Diagnosis and assessment of food allergy in children and young people in primary care and community settings

Full guideline
Draft for consultation, August 2010

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.
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Disclaimer

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Introduction

Food allergy is an adverse immune response to food allergens. It can be classified into IgE mediated, non-IgE mediated. Non-IgE reactions, which are poorly defined both clinically and scientifically, are believed to be T-cell
mediated. Some reactions involve a mixture of both IgE and non-IgE responses and are classified as mixed IgE and non-IgE allergic reactions.

In its review of allergy services in 2006, the Department of Health concluded that there was considerable variation in current practice for allergy care, with no agreed treatment pathways, referral criteria or service models. Specifically, it was reported that many people with allergies practised self-care, using alternative sources of support rather than NHS services (for example, complementary services with non-validated tests and treatments).

In the NHS, most allergy care 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. Some people with allergies, and the parents or carers of children and young people with allergies, also purchase over-the-counter medicines from community or high-street pharmacies. However, if there is diagnostic doubt or more severe disease, the GP may consider referral for a specialist opinion.
Patient-centred care

This guideline offers best practice advice on the care of children and young people with suspected food allergies.

Treatment and care should take into account the needs and preferences of children and young people with suspected food allergies, and their parents or carers where appropriate. They should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals.

If the child or young person is under 16, healthcare professionals should follow the guidelines in ‘Seeking consent: working with children’ (available from www.dh.gov.uk).

Good communication between healthcare professionals and children or young people with a suspected food allergy is essential. It should be supported by evidence-based written information tailored to the needs of the child or young person and their parent or carer. Treatment and care, and the information children and young people, and their parents or carers are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.
1 Summary

1.1 List of all recommendations

Assessment and allergy-focused clinical history

1.1.1 Consider the possibility of food allergy in children and young people who have one or more of the following signs and symptoms relating to:

- the skin:
  - pruritis
  - erythema
  - acute urticaria
  - angioedema
  - eczema

- the respiratory system:
  - upper respiratory tract symptoms (sneezing, itching, secretion or blockage)
  - lower respiratory tract symptoms (cough, wheezing or shortness of breath)
  - laryngeal stridor
  - rhino conjunctivitis

- the gastrointestinal system:
  - gastro-oesophageal reflux
  - vomiting
  - dysphagia
  - food refusal or aversion
  - infantile colic
  - abdominal pain
  - loose or frequent stools
  - blood or mucus in the stools
  - constipation
  - perianal redness
  - pallor and tiredness
− faltering growth
• anaphylaxis or other systemic allergic reactions.

1.1.2 Consider the possibility of food allergy in children and young people whose symptoms do not respond adequately to treatment for:

• atopic eczema¹
• gastro-oesophageal reflux disease
  − chronic constipation.

1.1.3 If food allergy is suspected (by a healthcare professional or the parent, carer, child, or young person) healthcare professional with the appropriate competencies (including GP’s) should take an allergy-focused clinical history tailored to the presenting symptom(s) and age of the child or young person. This should include:

• any family history of atopic disease (such as asthma, eczema or allergic rhinitis) 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 (see recommendation 1.2.1), including questions about:
  − age of onset
  − speed of onset
  − duration
  − severity
  − frequency
  − setting of reaction (for example, at school or home)
  − reproducibility of symptoms on repeated exposure
  − dose responsiveness.
• who suspects the food allergy

¹ For information about treatment for atopic eczema see ‘Atopic eczema in children’ (NICE clinical guideline 57)
• 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
• details of any previous treatment, including medication, for the presenting symptoms and the response to this
• any response to the exclusion and reintroduction of foods.

1.1.4 Based on the findings of the allergy-focused clinical history, physically examine the child or young person, paying particular attention to:

• growth and physical signs of malnutrition
• allergy-related co morbidities.

Diagnosis
Food allergy can be classified into IgE mediated and non-IgE mediated allergy. IgE mediated reactions are acute and frequently have rapid onset. Non-IgE mediated reactions are generally characterised by delayed and non-acute reactions.
Non-IgE mediated food allergy
1.1.5 Based on the results of the allergy-focused clinical history, if non-IgE mediated food allergy is suspected, trial elimination of the suspected allergen (normally for between 2–6 weeks) and reintroduce after the trial. Seek advice from a dietician if appropriate.

IgE-mediated food allergy
1.1.6 Based on the results of the allergy-focused clinical history, if IgE-mediated allergy is suspected, offer the child or young person a skin prick test or blood tests for specific IgE antibodies.

1.1.7 Skin prick tests should only be undertaken by healthcare professionals with the appropriate competencies and where there are facilities to deal with an anaphylactic reaction.

1.1.8 Choose between a skin prick test or a specific IgE antibody blood test based on:

- the results of the allergy-focused clinical history and
- whether the test is suitable for and acceptable to the child or young person (or their family or carer),
- which tests are available locally
1.1.9 Do not rely solely on allergy tests. Interpret the results of allergy tests in the context of information from the allergy focused clinical history.

1.1.10 Do not carry out allergy testing without first taking an allergy-focused clinical history.

1.1.11 Do not use atopy patch testing or oral food challenges to diagnose IgE-mediated allergy in primary care or community settings.

**Patient Information and support**

1.1.12 Based on the allergy-focused clinical history, offer the child or young person, or their parent or carer, information that is age appropriate about the:

- type of allergy suspected
- risk of severe allergic reaction
- potential impact of the suspected allergy on other healthcare issues, including vaccination
- diagnostic process, which may include:
  - an exclusion diet and oral food challenge or food reintroduction procedure
  - skin prick and IgE antibody testing, including the safety and limitations of these tests
  - referral to secondary or specialist care.

1.1.13 Offer the child or young person, or their parent or carer, information relevant to the suspected underlying mechanism.

1.1.14 If a food exclusion diet is advised as part of the diagnostic process (see recommendation 1.2.5), offer the child or young person, or their parent or carer, information 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 exclusion diet
• the proposed duration of the exclusion diet
• when, where and how the oral food challenge would be undertaken
• the safety and limitations of the oral food challenge or food reintroduction procedure.

1.1.15 For babies and young children with suspected cow’s milk allergy, offer:

• food avoidance advice to breastfeeding mothers, or
• information on the most appropriate hypoallergenic formula or milk substitute to mothers of formula-fed babies.

Seek advice from a dietitian if needed.

1.1.16 Offer the child or young person, or their parent or carer, information about the support available and details of how to contact support groups.

Referral to secondary or specialist care

1.1.17 Consider 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 of the gastrointestinal symptoms described in recommendation 1.2.1
  – not responded to a single-allergen exclusion diet
  – had acute systemic reactions or severe delayed reaction
  – confirmed IgE mediated food allergy and concurrent asthma
  – significant atopic eczema where multiple food allergies are suspected by the parents.

• There is:
− parental suspicion of food allergy (especially in children or young people with difficult or perplexing symptoms)
− strong clinical suspicion of IgE mediated food allergy but allergy tests are negative
− clinical suspicion of multiple food allergies.

**Alternative diagnostic tools**

1.1.18 Do not use the following alternative diagnostic tests in the diagnosis of food allergy:

- vega test
- applied kinesiology
- hair analysis

1.1.19 Do not use serum specific IgG testing in the diagnosis of food allergy.
1.2 Overview

1.2.1 Diagnosis of food allergy in children in primary and community settings

Food allergy is an adverse immune response to food allergens. It can be classified into IgE mediated, non-IgE mediated and mixed IgE and non-IgE mediated allergy. The IgE mediated reactions are acute, frequently have rapid onset and are characterised by:

- anaphylaxis
- angioedema
- asthma or respiratory symptoms, such as wheezing
- conjunctivitis
- oral allergy syndrome
- rhinitis
- urticaria

Non-IgE mediated reactions are generally characterised by:

- atopic eczema
- chronic pulmonary disease
- constipation
- enterocolitis
- enteropathy
- eosinophilic oesophagitis
- faltering growth
- gastro-oesophageal reflux disease
- proctitis
- proctocolitis

Non-IgE mediated food allergy is frequently delayed onset conditions and may need the opinion of a paediatrician or paediatric gastroenterologist.
a) Food allergy in the population is amongst the most common of the allergic disorders and has been recognised as a major paediatric health problem in western countries. This is because of the severity of reactions and a dramatic increase in prevalence over the past recent decades.

b) The prevalence of food allergy in Europe and North America has been reported to range from 6% to 8% in children up to the age of 3 years.

c) In the UK concerns have been expressed about the prevalence of food allergy in the general population, especially from individuals and families affected by food allergy, healthcare staff, schools, food producers and retailers, and government departments.

There is currently no evidence-based clinical guideline for use in England, Wales and Northern Ireland that addresses the diagnosis and assessment of food allergies in children and young people. This short clinical guideline aims to improve the care of children and young people with suspected food allergy by making evidence-based recommendations on diagnosis and assessment of food allergy.

1.2.2 Who this guideline is for

This document is intended to be relevant to staff in

a) Primary care NHS settings.

b) Community settings including the home environment and health visits, preschools, schools, children's centres and other childcare health settings, community pharmacy, community dietitian and community paediatrician services.

The target population is

- Children and young people up to their 19th birthday with suspected food allergy presenting with symptoms such as atopic eczema, anaphylaxis,
urticaria, rhinitis, conjunctivitis, asthma, gastrointestinal symptoms and oral allergy syndrome

- Children and young people up to their 19th birthday who are at higher risk of developing food allergy, specifically those with:
  - existing atopic diseases, such as asthma, atopic eczema or allergic rhinitis, or
- a first-degree relative (that is, a parent or sibling) with a food allergy or other atopic disease.

