explored.

5.2 Economic considerations

The number of specific IgE tests used to investigate allergy can vary from 1 test to more than 20 specific tests. The impact of this variation will be considered in the economic analyses.

6 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

There is wide variation in access to allergy specialists and allergy care, including challenge testing, across the UK.

7 Potential implementation issues

The adoption of the multiplex allergen testing may require the purchase of additional equipment in the laboratory. A lack of clinical confidence by some clinicians and reservations due to the possibility of indiscriminate use of the test is likely to be a major factor in its adoption within routine clinical practice. There is also a need for training of immunologists and allergy specialists in

the interpretation of results from multiplex allergen testing. Extensive training for dieticians may be needed.

Appendix A Glossary of terms

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by rapidly developing, life-threatening problems involving: the airway (pharyngeal or laryngeal oedema) and/or breathing (bronchospasm with tachypnoea) and/or circulation (hypotension and/or tachycardia). In most cases, there are associated skin and mucosal changes

Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens

Immunoglobin E (IgE) is a class of antibody that has been found only in mammals. It plays an essential role in type 1 hypersensitivity which manifests as a number of allergic conditions such as allergic asthma, most types of sinusitis, allergic rhinitis, food allergy and some types of chronic urticarial and atopic dermatitis. IgE plays a pivotal role in allergic conditions, such as anaphylactic reactions to certain drugs, bee stings and antigen preparations used in specific desensitisation immunotherapy.

Skin prick testing is mainly used to investigate allergies to airborne allergens, certain foods, insect venoms or certain drug allergies. The test involves putting a drop of liquid allergen onto the forearm, followed by a gentle pin prick through the drop. If the person has an allergy to the substance, an itchy, red bump will appear within 15 minutes.

Molecular allergy testing is based on the measurement of allergen-specific IgE reactivity to purified natural or recombinant allergenic molecules (components). It is used to map the allergen sensitisation at a molecular level, using allergen components instead of allergen extracts (as in skin prick testing).

Monosensitisation is sensitisation to one allergen source or to a closely related taxonomical family or group of allergen sources.

Paucisensitisation is a term used to describe sensitisation to between two and four allergens.

Polysensitisation usually refers to sensitisation to two or more allergen sources

Specific IgE testing is used to measure IgE antibodies against allergenic molecules. This involves testing a single allergenic molecule at one time and allows the clinician to select the individual allergenic molecules to be tested

based on the clinical history. More than 650 allergenic molecules are available for testing.

Subcutaneous Under the skin

Sublingual Under the tongue

Vasodilation is the widening of blood vessels that results from relaxation of the muscular walls of the vessels

Appendix B Abbreviations

IgE Immunoglobulin E

Appendix C Related guidance

NICE guidance

Atopic eczema in children. NICE quality standards, QS44, September 2014.

Drug allergy: the diagnosis and management of drug allergy in adults and children. NICE clinical guidelines, CG183: September 2014

Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201). NICE technology appraisals, TA278, April 2013

Atopic eczema in children. NICE Pathway, August 2012

Pharmalgen for the treatment of bee and wasp venom allergy. NICE technology appraisals, TA246, February 2012

Anaphylaxis. NICE Pathway, December 2011

Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode. NICE clinical guidelines, CG134, December 2011

Food allergy in children and young people. NICE Pathway, December 2011

Food allergy in children and young people: Diagnosis and assessment of food allergy in children and young people in primary care and community settings. NICE clinical guidelines, CG116, February 2011

Alitretinoin for the treatment of severe chronic hand eczema. NICE technology appraisals,TA177, August 2009.

Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. NICE technology appraisals, TA131, November 2007

Atopic eczema in children: Management of atopic eczema in children from birth up to the age of 12 years. NICE clinical guidelines, CG57. December 2007

Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisals, TA131, November 2007

Tacrolimus and pimecrolimus for atopic eczema. NICE technology appraisals, TA82, August 2004.

Frequency of application of topical corticosteroids for atopic eczema. NICE technology appraisals, TA81, August 2004.

Under development

Asthma: diagnosis and management. NICE clinical guideline referred, publication expected: June 2015

Relevant guidance from other organisations

Patient UK (June 2014) Skin Prick Allergy Test

BUPA (May 2014) Managing your allergies

NHS Choices (April 2014) Allergies

NHS Choices (April 2014) Food allergy

Map of Medicine (April 2014) Anaphylaxis - suspected

British Society for Allergy and Clinical Immunology (April 2014) Guideline for the diagnosis and management of cow's milk allergy

Anaphylaxis Campaign (February 2014) Latex allergy: The Facts

Anaphylaxis Campaign (February 2014) Food allergens in non-food items

World Allergy Organization (October 2013) A WAO - ARIA - GA²LEN consensus document on molecular-based allergy diagnostics

Children's Acute Transport Service (June 2013) Anaphylaxis/Latex Allergy

Anaphylaxis Campaign (April 2013) Celery Allergy: The Facts

Patient UK (December 2012) Anaphylaxis

Patient UK (May 2012) Food Allergy and Intolerance

British Society for Allergy and Clinical Immunology (March 2012) Standards for paediatric allergy services in secondary care

Patient UK (March 2012) Allergy - General Overview

Patient UK (March 2012) Nut Allergy

Patient UK (March 2012) House Dust Mite and Pet Allergy

Patient UK professional reference (February 2012) Anaphylaxis and its Treatment

Royal College of Paediatrics and Child Health (November 2011) Care pathway for food allergy in children: an evidence and consensus based national approach

Patient UK professional reference (November 2011) Food Allergy and Food Intolerance

World Allergy Organization (February 2011) Guidelines for the Assessment and Management of Anaphylaxis

QIPP (October 2011) Pharmacological interventions to prevent allergic and febrile non-haemolytic transfusion reactions

British Society for Allergy and Clinical Immunology (August 2011) Diagnosis and management of hymenoptera venom allergy

British Society for Allergy and Clinical Immunology (July 2011) Immunotherapy for allergic rhinitis

SIGN (March 2011) Management of atopic eczema in primary care

Royal College of Paediatrics and Child Health (2011) Care pathway for latex allergy

Royal College of Paediatrics and Child Health (2011) Care pathway for Venom allergy

Royal College of Paediatrics and Child Health (2011) Care pathway for Drug allergy

Royal College of Paediatrics and Child Health (2011) Care pathway for urticaria, angio-odema or mastocytosis

Royal College of Paediatrics and Child Health (2011) Care pathway for Eczema

Royal College of Paediatrics and Child Health (2011) Care pathway for asthma and/or rhinitis

Royal College of Paediatrics and Child Health (2011) Care pathway for food allergy

Royal College of Paediatrics and Child Health (2011) Care pathway for anaphylaxis

British Society for Allergy and Clinical Immunology (June 2010) Guidelines for the management of egg allergy

British Society for Allergy and Clinical Immunology (December 2008) Guidelines for the management of drug allergy

SIGN (July 2008 updated April 2014) Antibiotic prophylaxis in surgery

Royal College of Physicians of London (May 2008) Latex allergy: Occupational aspects of management

Royal College of Physicians of London (March 2008) Latex allergy guideline

Joint Royal Colleges Ambulance Liaison Committee (2007) Anaphylaxis and Allergic Reactions in Children

Joint Royal Colleges Ambulance Liaison Committee (2007) Anaphylaxis and Allergic Reactions in Adults

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Allergy UK (March 2013)The Disturbing Impact of Skin Allergy and Sensitivity in the UK

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