2 How this guideline was developed

2.1 Introduction

Diagnosis and assessment of food allergy in children and young people in primary care and community settings (NICE clinical guideline [XX]) is a NICE short clinical guideline. Wherever possible, grading of recommendations assessment, development and evaluation (GRADE) was used as a method to assess study quality; however, where GRADE tables were not appropriate, quality assessments were based on critical appraisal of the study design and limitations. Specifically, GRADE was not appropriate for clinical questions one, four and five, which addressed clinical history taking, the information needs of the child or young person and referral to secondary or specialist care respectively. In question one we didn't identify any studies that compared clinical history taking with no clinical history taking. So studies in which clinical history had been taken were evaluated to identify the relevant questions for an allergy-focused clinical history. A review of reviews was done to analyse the risk factors that would be associated with likely development of food allergy. For question four most of the papers identified were qualitative papers, for which it is inappropriate to use a modified GRADE assessment. For question five no studies were identified comparing cohorts of children who had been referred with those who had not. For a full explanation of how this type of guideline is developed, see 'The guidelines manual' (2009) at www.nice.org.uk/GuidelinesManual
2.2 Assessment and allergy-focused clinical history

What elements should be included in an allergy focused clinical history taking, physical examination and child/parent food diaries to diagnose and assess food allergy (IgE, non-IgE mediated or mixed IgE and non-IgE) effectively in children and young people?

Ten studies (Asarnoj et al 2009; Berg et al 2003, Dean et al 2007.; Hand et al. 2004; Hill et al. 2004; Kucukosmanoglu et al. 2008; Orhan et al. 2009; Roehr et al. 2004; Simeone et al. 2008; Skolnick et al. 2001) were selected for this question. These studies included papers that had carried out some form of clinical history taking. A further review of reviews was done to identify secondary studies that had reviewed risk factors associated with the prevalence and/or incidence of food allergy. Six studies (see table 1 below) were included in the analysis of risk factors. For identified and excluded studies see appendices 1 and 2.
### 2.2.1 Evidence review

Table 1. Evidence summary for review of reviews

Evidence was extracted from six reviews which showed that the following risk factors and/or symptoms were important in the development of food allergy.

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<tr>
<td>Genetic risk (atopic disease – especially food allergy in parents and/or siblings)</td>
<td>√</td>
<td>e.g. seven-fold increase in peanut allergy if the child has a parent or sibling with peanut allergy</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Other atopic disease (including eczema, asthma and allergic rhino conjunctivitis)</td>
<td>√</td>
<td>33–81% of children with infantile eczema have IgE-mediated food allergy. The presence of eczema in the first 6 months of life was associated with an increased risk of peanut allergy, and this risk increased with more severe eczema.</td>
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<tr>
<td>Early exposure of food allergens through breastfeeding and/or maternal diet</td>
<td>lack of evidence</td>
<td>variable results</td>
<td></td>
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<td></td>
<td>variable results</td>
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<tr>
<td>Delivery by caesarean section</td>
<td>√</td>
<td>A recent meta-analysis found six studies that confirmed a mild effect of c-section, increasing the risk of food allergy or atopy (OR 1.32; CI 1.12 to 1.55)</td>
<td></td>
<td>still unknown influence on development of food allergy</td>
<td></td>
<td>(Eggesbo 2003 OR 1.6; CI 0.5 to 5.1, Renz-Polster 2005 OR 1.34; variable results</td>
</tr>
<tr>
<td>Maternal smoking up to the end of pregnancy and after birth</td>
<td>√</td>
<td>CI 0.54 to 3.29</td>
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<tr>
<td>Gastrointestinal symptoms (including oral allergy syndrome, vomiting, colic, diarrhoea, gastro-oesophageal reflux, constipation, enterocolitis, eosinophilic gastroenteropathy and protein-losing enteropath)</td>
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<tr>
<td>Dermatological symptoms (including atopic dermatitis, acute urticaria/angioedema, contact rash, contact dermatitis and vasculitis)</td>
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<tr>
<td>Respiratory symptoms (including rhinitis, laryngeal edema, asthma, chronic otitis media, heiner syndrome and hypersensitivity pneumonitis)</td>
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<tr>
<td>Systemic anaphylaxis (including food dependent, exercise-induced anaphylaxis)</td>
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OR, odds ratio; CI, confidence interval
2.2.2 Evidence statements

2.2.2.1 No studies were identified that evaluated the use of a clinical history, or compared different items of a history, for the diagnosis of food allergy.

2.2.2.2 Reports of clinical history taking or questionnaires used in the diagnosis of food allergy documented use of the following items:

- Gender and current age of the child or young person
- Family history of atopic disease such as asthma and eczema
- Age of onset of perceived allergy
- Adverse reactions within 2 hours of consuming specific foods
- Symptoms experienced, including:
  - cutaneous (eruption, itching, rash, swelling)
  - nasal (sneezing, itching, secretion, blockage)
  - ocular (redness, itching, secretion)
  - bronchial (cough, wheezing, shortness of breath)
  - gastrointestinal (stomach ache, nausea, vomiting, diarrhoea)
  - laryngeal (difficulty swallowing or speaking)
  - cardiovascular (palpitations, tachycardia, hypotension)
- Previous food allergy
- Resolution or lack of resolution of reactions
- Duration of exclusive breastfeeding in babies
- Age of starting certain foods, such as cow’s milk, and solid foods when weaning
- Current dietary habits
- Smoking habits of children and cohabitants, such as parents.
- Any previous physician diagnosed symptoms and current medication
- Pet ownership
• Environmental allergen exposure and cross sensitization
• Questionnaire administered by trained allergy nurse/professional

2.2.2.3 Evidence from four reviews showed that atopic disease or food allergy in parent or siblings is a risk factor for the development of food allergy

2.2.2.4 Evidence from two reviews showed that children with other atopic disease were more likely to develop food allergy

2.2.2.5 Evidence from one review showed that children with more severe and earlier on set of eczema were more likely to develop food allergy

2.2.2.6 Three reviews showed a lack of evidence to show that early exposure to food allergens through breast feeding and maternal diet was a risk factor for food allergy.

2.2.2.7 Evidence from four reviews showed variable results for caesarean section as a risk factor for developing food allergy

2.2.2.8 Evidence from one review showed that maternal smoking up to the end of pregnancy may be a risk factor for food allergy

2.2.2.9 Evidence from one review showed that gastrointestinal, dermatological, respiratory symptoms and systemic anaphylaxis were signs of food allergy

2.2.3 Evidence to recommendations

The GDG considered the evidence within the framework of factors that would prompt investigation of possible food allergy: initial assessment, allergy-focused clinical history taking and further investigations. Following evidence from the review of reviews, the GDG felt that signs and symptoms should be highlighted as a first recommendation because it would be these that the child or young person would present to their GP. The group agreed that assessing for genetic risk and the presence of other atopic disease would form part of the allergy-focused clinical history and would not need to be included with the
initial signs and symptoms. It was also felt that smoking as a risk factor for developing food allergy was not typically used in clinical practice and the evidence was not strong enough to support a specific recommendation. The GDG agreed that the three main systems most commonly affected by food allergy were the gut, skin and respiratory systems. GDG consensus was used to list the most common symptoms of food allergy, based on their expertise and clinical experience.

In addition to the evidence the GDG considered suspicion of an adverse reaction to food by a healthcare professional or the parent, carer, child, or young person to be an important factor, although it also acknowledged that it may not be predictive of confirmed allergy. Therefore it was recommended that suspicion of food allergy should trigger an allergy-focused history and this was included as part of the recommendation about initial assessment. It was also agreed that the risk attributable to family history of atopy should be restricted to first degree relatives.

The GDG agreed that the evidence presented was limited and did not include all the important components of an allergy focussed clinical history. As a result many of the recommendations were made on the basis of consensus.

The GDG also felt that a physical examination should always follow on from an allergy focused clinical history. Although allergies do not always affect growth, there was a consensus that growth and nutrition were important aspects that should be highlighted. The group also discussed the importance of assessing co-morbidities that may be related to food allergy.
2.2.4 Recommendations

Recommendation 1.2.1
Consider the possibility of food allergy in children and young people who have one or more of the following signs and symptoms relating to:

- the skin:
  - pruritis
  - erythema
  - acute urticaria
  - angioedema
  - eczema
- the respiratory system:
  - upper respiratory tract symptoms (sneezing, itching, secretion or blockage)
  - lower respiratory tract symptoms (cough, wheezing or shortness of breath)
  - laryngeal stridor
  - rhino conjunctivitis
- the gastrointestinal system:
  - gastro-oesophageal reflux
  - vomiting
  - dysphagia
  - food refusal or aversion
  - infantile colic
  - abdominal pain
  - loose or frequent stools
  - blood or mucus in the stools
  - constipation
  - perianal redness
  - pallor and tiredness
  - faltering growth
- anaphylaxis or other systemic allergic reactions.
Recommendation 1.2.2
Consider the possibility of food allergy in children and young people whose symptoms do not respond adequately to treatment for:

- atopic eczema²
- gastro-oesophageal reflux disease
  - chronic constipation.

Recommendation 1.2.3
If food allergy is suspected (by a healthcare professional or the parent, carer, child, or young person) healthcare professional with the appropriate competencies (including GP’s) should take an allergy-focused clinical history tailored to the presenting symptom(s) and age of the child or young person. This should include:

- any family history of atopic disease (such as asthma, eczema or allergic rhinitis) 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 (see recommendation 1.2.1), including questions about:
  - age of onset
  - speed of onset
  - duration
  - severity
  - frequency
  - setting of reaction (for example, at school or home)
  - reproducibility of symptoms on repeated exposure
  - dose responsiveness.
- who suspects the food allergy
- what the suspected allergen is

² For information about treatment for atopic eczema see ‘Atopic eczema in children’ (NICE clinical guideline 57)
• the child or young person’s feeding history, including the age at which they were weaned and whether they were breastfed or formula-fed
• details of any previous treatment, including medication, for the presenting symptoms and the response to this
• any response to the exclusion and reintroduction of foods.

Recommendation 1.2.4
Based on the findings of the allergy-focused clinical history, physically examine the child or young person, paying particular attention to:

• growth and physical signs of malnutrition
• allergy-related co morbidities.
2.3 **Diagnosis of non-IgE mediated food allergy**

2.3.1 **Evidence review**

What diagnostic tools and strategy are most appropriate to diagnose non-IgE mediated and mixed IgE and non-IgE mediated food allergy in children and young people in primary care?

12 papers were included for critical appraisal for this question.

GRADE profile 1: Differential diagnosis for non-IgE, and mixed IgE and non-IgE mediated food allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Design</th>
<th>Diagnostic tests</th>
<th>Comparators</th>
<th>Type of food</th>
<th>Diagnosis</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six studies (Cavataio et al. 1996; Kalach et al. 2005; Ford et al. 1983; Fiocchi et al. 2004; Niggemann et al. 2002; Verini et al. 2007)</td>
<td>Observational</td>
<td>Specific IgE antibody test, Atopy patch test</td>
<td>Endoscopy biopsy and DBPCFC</td>
<td>Cows’ milk, soy, hens’ eggs, wheat, peanuts</td>
<td>Conflicting results. No clear-cut differential diagnosis. Studies more definite on IgE and very vague on non IgE</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>N</td>
</tr>
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</table>

Outcome: differential diagnosis of non–IgE and mixed IgE and non-IgE delayed onset and immediate using combinations of tests
### GRADE profile 2: The utility of different tools for the correct diagnosis of non-IgE and mixed IgE and non-IgE mediated food allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: utility of various tools for the correct diagnosis and assessment of non-IgE and mixed IgE and non-IgE mediated food allergy in children in primary care</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three studies (Cavataio et al. 1996; Nielsen et al. 2006; Lacono et al. 1995)</td>
<td>Combination of biopsy, atopy patch test, oesophageal endoscopy, 24-hour oesophageal pH monitoring and double-blind placebo-controlled food challenge to diagnose various forms of non-IgE food allergy. Each endoscopy, biopsy and/or food challenge was done in secondary or specialist care.</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>483 children with suspected gastro-oesophageal reflux disease and/or hypersensitivity to cows’ milk protein had to be referred to secondary or specialist care for a differential diagnosis. Upon evaluation it was found that 30 of 72 children with gastro-oesophageal reflux also had hypersensitivity to cows’ milk protein. In these children the 24-hour oesophageal pH monitoring was needed to identify cases of gastro-oesophageal reflux associated with the cows’ milk protein hypersensitivity. The pH monitoring was found to be 90% sensitive and 100% specific. Circulating eosinophil count also had sensitivity between 33% and 40% and specificity ranging from 57% to 100%.</td>
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</tbody>
</table>
GRADE profile 3: The diagnostic utility of the atopy patch test for diagnosis of non-IgE mediated food allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: diagnostic utility of atopy patch test in diagnosing non-IgE mediated food allergy</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four studies (Kalach et al. 2005, Fogg et al. 2006 and Niggeman et al. 2002, Nielsen 2004)</td>
<td>Positive predictive values ranged from 75% to 95%. Negative predictive values ranged from 51.7% to 100%</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>-</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>Sensitivities ranged from 44% to 100% Specificities ranged from 71% to 100%</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

Sensitivity, specificity and predictive values for atopy patch test for diagnosis of non-IgE mediated food allergy

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GRADE profile 4: The utility of food elimination and other diagnostic tools in the differential diagnosis of non-IgE mediated food allergy and gastro-oesophageal reflux disease

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: utility of food elimination in combination with other diagnostic tools for the differential diagnosis of non-IgE mediated food allergy and gastro-oesophageal reflux disease</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three studies (Cavataio et al. 1996; Nielson 2004,2006)</td>
<td>Evaluation of the studies showed that in 200 children, food elimination was used initially to identify possible food allergy and to differentiate between food allergy and primary gastro-oesophageal reflux disease. A cohort of 140 children was differentially diagnosed either cows’ milk allergy or primary gastro-oesophageal reflux disease or both, using a combination of food elimination, food challenge and biopsy.</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

3 Limitations: not all cases of food challenge were carried out blind.  
4 Inconsistencies: there was no consistent definition of non-IgE mediated food allergy diagnosis, causing heterogeneity across study population characteristics.  
5 Indirectness: not all papers compared the same tests with Double Blind Placebo Controlled Food Challenge. Endoscopy was needed to confirm diagnosis in some cases.  
6 Imprecision: not measurable.
Studies | Outcome: utility of food elimination in combination with other diagnostic tools for the differential diagnosis of non-IgE mediated food allergy and gastro-oesophageal reflux disease | Limitations\(^7\) | Inconsistency\(^8\) | Indirectness\(^9\) | Imprecision\(^{10}\) | Other Considerations | Quality
---|---|---|---|---|---|---|---
Three studies (Cavatoio et al. 1996; Nielson 2004,2006) | Serum IgG 24-hour oesophageal pH metric testing, 48-hour testing in combination with food elimination needed for differential diagnosis of non-IgE food allergy. | Y | Y | Y | - | N | Low

\(^{7}\) Limitations: not all cases of food challenge were carried out blind.

\(^{8}\) Inconsistencies: there was no consistent definition of non-IgE mediated food allergy diagnosis, causing heterogeneity across study population characteristics.

\(^{9}\) Indirectness: not all papers compared the same tests with DBCPFC. Endoscopy was needed to confirm diagnosis in some cases

\(^{10}\) Imprecision: Not measurable
2.3.2 Evidence statements

2.3.2.1 Low quality evidence from six studies of 618 children aged between 1 month and 15 years showed that there is ambiguity in the differential diagnosis of IgE, non IgE, and mixed IgE and non-IgE food allergy. The studies used a combination of tests such as specific IgE antibody test, skin prick test, atopy patch test, endoscopy, biopsy, and double-blind placebo-controlled food challenge.

2.3.2.2 Low quality evidence from three studies of 483 children aged up to 15 years showed that a combination of diagnostic tests was needed to diagnose various forms of non-IgE mediated food allergy. These tests included biopsy, atopy patch test, 24-hour oesophageal pH monitoring and double-blind placebo-controlled food challenge. The confirmatory tests, such as endoscopy, biopsy (in the case of Eosinophil Esophagitis EE), and food challenge, were undertaken in secondary and or specialist care.

2.3.2.3 Low quality evidence from four studies of 161 children in secondary or specialist care showed that the atopy patch test was a useful diagnostic tool in the diagnosis of non IgE mediated food allergy to foods such as cow’s milk, wheat, soy, oats, rice, and hen’s egg in children aged between 2 months to 178 months. Sensitivity ranged from 44% to 100% with associated specificities ranging from 71% to 100%.

2.3.2.4 Low quality evidence from nine studies of 712 children aged up to 15 years showed that food elimination and reintroduction was a useful diagnostic tool for non IgE mediated food allergy.

2.3.2.5 Low quality evidence from three studies of 200 children aged up to 15 years showed that food elimination and re challenge in combination with other tests was useful in differentiating between food allergy and primary gastro-oesophageal reflux disease.
2.3.3 Health economic modelling

Approach
The GDG concluded on the basis of the data that the preferred clinical pathway for children and young people with a suspected non-IgE mediated food allergy would be a full allergy-focused clinical history followed by a food elimination diet.

Food elimination in this situation represents not only a diagnostic tool for food allergy but also its treatment. If a person’s symptoms do not improve then they should be referred to secondary or specialist care. If their symptoms do improve then the allergy is diagnosed and the treatment can be continued. Therefore, the economic question is not immediately apparent.

This guideline is restricted to the diagnosis of food allergy in children and young people, so it is not possible to evaluate how food elimination is used to manage food allergy. This also means that reintroducing the food at a later date cannot be evaluated.

In conclusion, there does not appear to be any economic question to answer, as there is no opportunity cost involved. Work has been done by Sladkevicius et al. 2010 to examine the resource use of diagnosing and managing cows’ milk allergy (the majority of which is non-IgE mediated) in the UK. This paper will be used to see where potential efficiencies could be made in the diagnosis of non-IgE mediated food allergy.

Sladkevicius et al.2010
Sladkevicius et al.2010 used data from the Health Improvement Network database, which has data from 300 GP practices and 5 million people. The study selected at random 1000 babies (aged under 1 year) with newly diagnosed cows’ milk allergy and followed them for 12 months after their initial presentation. Data recorded included age, sex, diagnosis, other symptoms and morbidities and duration of symptoms. Several resource uses were recorded; these included appointments with specialists and GP visits.

A health economic model was devised which depicted the management of these babies. This model was based on a previous model (Guest and Nagy et Food Allergy in Children NICE guideline DRAFT (August 2010) Page 32 of 83
al. 2009). Several pathways were modelled which accounted for co-
morbidities and symptoms. All resource costs were from 2006/07 using the
PSSRU and NHS reference costs.

Results
This paper indicated that the key issues are the high number of GP visits (on
average 18.2 visits per baby) and, in particular, the high number of GP visits
before starting a food elimination diet (4.2 visits) and the time taken to identify
an appropriate milk formula (2.9 months). On average, it was 3.6 months until
diagnosis, indicating that current practice is to use the food elimination diet as
a diagnostic tool. The key to reducing healthcare resource use is faster
diagnosis and starting the appropriate formula.

Review
A full review is included in appendix 3. This review indicates that the paper is
of good quality and is applicable to the question. The GDG expressed
concerns about the GP-centric focus and the possibility that community
nurses and other services may have been excluded. This was echoed by
examination of the model used in previous analyses, in which all pathways
focused on the GP (or equivalent). No model structure was produced in the
2010 paper, which makes it difficult to identify whether the paper includes
NHS-specific pathways. However, as it is based on GP data and uses NHS
costs it should be applicable. The paper is appropriate to generalise the
diagnosis of non-IgE mediated food allergy.

Recommendations made in this guideline on involving a dietitian in diagnosis
should reduce the time to diagnosis and appropriate milk formula chosen. This
should lead to an economic saving for the NHS brought about by reduced GP
visits

2.3.4 Evidence to recommendations
Although the evidence showed that the atopy patch test may be useful in the
diagnosis of non-IgE mediated food allergy, it was recognised that there was
wide variation in the sensitivities and specificities of this test. The GDG
discussed the methodology and interpretation of the atopy patch test and felt it
was less well-standardised and more variable than other tests. The group also felt that the results may not be directly applicable to a diverse primary care population as the papers reviewed were all conducted in secondary or specialist settings where the test may have performed better. As a result the GDG concluded that the test was of little value in diagnosing non-IgE mediated food allergy in primary care settings.

The GDG discussed the limited evidence on the utility of the tests and, while there was no evidence showing the value of taking a clinical history, there was consensus that taking a history would minimise the chance of misdiagnosis – especially in situations where the food elimination had resolved symptoms.

Although the evidence evaluating food elimination was of low quality, the GDG felt that a well-managed and supervised food elimination diet in combination with a correctly carried out allergy-focused clinical history was a sensible way to diagnose non-IgE mediated food allergy in primary care. The GDG discussed the duration of food elimination diets and the competencies needed by healthcare professionals to do them. There was also discussion about whether food elimination included food reintroduction. Evidence was very poor in addressing food elimination for various age groups, but the GDG felt that the principle of food elimination would be applicable to all age groups. The GDG also recognised the potential risks of an immediate allergic reaction on reintroduction following a period of elimination in children who have presented with an apparently non-IgE mediated food allergy (particularly eczema). GDG consensus suggests this is a rare occurrence, and is generally limited to cows’ milk and hens’ egg allergies. It did not justify a recommendation to perform diagnostic tests on all children before reintroduction in suspected non-IgE mediated food allergy.
2.3.5 Recommendations

<table>
<thead>
<tr>
<th>Recommendation 1.2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on the results of the allergy-focused clinical history, if non-IgE mediated food allergy is suspected, trial elimination of the suspected allergen (normally for between 2–6 weeks) and reintroduce after the trial. Seek advice from a dietician if appropriate.</td>
</tr>
</tbody>
</table>
2.4 Diagnosis of IgE-mediated food allergy

2.4.1 Evidence review

What diagnostic tools and strategy are most appropriate to diagnose IgE mediated food allergy in children and young people in primary care?

Twenty-three studies were included for critical appraisal for this question.


Five studies (Hill et al. 2004; Vierrucci et al. 1989; Sampson et al. 1998; Eigenmann & Sampson 1998; Rance 2002) and three studies (Vierrucci et al. 1989; Sampson et al 1998; Rance 2002) assessed the value of the skin prick test and specific IgE antibody test in the diagnosis of peanut allergy respectively.
### GRADE profile 5: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE mediated hens' egg allergy

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 Limitations: studies had verification problems. There were problems with how many food challenges were done for each child. In certain cases, challenges were not done for all children. It also appeared that some of the studies did more tests than challenges (for example, one study carried out more skin prick tests for a particular food than they did food challenges). In studies which did tests for multiple foods, challenges were not done for all foods.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Inconsistency: studies did not explicitly group the children by age group.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Imprecision: even though summary statistics were not calculated, the individual measures show that the sensitivities, specificities, positive and negative predictive values were wide for each test and each food.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Other considerations: some studies based their reported outcomes on various thresholds, the validation of which had not been determined.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Studies

<table>
<thead>
<tr>
<th>Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated hens' egg allergy</th>
<th>Age range</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of 18 individual studies for hens' egg allergy</td>
<td>0–17.9 years</td>
<td>SPT Y Y N Y Y Low</td>
</tr>
</tbody>
</table>

#### Sensitivity, specificity and predictive values for skin prick test, specific IgE antibody test and atopy patch test for diagnosis of IgE-mediated hens' egg allergy

| Sensitivities ranged from 57.8% to 100% Specificities ranged from 20% to 99% Positive predictive values ranged from 40% to 93%. Negative predictive values ranged from 50% to 100% | 0–17.9 years | SPT Y Y N Y Y Low |

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sensitivities</th>
<th>Specificities</th>
<th>Positive Predictive Values</th>
<th>Negative Predictive Values</th>
<th>Age Range</th>
<th>Test Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 studies (Vierrucci et al. 1989, Sampson et al. 1998, Roehr et al. 2001, Celik-Bilgili et al. 2005, Dieguez et al. 2009, Mehl et al. 2006, Ando et al. 2008, Caffarelli et al. 1995, Knight et al. 2006, Canani et al. 2007, Osterballe et al. 2004)</td>
<td>Sensitivities ranged from 31.5% to 100% Specificities ranged from 20% to 89% Positive predictive values ranged from 40% to 84%. Negative predictive values ranged from 50% to 100%</td>
<td>0-17.9 years</td>
<td>IgE</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>6 studies (Niggemann et al. 2002, Roehr et al. 2001, Mehl et al. 2006, Hansen et al. 2004, Canani et al. 2007, Osterballe et al. 2004)</td>
<td>Sensitivities ranged from 5.26% to 84.2% Specificities ranged from 87% to 100% Positive predictive values ranged from 75% to 100%. Negative predictive values ranged from 43% to 90%</td>
<td>2 months-14 years</td>
<td>APT</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>
GRADE profile 6: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE mediated cows' milk allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated cows’ milk allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evaluation of 15 individual studies for cows’ milk allergy</td>
</tr>
<tr>
<td></td>
<td><strong>Age range</strong></td>
</tr>
</tbody>
</table>

15 Limitations: studies had verification problems. There were problems with how many food challenges were done for each child. In certain cases, challenges were not done for all children. It also appeared that some of the studies did more tests than challenges (for example, one study carried out more skin prick tests for a particular food than they did food challenges). In studies which did tests for multiple foods, challenges were not done for all foods.

16 Inconsistency: studies did not explicitly group the children by age group

17 Imprecision: Even though summary statistics were not calculated, the individual measures show that the sensitivities, specificities, positive and negative predictive values were wide for each test and each food.

18 Other considerations: Some studies based their reported outcomes on various thresholds, the validation of which had not been determined.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Sensitivities ranged from</th>
<th>Specificities ranged from</th>
<th>Positive predictive values ranged from</th>
<th>Negative predictive values ranged from</th>
<th>Age</th>
<th>IgE</th>
<th>Y</th>
<th>Y</th>
<th>N</th>
<th>Y</th>
<th>Y</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 studies (Vierrucci et al. 1989, Sampson et al. 1998, Roehr et al. 2001, Celik-Bilgili et al. 2005, Mehl et al. 2006, Osterballe et al. 2004, Garcia-Ara et al. 2001, Canani et al. 2007)</td>
<td>22.5% to 100%</td>
<td>30% to 98%</td>
<td>57% to 71%</td>
<td>50% to 100%</td>
<td>0–17.9 years</td>
<td>IgE</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Low</td>
</tr>
<tr>
<td>7 studies (Niggemann et al. 2002, Roehr et al. 2001, Mehl et al. 2006, Cudowska et al. 2005, Osterballe et al. 2004, De Boissieu et al. 2003, Canani et al. 2007)</td>
<td>0% to 80%</td>
<td>70% to 100%</td>
<td>0% to 100%</td>
<td>11% to 73%</td>
<td>2 months–14 years</td>
<td>APT</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Low</td>
</tr>
</tbody>
</table>
### GRADE profile 7: The diagnostic utility of skin prick test and specific IgE antibody test in diagnosing IgE mediated peanut allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: Diagnostic utility of Skin Prick Test (SPT) and specific IgE test in diagnosing IgE mediated peanut allergy</th>
<th>Age range</th>
<th>Diagnostic test</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 studies; Vierrucci et al.1989, Hill et al.2004, Sampson et al.1998, Eigenmann &amp; Sampson 1998, Rance et al.2002,</td>
<td>Sensitivities ranged from 80% to 100% Specificities ranged from 29% to 72% Positive predictive values ranged from 55% to 94%. Negative predictive values ranged from 50% to 100%</td>
<td>0-17.9 years</td>
<td>SPT</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Low</td>
</tr>
<tr>
<td>3 studies; Vierrucci et al.1989, Sampson et al.1998, Rance et al.2002,</td>
<td>Sensitivities ranged from 25% to 97% Specificities ranged from 38% to 100% Positive predictive values ranged from 33% to 78%. Negative predictive values ranged from 25% to 95%</td>
<td>0-17.9 years</td>
<td>IgE</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Low</td>
</tr>
</tbody>
</table>

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19 Limitations: studies had verification problems. There were problems with how many food challenges were done for each child. In certain cases, challenges were not done for all children. It also appeared that some of the studies did more tests than challenges (for example, one study carried out more skin prick tests for a particular food than they did food challenges). In studies which did tests for multiple foods, challenges were not done for all foods.

20 Inconsistency: studies did not explicitly group the children by age group.

21 Imprecision: Even though summary statistics were not calculated, the individual measures show that the sensitivities, specificities, positive and negative predictive values were wide for each test and each food.

22 Other considerations: Some studies based their reported outcomes on various thresholds, the validation of which had not been determined.
GRADE profile 8: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE mediated wheat allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated wheat allergy</th>
<th>Age range</th>
<th>Diagnostic test</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of 8 individual studies for wheat allergy</td>
<td>Sensitivity, specificity and predictive values for skin prick test, specific IgE antibody test and atopy patch test for diagnosis of IgE-mediated wheat allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Specificities ranged from 51% to 100%
Positive predictive values ranged from 35% to 68%. Negative predictive values ranged from 60% to 94% | 2 months–17.9 years | SPT | Y | Y | N | Y | Y | Low |
| 4 studies; Sampson et al.1998, Roehr et al.2001, Celik-Bilgili et al.2005, Mehl et al.2006; | Sensitivities ranged from 67% to 96%
Specificities ranged from 20% to 47%
Positive predictive values ranged from 14% to 57%. Negative predictive values ranged from 57% to 97% | 1 month–17.9 years | IgE | Y | Y | N | Y | Y | Low |
| 4 studies (Niggemann et al.2002, Roehr et al.2001, Mehl et al.2006, Jarvinen et al.2003) | Sensitivities ranged from 0% to 100%  
Specificities ranged from 89% to 100%  
Positive predictive values ranged from 0% to 94%. Negative predictive values ranged from 69% to 100% | 2 months–14 years | APT | Y | Y | N | Y | Y | Low |

23 Limitations: studies had verification problems. There were problems with how many food challenges were done for each child. In certain cases, challenges were not done for all children. It also appeared that some of the studies did more tests than challenges (for example, one study carried out more skin prick tests for a particular food than they did food challenges). In studies which did tests for multiple foods, challenges were not done for all foods.

24 Inconsistency: studies did not explicitly group the children by age group.

25 Imprecision: Even though summary statistics were not calculated the individual measures show that the sensitivities, specificities, positive and negative predictive values were wide for each test and each food.

26 Other considerations: Some studies based their reported outcomes on various thresholds, the validation of which had not been determined.
### GRADE profile 9: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE mediated soy allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated soy allergy</th>
<th>Age range</th>
<th>Diagnostic test</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 studies; Niggemann et al.2002, Sampson et al.1998, Eigenmann &amp; Sampson 1998, Roehr et al.2001, Verstege et al.2005, Mehl et al.2006,</td>
<td>Sensitivities ranged from 21% to 76% Specificities ranged from 47% to 100% Positive predictive values ranged from 29% to 100%. Negative predictive values ranged from 58% to 90%</td>
<td>2 months–17.9 years</td>
<td>SPT</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Low</td>
</tr>
<tr>
<td>4 studies; Sampson et al.1998, Roehr et al.2001, Celik-Bilgili et al.2005, Mehl et al.2006,</td>
<td>Sensitivities ranged from 65% to 94% Specificities ranged from 25% to 52% Positive predictive values ranged from 21% to 23%. Negative predictive values ranged from 86% to 95%</td>
<td>1 month–17.9 years</td>
<td>IgE</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Low</td>
</tr>
</tbody>
</table>

27 Limitations: studies had verification problems. There were problems with how many food challenges were done for each child. In certain cases, challenges were not done for all children. It also appeared that some of the studies did more tests than challenges (for example, one study carried out more skin prick tests for a particular food than they did food challenges). In studies which did tests for multiple foods, challenges were not done for all foods

28 Inconsistency: studies did not explicitly group the children by age group

29 Imprecision: Even though summary statistics were not calculated the individual measures show that the sensitivities, specificities, positive and negative predictive values were wide for each test and each food.

30 Other considerations: Some studies based their reported outcomes on various thresholds, the validation of which had not been determined.
| 3 studies; Niggemann et al.2002, Roehr et al.2001, Mehl et al.2006, | Sensitivities ranged from 0% to 100% Specificities ranged from 86% to 100% Positive predictive values ranged from 0% to 100%. Negative predictive values ranged from 82% to 100% | 2 months-14 years | APT | Y | Y | N | Y | Y | Low |
GRADE profile 10: The diagnostic utility of skin prick test and specific IgE antibody test in diagnosing IgE mediated allergy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Outcome: diagnostic utility of skin prick test and specific IgE antibody test in diagnosing IgE-mediated allergy</th>
<th>Food tested</th>
<th>Age range</th>
<th>Diagnostic test</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study (Vierrucci et al. 1989)</td>
<td>Sensitivity 100%, Specificity 66% Positive predictive value 40% Negative predictive value 100%</td>
<td>Tomato</td>
<td>0–5 years</td>
<td>SPT</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Sensitivity 14%, Specificity 50% Positive predictive value 33% Negative predictive value 25%</td>
<td>Tomato</td>
<td>0–5 years</td>
<td>IgE</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>Low</td>
</tr>
</tbody>
</table>

31 Limitations: studies had verification problems. There were problems with how many food challenges were done for each child. In certain cases, challenges were not done for all children. It also appeared that some of the studies did more tests than challenges (for example, one study carried out more skin prick tests for a particular food than they did food challenges). In studies which did tests for multiple foods, challenges were not done for all foods.

32 Inconsistency: studies did not explicitly group the children by age group.

33 Imprecision: Even though summary statistics were not calculated the individual measures show that the sensitivities, specificities, positive and negative predictive values were wide for each test and each food.

34 Other considerations: Some studies based their reported outcomes on various thresholds, the validation of which had not been determined.
1 study (Sampson et al. 1998)

<table>
<thead>
<tr>
<th>Sensitivity 90%, Specificity 57%</th>
<th>Fish</th>
<th>0.6–17.9 years</th>
<th>SPT</th>
<th>Y</th>
<th>Y</th>
<th>N</th>
<th>-</th>
<th>Y</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive value 77%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative predictive value 80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 study (Sampson et al. 1998)

<table>
<thead>
<tr>
<th>Sensitivity 94%, Specificity 65%</th>
<th>Fish</th>
<th>0.6–17.9 years</th>
<th>SPT</th>
<th>Y</th>
<th>Y</th>
<th>N</th>
<th>-</th>
<th>Y</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive value 49%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative predictive value 97%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 study (Fiocchi et al. 2002)

<table>
<thead>
<tr>
<th>Sensitivities ranged from 90% to 100%</th>
<th>Beef</th>
<th>1–4.41 years</th>
<th>SPT</th>
<th>Y</th>
<th>Y</th>
<th>N</th>
<th>-</th>
<th>Y</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificities ranged from 78% to 100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive predictive values ranged from 87% to 100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative predictive values ranged from 88% to 100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.4.2 Evidence statements

2.4.2.1 Low quality evidence from 18 quality studies of 3165 children showed that the sensitivities of the three tests for *hens’ egg allergy* in children under 18 years ranged from 58% to 100%, 32% to 100% and 5% to 84% for skin patch test, specific IgE antibody test and atopy patch test respectively. The corresponding specificity ranges were 20% to 99%, 20% to 89% and 87% to 100%.

2.4.2.2 Low quality evidence from 15 studies of 3031 children showed that the sensitivities of the three tests for *cows’ milk allergy* in children under 18 years ranged from 28% to 96%, 23% to 100% and 0% to 80% for skin patch test, specific IgE antibody test and atopy patch test respectively. The corresponding specificity ranges were 46% to 100%, 30% to 98% and 70% to 100%.

2.4.2.3 Low-quality evidence from five studies of 1392 children showed that the sensitivities of the two tests for *peanut allergy* in children under 18 years ranged from 80% to 100% and 25% to 97% for skin patch test and specific IgE antibody test respectively. The corresponding specificity ranges were 29% to 72% and 38% to 100%.

2.4.2.4 Low-quality evidence from eight studies of 1991 children showed that the sensitivities of the three tests for *wheat allergy* in children aged between 1 month and 18 years ranged from 23% to 90%, 67% to 96% and 0% to 100% for skin patch test, specific IgE antibody test and atopy patch test respectively. The corresponding specificity values were 51% to 100%, 20% to 47% and 89% to 100%.

2.4.2.5 Low-quality evidence from seven studies of 1901 children showed that the sensitivities of the three tests for *soy allergy* in children aged between 1 month and 18 years ranged from 21% to 76%,
65% to 94% and 0 to 100% for skin patch test, specific IgE antibody test and atopy patch test respectively. The corresponding specificity values were 47% to 100%, 25% to 52% and 86% to 100%.

2.4.2.6 Low-quality evidence from three studies of 346 children showed that the sensitivities of the two tests for tomato, fish and beef allergies in children under 18 years ranged from 90% to 100%, and 14 to 94% in skin patch test and specific IgE antibody test respectively. The corresponding specificity values were 57% to 100%, and 50% to 65%.

2.4.3 Health economic modelling

The decision problem for the health economic analysis was to consider the cost effectiveness of skin prick and specific IgE antibody tests for diagnosing food allergy in children and young people. The atopy patch test and other tests were excluded on clinical grounds. It was also considered impractical for all children and young people to be referred to secondary or specialist care, so this option was not considered. The population examined was those suspected of having an allergy after the clinical history was taken. Only peanut allergies were considered as it was suggested that more information was available on this allergy, especially on long-term outcomes. The GDG agreed that it would be possible to extrapolate the results derived from peanut allergies to other food allergies.

No suitable cost-effectiveness papers were identified from the literature search, so a new economic analysis was constructed. A decision tree model was developed to model the short-term outcomes of testing, and a Markov model was used for long-term outcomes.

The clinical data on sensitivity and specificity for the two chosen tests were obtained from Rance et al. 2002. This study was chosen because its population most closely matched that of the decision problem and it was associated with the highest score in the Youden Index.
The information on the natural history of the condition was based on a long-term prospective study (Ewan et al. 1996) of children with peanut allergies. This accounts for the desensitisation from allergies. Various sources were used for the percentage of people having major, minor and fatal allergic reactions. Age-related mortality was not included, given the age group. For more details see appendix 3.

Given the generally low quality of the evidence and the lack of full reviews to support the inputs into this analysis, the results should be considered exploratory.

The model was run with a relatively short time horizon of 4 years. This was chosen to match the time horizon of Ewan et al. 1996. It was considered that longer time horizons would be associated with greater uncertainty. Longer time horizons were considered in sensitivity analysis. In addition, full one-to-one and probabilistic sensitivity analysis was carried out and scenario analyses included epinephrine-pens prescription, retesting, inclusion of parents’ or carers’ quality of life and the accuracy of the GP history taking. Value-of-information analysis was also carried out to identify whether further research was valuable, and expected value of perfect parameter information (EVPPI) analysis was conducted to identify which variables should be prioritised for research.

The deterministic and probabilistic base-case results are presented in table 2.

Table 2: deterministic and probabilistic base case results

<table>
<thead>
<tr>
<th></th>
<th>Quality-adjusted life year (QALY)</th>
<th>Cost (£)</th>
<th>Incremental QALYs</th>
<th>Incremental costs (£)</th>
<th>Incremental cost-effectiveness ratio (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deterministic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP only</td>
<td>3.38</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Specific IgE antibody test</td>
<td>3.50</td>
<td>365</td>
<td>0.12</td>
<td>320</td>
<td>2,685</td>
</tr>
<tr>
<td>Skin prick test</td>
<td>3.51</td>
<td>286</td>
<td>0.13</td>
<td>241</td>
<td>1,909</td>
</tr>
<tr>
<td><strong>Probabilistic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP only</td>
<td>3.36</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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The difference between the probabilistic costs and deterministic costs is due to the number of uniform distributions applied to the cost inputs.

The probabilities of these tests being cost effective are presented in table 3 and of being the optimum choice in table 4.

**Table 3: Cost-effectiveness acceptability curves results**

<table>
<thead>
<tr>
<th>Threshold</th>
<th>IgE antibody test</th>
<th>Skin prick test</th>
</tr>
</thead>
<tbody>
<tr>
<td>£20,000 per QALY</td>
<td>83%</td>
<td>88%</td>
</tr>
<tr>
<td>£30,000 per QALY</td>
<td>88%</td>
<td>92%</td>
</tr>
</tbody>
</table>

**Table 4: Cost-effectiveness acceptability frontier results**

<table>
<thead>
<tr>
<th>Threshold</th>
<th>GP alone</th>
<th>IgE antibody test</th>
<th>Skin prick test</th>
</tr>
</thead>
<tbody>
<tr>
<td>£20,000 per QALY</td>
<td>12%</td>
<td>39%</td>
<td>49%</td>
</tr>
<tr>
<td>£30,000 per QALY</td>
<td>8%</td>
<td>42%</td>
<td>50%</td>
</tr>
</tbody>
</table>

These results indicate that the tests are likely to be cost effective. The cost-effectiveness acceptability frontiers indicate that the skin prick test is the optimum choice; however, this is not significant. In addition, since potential wastage was not explicitly considered, the choice between the tests will depend on the numbers being tested.

Sensitivity analysis indicated that issues around re-testing and management of allergies are unlikely to cause the cost effectiveness estimates to increase beyond the usual cost-effectiveness thresholds. In addition, if parents’ or carers’ quality of life was included, the cost-effectiveness estimates improved significantly.

Value-of-information analysis carried out on a £20,000 per QALY threshold (and assuming 1.8% of children of school age have an allergy) indicated that research was very valuable in this area, with uncertainty in the model worth
£34,697,442 to resolve. Expected value of perfect information analysis indicated that the quality of life of children with allergies, and the specificity of the tests, are priorities for research. For full results and details of analysis see appendix 3.

### 2.4.4 Evidence to recommendations

The GDG considered the evidence presented and agreed that it was of low quality and that overall the tests had a wide range of specificities and sensitivities. Although the evidence showed that the atopy patch test may be useful in the diagnosis of IgE-mediated food allergy, the GDG discussed the methodology and interpretation of the atopy patch test and felt it was less well-standardised and more variable than other tests. The mechanism of action of the test was also discussed, and the GDG viewed the atopy patch test as inappropriate for the diagnosis of IgE mediated food allergy.

The GDG noted the health economic evidence that indicated that the IgE blood and skin prick test were cost effective compared to no test, but that the skin prick test was cheaper per test. However, it noted that the relative cost effectiveness of the two tests depends on the number of people being tested every year. This was because that the resources required to conduct skin prick testing are brought in bulk and therefore to prevent wastage sufficient numbers are required to be tested. Therefore, it was not possible to definitively conclude that one test was more cost effective than the other as it depended on the numbers tested each year.

The GDG raised concerns about the competencies that healthcare professionals needed to perform and read the results of the allergy tests. The safety of conducting the tests in the community was also highlighted as there is a risk of anaphylactic reaction with skin prick tests. The GDG held the view that the tests could be carried out in community settings where the facilities are similar to those available for routine childhood vaccinations. Healthcare professionals undertaking such tests should be competent and aware of the potential risks of such tests. It was emphasised by the GDG that allergy tests should not be carried out without taking an allergy-focused clinical history. The value of a positive of negative test in the context of a previously taken history
was also discussed. The GDG believed that the tests would be useful in confirming allergy status only if a proper history had been performed. The importance of communicating to children and young people with a suspected food allergy, and their parents and carers, the accurate interpretation of a test result in the context of the allergy focused clinical history and further action was also discussed.
2.4.5  Recommendations

Recommendation 1.2.6
Based on the results of the allergy-focused clinical history, if IgE-mediated allergy is suspected, offer the child or young person a skin prick test or blood tests for specific IgE antibodies.

Recommendation 1.2.7
Skin prick tests should only be undertaken by healthcare professionals with the appropriate competencies and where there are facilities to deal with an anaphylactic reaction.

Recommendation 1.2.8
Choose between a skin prick test or a specific IgE antibody blood test based on:

- the results of the allergy-focused clinical history and
- whether the test is suitable for and acceptable to the child or young person (or their family or carer),
- which tests are available locally

Recommendation 1.2.9
Do not rely solely on allergy tests. Interpret the results of allergy tests in the context of information from the allergy focused clinical history.

Recommendation 1.2.10
Do not carry out allergy testing without first taking an allergy-focused clinical history.

Recommendation 1.2.11
Do not use atopy patch testing or oral food challenges to diagnose IgE-mediated allergy in primary care or community settings.
2.5 Providing information and support

What information and support should be offered to children and young people with suspected food allergy and their parents or carers during the diagnostic process?

2.5.1 Evidence review

The review considered the information and support needed by children and young people with suspected food allergy, and their parents or carers, during the diagnostic process. This did not include assessing the knowledge or educational needs of healthcare professionals. The search strategy was designed to identify studies that focused specifically on the needs of the child or young person. In total, 976 papers were identified, of which 88 were considered for inclusion. Studies with children who had previously been diagnosed with food allergy were excluded unless the study was related specifically to the initial diagnosis. Studies that were validating questionnaires or surveys were also excluded (see appendix 2 for full excluded list). Seven papers were included: these consisted of one randomised controlled trial, five qualitative papers and one observational study (see appendix 1 for the detailed evidence table).

The evidence was synthesised and presented as two evidence summaries. The first summary showed the studies that provided particular information or advice and the stage at which this was provided. The stages of the diagnostic process were:

- the first consultation (1)
- during the diagnostic process (2)
- after diagnosis or referral (3).

As the studies were not explicit about the stage in the diagnostic process, this was assumed based on whether the children had suspected or diagnosed food allergy, had received diagnostic testing during the study and whether they were already on an elimination diet or were started on one during the study. The second evidence review related specifically to qualitative
components and showed specific information or advice that parents or carers of children and young people with suspected food allergy considered important.
### Table 5: Evidence summary of information needs

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Dietary advice</th>
<th>Food label advice</th>
<th>Education by community pharmacist</th>
<th>Findings</th>
<th>Details of advice</th>
<th>Stage in diagnostic process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lever 1998 (Ref ID: 893)</td>
<td>Children with atopic eczema with suspected hens' egg allergy</td>
<td>√</td>
<td>√</td>
<td></td>
<td>Diet advice on elimination diets and food labelling advice was effective in improving eczema</td>
<td>The dietitian advised children to exclude all foods containing egg. Children and their parents were given a list of foods known to contain egg, and egg-free foods. Food label advice was given.</td>
<td>2</td>
</tr>
<tr>
<td>Mikkelsen 2005 (Ref ID: 290)</td>
<td>Children with diagnosed or suspected cows' milk allergy</td>
<td>√</td>
<td>√</td>
<td></td>
<td>Most parents were satisfied with information received during the 'milk allergy school'</td>
<td>At group sessions, the dietitian provided information, answered questions and corrected misconceptions. This included label reading from packages in a typical household. Children were given written instructions on how to follow a milk-free diet and booklets of recipes.</td>
<td>2 and/or 3</td>
</tr>
<tr>
<td>Barnett 2005 (Ref ID:265)</td>
<td>Members of FANN recall about initial diagnosis of food allergy and use of epi-pen</td>
<td></td>
<td>√</td>
<td></td>
<td>The overall attitude to education was between neutral and favourable</td>
<td>Recall of advice from a community pharmacist. The study examined information and training provided from six possible categories: general food allergy information, signs of allergic reaction, training in epi-pen use, avoidance of specific foods, drug information about epinephrine, and day-to-day management of food allergy.</td>
<td>3</td>
</tr>
<tr>
<td>Arvola 2000 (Ref ID: 678)</td>
<td>Breastfed babies with atopic eczema and suspected food allergy</td>
<td>√</td>
<td></td>
<td></td>
<td>Majority of parents reported alleviation in children's symptoms and satisfaction with advice</td>
<td>Individual dietary advice was given by a dietitian, advice on skin treatment by a dermatologist when skin prick tests were performed, and practical advice on elimination diets from a paediatric nurse.</td>
<td>1 and/or 2</td>
</tr>
<tr>
<td>Weber 2007 (Ref ID: 144)</td>
<td>Children on cows' milk exclusion diet</td>
<td></td>
<td>√</td>
<td></td>
<td>Although not all parents had previously received advice, the study group generally performed better in correctly identifying milk-containing products</td>
<td>All of the study group were instructed to exclude milk-containing food products; 80% received product label reading instructions; and 38% received previous instructions on words associated with cows' milk from physician and/or nutritionist.</td>
<td>2 and/or 3</td>
</tr>
</tbody>
</table>

35 1=at first consultation, 2=during the diagnostic process, 3=Following diagnosis/ referral
Table 6: Evidence summary for information needs

<table>
<thead>
<tr>
<th>Information need</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hu et al.2007</td>
</tr>
<tr>
<td><strong>Information content</strong></td>
<td></td>
</tr>
<tr>
<td>Practical dietary advice</td>
<td>✓</td>
</tr>
<tr>
<td>Advice on diagnostic techniques and interpretation</td>
<td>✓</td>
</tr>
<tr>
<td>Recognition and management of reactions</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Information sources or types</strong></td>
<td></td>
</tr>
<tr>
<td>Written take-home information</td>
<td>✓</td>
</tr>
<tr>
<td>Videos (for educating child, extended family and other carers)</td>
<td>✓</td>
</tr>
<tr>
<td>Nurse-led education sessions</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Referral to other parents</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Physician’s role</strong></td>
<td></td>
</tr>
<tr>
<td>Expert knowledge</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Supportive role</td>
<td>✓</td>
</tr>
<tr>
<td>Provide trustworthy, reliable information</td>
<td>✓ ✓</td>
</tr>
<tr>
<td><strong>Amount of information</strong></td>
<td></td>
</tr>
<tr>
<td>More information</td>
<td>✓ (at first visit)</td>
</tr>
</tbody>
</table>

2.5.2 Evidence statements

2.5.2.1 Evidence from one randomised controlled trial and one qualitative study showed that at the initial diagnosis or during the diagnostic process, education about reading and interpreting food labels and/or dietary advice about elimination diets was successful in alleviating children’s symptoms of eczema, and parents were generally satisfied with the advice they received.

2.5.2.2 Evidence from two qualitative studies and one observational study showed that during the diagnostic process or following diagnosis, education about reading and interpreting food labels, dietary advice about elimination diets and/or education by a community pharmacist were generally favoured by parents of children with suspected or diagnosed food allergy.
2.5.2.3 Evidence from two qualitative studies showed that the following were valued by parents of children with suspected food allergy:

- information content (including advice on diet, diagnostic techniques and interpretation, and recognition and management of reactions)
- the type of information received (including written, video, nurse-led sessions and referral to other parents)
- the physician’s role (including their expert knowledge, their supportive role and the provision of reliable information)
- the amount of information received.

2.5.3 Evidence to recommendations

The GDG agreed that the evidence presented was limited and did not fully address the clinical question. The group also decided that applying the evidence would be difficult because some of the studies focused on the impact of information or advice on symptoms. There was only one study which directly compared giving additional specific advice about elimination with general advice. That study included only 55 children. Most of the other evidence was from qualitative studies and the conclusions were not as robust as the one from the randomised controlled trial. As a result many of the recommendations were made on the basis of consensus.

The group agreed that children and young people with suspected food allergy would fit into three main groups based on the outcome of an allergy-focused clinical history: those with a low chance of having an allergy; those with a high chance of having an allergy; and those in whom there is uncertainty. It was agreed that information would only need to be provided for the groups where an allergy was probable or possible. The recommendations were based loosely on the diagnostic stages as set out in the review protocol (see appendix 1), although it was noted that these categories were overlapping.

The GDG agreed that, although some general information would be needed, the healthcare professional should tailor most of the information to the specific needs and background of the child or young person. It was agreed that further
information would be needed during the diagnostic process when exclusion diets and tests were carried out. The group also considered it important to provide information of what to do while children were awaiting results of diagnostic tests and confirmation of food allergy. This was because there may be a delay between a child having tests carried out and receiving the results.

Although evidence related to the safety of vaccination in children with food allergy was not reviewed, anecdotally the GDG felt that this was one of the most common queries from parents of children with suspected food allergy and therefore included this as a recommendation.
### 2.5.4 Recommendations

#### Recommendation 1.2.12
Based on the allergy-focused clinical history, offer the child or young person, or their parent or carer, information that is age appropriate about the:

- type of allergy suspected
- risk of severe allergic reaction
- potential impact of the suspected allergy on other healthcare issues, including vaccination
- diagnostic process, which may include:
  - an exclusion diet and oral food challenge or food reintroduction procedure
  - skin prick and IgE antibody testing, including the safety and limitations of these tests
  - referral to secondary or specialist care.

#### Recommendation 1.2.13
Offer the child or young person, or their parent or carer, information relevant to the suspected underlying mechanism.

#### Recommendation 1.2.14
If a food exclusion diet is advised as part of the diagnostic process (see recommendation 1.2.5), offer the child or young person, or their parent or carer, information 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 exclusion diet
- the proposed duration of the exclusion diet
- when, where and how the oral food challenge would be undertaken
- the safety and limitations of the oral food challenge or food
Recommendation 1.2.15
For babies and young children with suspected cow’s milk allergy, offer:

- food avoidance advice to breastfeeding mothers, or
- information on the most appropriate hypoallergenic formula or milk substitute to mothers of formula-fed babies.

Seek advice from a dietitian if needed.

Recommendation 1.2.16
Offer the child or young person, or their parent or carer, information about the support available and details of how to contact support groups.

2.6 Referral to secondary or specialist care
At which stage in the diagnostic process should and young people with symptoms of IgE, non-IgE or mixed IgE and non-IgE mediated food allergy be referred to secondary or specialist care?

2.6.1 Evidence review
The review considered indications for referring a child with suspected food allergy from primary or community settings to secondary or specialist care. This did not include referrals from secondary or specialist settings, such as dermatology and gastroenterology to specialist allergy clinics. The search strategy was designed to identify studies that focused specifically on referrals to secondary or specialist care. In total, 856 papers were identified, of which 70 were considered for this clinical question. No relevant primary studies were identified and there was no direct evidence explicitly related to referrals from primary or community settings to secondary care (see appendix 2 for a full list of excluded papers). Six papers were included: these consisted of three review articles and three guidelines (see appendix 1 for detailed evidence tables). The evidence was synthesised and presented in the form of evidence summaries showing the papers that supported referral based on specific
identified indications. A graph of this information was also presented, categorising these indications into three main reasons for referral.

### Table 7: Indications for referral to secondary or specialist care

<table>
<thead>
<tr>
<th>Indication for referral</th>
<th>Study</th>
</tr>
</thead>
</table>
| Gastrointestinal symptoms and other related conditions (specify) | Allen et al.2009 (Ref ID: 452)  
|                                                               | Robinson & Smart 2008 (Ref ID:1034)  
|                                                               | Allen 2007 (Ref ID: 1037)  
|                                                               | Vandenplas et al.2007 (Ref ID: 514)  
|                                                               | Kalia et al.2008  
|                                                               | Leung & Schatz 2006 |
| Asthma and other respiratory symptoms                        | √  
|                                                               | √  
|                                                               | √  |
| Systemic symptoms                                             | √  
|                                                               | √  
|                                                               | √  |
| Atopic dermatitis or eczema, and other related symptoms       | √  
|                                                               | √  
|                                                               | √  
| Dietary restrictions                                          |  
|                                                               | √  
|                                                               | √  |
| Parental suspicion                                            |  
|                                                               | √  

GI, gastrointestinal; FPIES, food protein-induced enterocolitis syndrome; AD, atopic dermatitis
Figure 1: Indications for referral to secondary or specialist care

- **Based on symptoms** – especially when suspected to be linked to specific foods
  - Gastrointestinal symptoms e.g.: failure to thrive, diarrhoea (particularly with blood), vomiting, protein-losing enteropathy and blood in stools

- **Comorbidities** – especially when unresponsive or poorly responsive to treatment and linked to food
  - Asthma when assessing role of environmental allergens
  - Atopic dermatitis/eczema especially with severe or widespread disease

- **Other reason**
  - Dietary reasons, including children with limited diet or where diet may become too limited due to perceived adverse reactions to food
  - Parental suspicion of food allergy especially in babies with difficult or perplexing symptoms

- **Systemic reactions** including IMMEDIATE or URGENT REFERRAL for anaphylactic shock

- **Asthma** when assessing role of environmental allergens

- **Other related symptoms** including:
  - Respiratory symptoms including: acute laryngoedema or bronchial obstruction with difficulty breathing
  - Other related symptoms such as rhinoconjunctivitis

- **Other related conditions** (suspected or diagnosed) including: gastro-oesophageal reflux disease and food protein-induced enterocolitis syndrome
2.6.2 Evidence statements

2.6.2.1 Evidence from four studies showed that gastrointestinal symptoms and other related conditions, such as food protein-induced enterocolitis syndrome) and gastro-oesophageal reflux disease, were indications to refer a child to secondary or specialist care.

2.6.2.2 Evidence from two studies showed that asthma and other respiratory symptoms, such as acute laryngoedema or bronchial obstruction with difficulty breathing, were indications to refer a child to secondary or specialist care.

2.6.2.3 Evidence from two studies showed that systemic reactions such as anaphylaxis were indications to refer a child to secondary or specialist care.

2.6.2.4 Evidence from three studies showed that atopic dermatitis and other related symptoms, such as rhino conjunctivitis, were indications to refer a child to secondary or specialist care.

2.6.2.5 Evidence from two studies showed that dietary restriction was an indication to refer a child to secondary or specialist allergy care.

2.6.2.6 Evidence from one study showed that parental suspicion of food allergy, especially in children with difficult or perplexing symptoms, was an indication to refer a child to secondary or specialist care.

2.6.3 Evidence to recommendations

The GDG agreed that the evidence was of low quality but decided it was important to make a recommendation to guide primary care practitioners as to when to refer a child with suspected food allergy to secondary or specialist care.

The GDG used the evidence presented as a basis for discussion and considered each indication for referral. There was a consensus that having
certain some symptoms or conditions alone would not warrant referral; it was agreed that symptoms in combination with other factors would be necessary before the healthcare practitioner should consider a referral.

The GDG also discussed that children and young people with anaphylaxis would present directly to secondary care and be managed there, so this group would not need to be considered here. They did feel, however, that acute systemic reactions and severe delayed reactions were important indications for referral that had not been highlighted in the evidence. The group also decided that the following indications should lead to referral:

- a positive clinical history with negative allergy tests
- clinical suspicion of multiple food allergies
- failure to respond to a single-allergen exclusion diet.
2.6.4 Recommendations

Recommendation 1.2.17
Consider 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 of the gastrointestinal symptoms described in recommendation 1.2.1
  - not responded to a single-allergen exclusion diet
  - had acute systemic reactions or severe delayed reaction
  - confirmed IgE mediated food allergy and concurrent asthma
  - significant atopic eczema where multiple food allergies are suspected by the parents.

- There is:
  - parental suspicion of food allergy (especially in children or young people with difficult or perplexing symptoms)
  - strong clinical suspicion of IgE mediated food allergy but allergy tests are negative
  - clinical suspicion of multiple food allergies.

2.7 Alternative diagnostic tools

2.7.1 Evidence review

To assess the use of alternative diagnostic tools to diagnose IgE, non IgE and mixed IgE and non IgE food allergy in children and young people in primary care

Twenty-five papers were identified and considered for inclusion. Studies that did not use a food challenge as a reference standard to confirm food allergy were excluded (see appendix 2 for full list of excluded studies). Two papers
were included which assessed the use of the basophil activation test and the leukotriene C4 release test (see appendix 3 for detailed evidence table).

2.7.2 Evidence statements

2.7.2.1 Low-quality evidence from one paper of 21 children aged up to 15 years showed that the sensitivity of the basophil activation test ranged from 48% to 80% and specificity ranged from 94% to 100%.

2.7.2.2 Low-quality evidence from one paper of 21 children aged up to 15 years showed that the sensitivity of the leukotriene C4 release test ranged from 52% to 85% and specificity was 100%.

2.7.2.3 Low-quality evidence from one paper of 22 children aged 3 years old showed that the sensitivity and specificity of the basophil activation test was 71% and 96% respectively for hens’ egg allergy.

2.7.2.4 Low-quality evidence from one paper of 22 children aged 3 years old showed that the sensitivity and specificity of basophil activation test was 67% and 94% respectively for cow’s milk allergy.

2.7.2.5 No evidence on the utilities of vega testing, applied kinesiology, hair analysis or serum specific IgG in primary care was identified.

2.7.3 Evidence to recommendations

The GDG agreed that good-quality evidence for the alternative tests was lacking. Evidence was scarce and of poor quality.

The GDG agreed that serum specific IgG tests were not appropriate for diagnosis and assessment of food allergy.
2.7.4 Recommendations

<table>
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<th>Recommendation 1.2.18</th>
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<tr>
<td>Do not use the following alternative diagnostic tests in the diagnosis of food allergy:</td>
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<td>- vega test</td>
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<td>- applied kinesiology</td>
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<td>- hair analysis</td>
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<th>Recommendation 1.2.19</th>
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<tr>
<td>Do not use serum specific IgG testing in the diagnosis of food allergy.</td>
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3 Research recommendations

We have made the following recommendations for research, based on our review of evidence, to improve NICE guidance and patient care in the future.

The focus of this guideline was the diagnosis and assessment of food allergy in children and young people in primary care and community settings. Therefore, the management of food allergy after a confirmed diagnosis was not reviewed. The research recommendations below focus on assessment and diagnosis.

3.1 Prevalence and natural history of non-IgE mediated food allergy

How common are non-IgE mediated food allergies in children and young people in primary and community settings and when are food allergies outgrown?

Why this is important

Food allergy has many presentations. IgE mediated food allergy manifests itself with a relatively homogenous group of presentations. Coupled with objective tests, measures of prevalence in the relevant settings and later development of tolerance have yielded useful information on the burden of food allergy in children. However, non-IgE mediated food allergies are less well understood.

The objective of this research is to determine the prevalence of non-IgE mediated food allergies in children and young people and to identify the age at which these allergies may be outgrown. This information will help inform the development of guidance on the management of non-IgE mediated food allergies.

Additional research is also needed to investigate the factors that contribute to the development and resolution of non-IgE mediated food allergies. This could include genetic, environmental, and psychological factors. Understanding these factors is important for developing effective interventions to prevent and manage non-IgE mediated food allergies.

3.2 Development of food allergy and tolerance

How do food allergies develop and resolve over time? What factors influence the development and resolution of food allergy?

Why this is important

Understanding the development and resolution of food allergies is crucial for developing effective strategies to prevent and manage these conditions. This research could help identify early warning signs of food allergy and develop targeted interventions to prevent the development of food allergies. It could also inform strategies for managing food allergies in the early stages, such as dietary education and desensitization.

3.3 Identifying foods that cause food allergy

What are the common foods that cause food allergy in children and young people? Are there any foods that are more commonly associated with severe reactions?

Why this is important

Identifying foods that cause food allergy is essential for developing effective strategies to prevent and manage these conditions. This research could help identify high-risk foods and develop targeted interventions to prevent allergic reactions to these foods. It could also inform strategies for managing food allergies in the early stages, such as dietary education and desensitization.

3.4 Development of diagnosis and management guidelines

What are the current guidelines for the diagnosis and management of food allergy? Are there any gaps in the current guidelines that need to be addressed in future versions?

Why this is important

Developing evidence-based guidelines for the diagnosis and management of food allergy is crucial for improving patient care and outcomes. This research could help identify gaps in the current guidelines and develop targeted interventions to address these gaps. It could also inform strategies for improving patient education and support, such as developing patient-friendly resources and education programs.
disease. However, non IgE mediated food allergy has a more heterogeneous group of presentations and the lack of validated diagnostic tests make it very difficult to assess prevalence without formal diagnostic food challenges. Until high-quality prevalence studies in primary and community settings are done, the burden of this disease will remain unknown. Studies should also evaluate prevalence rates and the resolution of allergies in subgroups, such as food groups, or by method of infant feeding (exclusive formula, exclusive breast feeding, or mixed).

3.2 Clinical predictors of non IgE mediated food allergy

Which features in the clinical history best predict for the presence of non IgE mediated food allergy for children and young people in a primary care or community setting?

Why this is important

Non IgE mediated food allergy often presents with non specific problems that are common place in children and often non allergy related such as colic, reflux, diarrhoea, eczema or faltering growth. Failure to recognise food allergy results in unnecessary ongoing morbidity whilst appropriate food exclusion can result in rapid symptom improvement. In the absence of simple diagnostic test, it remains for the history to provide the best diagnostic clues as to which child may benefit from trial of an exclusion diet. A validated, primary care focussed questionnaire, developed by comparison with proven DBPCFC outcomes, would significantly aid the process of diagnosis.

3.3 Information needs for children and young people during their care pathway to diagnosis of food allergy

What do children and young people with IgE mediated food allergy and their families want to know during the process of diagnosis and how is this demand best met?

Why this is important

The patient journey to diagnosis, through testing, can be several months. The needs of patients and the most effective method of information and support provision during this time of uncertainty need to be established.
3.4 Values of SPT and specific IgE and their predictive value

Can skin prick test and specific IgE cut off points be established to diagnose IgE mediated food allergy in children and to predict the severity of reaction?

Why this is important?
It is well described that about 1 in 5 patients reporting an adverse reaction to food, truly suffer from food allergy. Of these, the majority will suffer from non-IgE mediated allergies. Food challenges are cumbersome and time-consuming and there are some safety risks involved. The availability of skin prick test and specific IgE cut-off points to diagnose food allergy and to predict the severity of reaction will therefore lead to huge cost-savings in the NHS and reduce patient risk. There are published data available from the USA, Australia and Europe, but allergists argue that these cut off points are population specific and should not be used in the United Kingdom.

3.5 Modes of provision of support to healthcare professionals

What would be the impact of dietetic telephone support to health professionals to aid in the diagnosis and assessment of infants demonstrating non-IgE mediated food allergy symptoms in primary care and community care?

Why is this important?
There is currently no evidence to assess the impact of early diagnosis of non-IgE mediated food allergy on the quality of life for infants and their families. The standard method of written referral is not timely (within the first month of presentation), yet there is no evidence to demonstrate that provision of indirect advice via a health professional is acceptable to the family. This system however could result in reduced attendances at GP surgeries and health clinics, reduced need for unnecessary medications and treatment, improved health for the whole family and improved skills of the health professionals being supported in the diagnosis. However, it would require increased dietetic support and skills. A community-based randomised controlled trial is required to compare the standard written dietetic referral...
method with indirect advice via a health professional following consultation with a dietitian, for families with infants under 1 year who present with symptoms of non-IgE mediated food allergy. Primary outcomes should be an assessment of the quality of life and acceptability of this service to the family. Secondary outcome measure could be related to attendance at GP surgeries, and medications and other interventions implemented.

4 Other versions of this guideline

This is the full guideline. It contains details of the methods and evidence used to develop the guideline. It is available from our website (www.nice.org.uk/guidance/CG[XX]Guidance). [Note: these details will apply to the published full guideline.]

Quick reference guide


For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). [Note: these details will apply when the guideline is published.]

‘Understanding NICE guidance’

A summary for patients and carers (‘Understanding NICE guidance’) is available from www.nice.org.uk/guidance/CG[XX]PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). [Note: these details will apply when the guideline is published.]
We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about diagnosis and assessment of food allergy in children and young people.

5 Related NICE guidance

Published


6 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

7 References, glossary and abbreviations

7.1 References


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Knight AK, Shreffler WG, Sampson HA et al. (2006) Skin prick test to egg white provides additional diagnostic utility to serum egg white-specific IgE antibody concentration in children. Journal of Allergy and Clinical Immunology 117: 842-7.


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Vierrucci A, Novembre E, de MM et al. (1989) Reliability of tests for specific IgE to food in atopic dermatitis. Allergy: European Journal of Allergy and Clinical Immunology, Supplement 44: 90-6.


### 7.2 Glossary

### 7.3 Abbreviations

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8.2 The short clinical guidelines technical team

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8.5 **The Guideline Review Panel**

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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8.6 Declarations of interest

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).

8.7 Authorship and citation

Authorship of this document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

The guideline should be cited as: