Food Allergy in Children Appendix 1

Appendix 1.0 – Scope

Appendix 1.1 – Review protocol

Appendix 1.2 – Literature search & Search Strategies

Appendix 1.3 – Evidence Tables

- 1.3.1 – Clinical question 1
- 1.3.2 – Clinical question 2
- 1.3.3 – Clinical question 3
- 1.3.4 – JAMA review
- 1.3.5 – Clinical question 4
- 1.3.6 – Clinical question 5
- 1.3.7 – Alternative tests

Appendix 1.0

SCOPE

1 Guideline title

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

1.1 Short title

Food allergy in children and young people

2 The remit

The Department of Health has asked NICE: ‘To produce a short clinical guideline on the diagnosis and assessment of food allergy in children in primary care and community settings.'

3 Clinical need for the guideline

3.1 Epidemiology

a) Food allergy is an adverse immune response to food allergens. It can be classified into IgE-mediated, non-IgE-mediated (including T cell, IgG and eosinophil mediated) and mixed 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 food allergy reactions are generally in the form of food intolerance and are characterised by:

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

These are frequently delayed onset conditions and may need the opinion of a paediatrician or paediatric gastroenterologist.

b) Sensitisation to food and inhalant allergens increases with increasing eczema disease severity, suggesting a role for the skin barrier in initiating allergic disease.

c) 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.

d) 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.

e) In the UK there have been concerns 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.

f) There has also been discrepancy between self -reported food allergy and confirmed correct diagnoses of food allergy. In view of this, there is inconsistency in the reported prevalence of food allergies in children and young people.

g) Only 25–40% of self-reported food allergy is confirmed as true clinical food allergy by an oral food challenge.

h) The following are the most common foods to which children and young people are allergic:

- cows' milk
- hens' eggs
- peanuts
- wheat
- soy
- shellfish
- fish
- sesame
- kiwi fruit
- tree nuts.

Less commonly, there are reported allergies to certain fruits, for instance, banana.

i) Recent evidence suggests that the prevalence of self-reported food allergy differs for individual foods and ranges from 3% to 35%.

j) Correct diagnosis of food allergy, followed by counselling and advice based on reliable criteria, is important because it will help decrease the incidence of adverse food reactions resulting from true food allergies and also help prevent the unnecessary dietary

exclusion of foods which are safe and which should be eaten as part of a normal, healthy diet.

3.2 Current practice

a) In their review of services for allergy (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 allergy 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 within 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 parents and/or carers of children and young people and young people with allergies, also purchase over-the-counter medicines from community pharmacies or high street chains. However, if there is diagnostic doubt or more severe disease the GP may consider referral for a specialist opinion. Depending on the local service provision this may be delivered:

- in an allergy clinic run by an allergist or a paediatric allergist
- in an allergy clinic run by a consultant in another specialty (such as respiratory or immunology)
- within children's services (although many children are seen within adult services).

b) The Department of Health review also suggested, following consensus, that primary care practitioners have limited knowledge or awareness of allergy, are not sufficiently trained in allergy, may overlook multi-system atopy, and lack guidelines for therapy and referral.

c) The Map of Medicine pathway for suspected food allergy shows that on clinical presentation of food allergic symptoms, primary care practitioners should:

- carry out a thorough clinical history, including symptoms, history of episodes, family history of atopy or food allergy, other possible causes, current diet, recent changes in diet and feeding history in young children
- conduct a physical examination to assess factors such as nutritional status and growth patterns, signs of atopy and/or co morbidity
- consider differential diagnoses, such as non-IgE-mediated immune reactions, toxic reactions and asthma
- consider referral to an allergy specialist when, for instance, there is doubt about the diagnosis, a history of anaphylaxis or severe reaction, or the need for several and/or nutritionally important foods to be eliminated.

d) 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.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Children and young people up to their 19th birthday presenting with suspected food allergy and symptoms such as atopic eczema, anaphylaxis, urticaria, rhinitis, conjunctivitis, asthma, gastrointestinal symptoms and oral allergy syndrome on eating certain foods. Children will be separated into age specific sub-groups (0–6 months, 6–12 months, 1–2 years, 2–5 years, 5–10 years and 10–18 years) as appropriate.

b) Children and young people up to their 19th birthday who are at higher risk of developing a food allergy, specifically:

- children with existing atopic diseases such as asthma, atopic eczema and allergic rhinitis
- children with a first degree relative (that is, a parent or sibling) with a food allergy or other atopic disease.

4.1.2 Groups that will not be covered

a) Adults aged 19 years and over.

b) Children and young people with non-immunologically mediated (that is, non-allergic) food intolerance such as an intolerance to lactose.

c) Children and young people with a toxic reaction to food, such as protease inhibitors in legumes.

d) Children and young people with a pharmacological reaction to food, such as tyramine in cheese and pickled herrings.

e) Children and young people with a psychological reaction to food, such as food avoidance.

4.2 Healthcare setting

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.

4.3 Clinical diagnosis

4.3.1 Key clinical issues that will be covered

a) Physical examination and assessment, including clinical history for the diagnosis of food allergy.

b) Use of child or parent diaries of episodes of suspected food allergy, including symptoms and food ingested.

c) Evaluation of the following diagnostic tests either alone or in combination, in the diagnosis and assessment of food allergy:

- food elimination
- skin prick test (fresh foods and commercial extracts will be assessed)
- serum specific IgE
- atopy patch test.
- double-blind placebo-controlled food challenge will be included as the comparator for the above tests

d) Determination of a differential diagnosis for IgE, non-IgE and mixed-IgE-mediated food allergy to specific foods.

e) Referral to secondary care or other services, such as allergists, dieticians, respiratory medicine specialists, ENT, immunologists, general paediatricians, as appropriate.

f) The specific information and support needs of children with suspected food allergy and their parent/carers

g) Evaluation of the following alternative diagnostic tools, either alone or in combination, in the diagnosis of food allergy:

- Vega test
- applied kinesiology
- hair analysis
- leucocytotoxic test
- IgG test.

4.3.2 Clinical issues that will not be covered

a) Diagnosis of food intolerance.

b) Diagnosis of food allergy in adults aged 19 years and over.

c) Diagnosis of food allergy in children and young people in secondary and tertiary care.

d) Prevention and treatment of food allergy in children and young people in primary care and community settings

4.4 Main outcomes

a) Utility of various tools, history taking and physical examination for the correct diagnosis and assessment of IgE, non-IgE or mixed-IgE-mediated food allergy in children and young people.

b) Rates of referral to secondary or specialist care.

c) Adverse events associated with diagnostic tools.

d) Health-related quality of life associated with diagnosis or misdiagnosis of food allergy.

e) Resource use and costs.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative tests. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

4.6 Status

4.6.1 Scope

This is the final version of the scope.

4.6.2 Timing

The development of the guideline recommendations will begin in March 2010.

5 Related NICE guidance

- Coeliac disease. NICE clinical guideline 86 (2009). Available from www.nice.org.uk/guidance/CG86
- Diarrhoea and vomiting in children. NICE clinical guideline 84 (2009). Available from www.nice.org.uk/guidance/CG84
- Atopic eczema in children. NICE clinical guideline 57 (2007). Available from www.nice.org.uk/guidance/CG57
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisal guidance 131 (2007). Available from www.nice.org.uk/guidance/TA131

5.1 Guidance under development in parallel with NICE

- The Royal College of Paediatrics and Child Health is currently developing the following related guidance: Food and Gastrointestinal Allergy Care Pathway. The Royal College of Paediatrics and Child Health. Publication expected December 2010

6 Further information

Information on the guideline development process is provided in:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’
- ‘The guidelines manual’.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix 1.1

Review Protocol

KEY CLINICAL QUESTION 1		
	Details	Comments
REVIEW QUESTION 1	What elements should allergy focused clinical history taking, physical examination and patient/parent food diaries include in order to effectively diagnose and assess food allergy (IgE, non-IgE-mediated or mixed) in children?	
OBJECTIVES	To determine how and when clinical history and physical examinations should be carried out in order to assess food allergy in children effectively. To determine how and when food diaries should be used within the diagnostic process.	
CRITERIA FOR CONSIDERING STUDIES	All studies-no restrictions	
POPULATION	Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups; Those with existing atopic diseases Those with a first degree relative with a food allergy or other atopic disease Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years)	
DIAGNOSTIC TOOL	Key elements of clinical history, physical examination and patient/parent food diary	
COMPARATORS	N/A	
OUTCOMES	Examining the accuracy of documentation in patient/parent food diaries of episodes of suspected	

	food allergy to specific foods at specific times Utility of history taking and physical examination for the correct diagnosis and assessment of food allergy in children Resource use and cost	

KEY CLINICAL QUESTION 2		
	Details	Comments
REVIEW QUESTION 2	Which diagnostic tools and strategy are most appropriate and accurate to diagnose non-IgE-mediated and mixed IgE-mediated food allergy in children?	
OBJECTIVES	To determine whether diagnosis of non-IgE & mixed IgE food allergy can be carried out in primary care To investigate whether there is a clearly focussed and definite diagnosis of non-IgE and mixed IgE food allergy. To determine whether diagnostic tools have differing acceptability within subgroups of the population.	
CRITERIA FOR CONSIDERING STUDIES	All studies (no restrictions)	
POPULATION	Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups; Those with existing atopic diseases Those with a first degree relative with a food allergy or other atopic disease Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years)	

DIAGNOSTIC TOOL	Endoscopic procedures Skin Prick Test (SPT) Serum Specific IgE tests Elimination diet Atopy Patch Test (APT) Vega test/Applied kinesiology/Hair analysis/ Leucocytotoxic test/IgG test Other diagnostic tests	Most endoscopies carried out in local hospital but some may be offered in larger GP clinics. May be performed by GPwSI in Gastroenterology-not sure if this applies to children? Also may be referred to community endoscopy service provider (CESP).
COMPARATORS	Double Blind Placebo Controlled Food Challenge (DBPCFC)	No reference standard as issues of delayed symptoms for non IgE and mixed IgE FA.
OUTCOMES	Utility of various tools for the correct diagnosis and assessment of non-IgE and mixed IgE-mediated food allergy in children Acceptability of diagnostic strategies to age-specific subgroups Adverse events associated with diagnostic tools Health related quality of life associated with diagnostic tools in primary care and community settings Resource use and costs	

KEY CLINICAL QUESTION 3		
	Details	Comments
REVIEW QUESTION 3	Which diagnostic tools and strategy are most appropriate and accurate to diagnose IgE-mediated food allergy in children?	
OBJECTIVES	To determine whether test accuracy varies within subgroups of the population. To determine whether threshold values for diagnostic tests differ within subgroups of the population. To determine whether diagnostic tools have differing acceptability within subgroups of the population.	

CRITERIA FOR CONSIDERING STUDIES	All study designs (no restrictions)	
POPULATION	Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups; Those with existing atopic diseases Those with a first degree relative with a food allergy or other atopic disease Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years)	
DIAGNOSTIC TOOL	Skin Prick Test (SPT) using fresh or commercial extracts Serum Specific IgE tests Elimination diet Atopy Patch Test (APT) Vega test/Applied kinesiology/Hair analysis/ Leucocytotoxic test/IgG test Other diagnostic tests	APT is experimental in diagnosing IgE reactions.
COMPARATORS	Double Blind Placebo Controlled Food Challenge (DBPCFC)	NB: Not appropriate for all age groups and may not be used within primary care (need to consider).
OUTCOMES	Utility of various tools for the correct diagnosis and assessment of IgE-mediated food allergy in children Diagnostic accuracy of diagnostic tools Threshold values of diagnostic tools for the correct diagnosis of IgE-mediated food allergy in children Acceptability of diagnostic strategies to age-specific subgroups Adverse events associated with diagnostic tools Health related quality of life associated with diagnostic tools in primary care and community settings	

	Resource use and costs	
KEY CLINICAL QUESTION 4		
	Details	Comments
REVIEW QUESTION 4	At which stage in the diagnostic process should children with symptoms of IgE, non IgE or mixed mediated food allergy be referred to secondary/specialist care?	
OBJECTIVES	To determine to what extent GP's are equipped to diagnose IgE and non IgE-mediated food allergy. To determine when children with high risk co morbid states should be referred to secondary/specialist care.	
CRITERIA FOR CONSIDERING STUDIES	All studies-no restrictions	
POPULATION	Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups; Those with existing atopic diseases Those with a first degree relative with a food allergy or other atopic disease Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years)	
DIAGNOSTIC TOOL	Clinical signs and symptoms that lead to a referral to secondary/specialist care	
COMPARATORS	N/A	
OUTCOMES	Health related quality of life associated with diagnostic tools in primary care and community settings Resource use and costs Appropriate referral to secondary care	

KEY CLINICAL QUESTION 5		
	Details	Comments
REVIEW QUESTION 5	What information should children with suspected food allergy and their parents/carers receive during the diagnostic process?	
OBJECTIVES	To determine what information should be provided to children and their parents/carers at first consultation during the diagnostic process following diagnosis/referral	
CRITERIA FOR CONSIDERING STUDIES	All studies-no restrictions	
POPULATION	Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups; Those with existing atopic diseases Those with a first degree relative with a food allergy or other atopic disease Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years)	
DIAGNOSTIC TOOL	Information provided to patients and their parents/carers.	
COMPARATORS	N/A	
OUTCOMES	Health related quality of life associated with diagnostic tools in primary care and community settings The use of food diaries to record patient and parent/carer experiences of adverse reactions to food Appropriate referral to secondary care Patient and parent/carer information and support	

	needs Adverse reactions to diagnostic tests	

Appendix 1.2

Literature search

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in ‘The guidelines manual' (2009). The purpose of systematically searching the literature is to attempt to comprehensively identify the published evidence to answer the key clinical questions developed by the Guideline Development Group and Short Clinical Guidelines Technical Team.

The search strategies for the key clinical questions were developed by the Information Services Team with advice from the Short Clinical Guidelines Technical Team. Structured clinical questions were developed using the PICO (population, intervention, comparison, outcome) model and were translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches.

To identify economic evaluations the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched. Search filters to identify economic evaluations and quality of life studies were used to interrogate bibliographic databases. There were no date restrictions imposed on the searches.

In addition to the systematic literature searches, the Guideline Development Group members were asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between January to March 2010.

Scoping searches were undertaken in October 2009 using the following websites and databases (listed in alphabetical order); browsing or simple search strategies were employed. The search results were used to provide information for scope development and project planning.

Guidance/guidelines	Systematic reviews/economic evaluations
Allergy UK American Academy of Allergy, Asthma and Immunology The Anaphylaxis Campaign British Dietetic Association British Paediatric Allergy Immunology and Infection Group British Society for Allergy and Clinical Immunology British Society for Gastroenterology Canadian Medical Association Infobase Clinical Knowledge Summaries College of Emergency Medicine Department of Health Food Allergy and Anaphylaxis Network (US) Food Allergy Initiative (US) Food Standards Agency Guidelines International Network (GIN) National Guideline Clearing House (US) National Health and Medical Research Council (Australia) National Institute for Health and Clinical Excellence (NICE) – guidance published & in development National Institute for Health and Clinical Excellence (NICE) – topic selection National Institute of Allergy and Infectious Diseases (US) New Zealand Guidelines Group NHS Evidence Resuscitation Council Royal College of Physicians of London Royal College of Surgeons of Edinburgh Royal College of Surgeons of England Scottish Intercollegiate Guidelines Network (SIGN) Vegetarian Society World Allergy Organization	Clinical Evidence Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Health Economic Evaluations Database (HEED) Health Technology Assessment (HTA) Database NHS Economic Evaluation Database (NHS EED) NHS R&D Service Delivery and Organisation (NHS SDO) Programme National Institute for Health Research (NIHR) Health Technology Assessment Programme TRIP Database

Search strategies

The following sources were searched for the topics presented in the sections below.

• Clinical Trials.gov

• Current Controlled Trials

• Cochrane Database of Systematic Reviews – CDSR (Wiley)

• Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)

• Database of Abstracts of Reviews of Effects – DARE (CRD)

• Health Technology Assessment Database – HTA (CRD)

• CINAHL (HDAS via NHS Evidence)

• EMBASE (Ovid)

• MEDLINE (Ovid)

• MEDLINE In-Process (Ovid)

• National Research Register Archive

• UK Clinical Research Network

The searches addressed questions about diagnosis and referral to secondary care as well as patient information needs. A review of reviews was undertaken to attempt to focus in on reviews of the evidence and in this case a systematic review filter was applied, the other searches were not limited by study design.

The MEDLINE search strategies are presented below. They were translated for use in all of the other databases.

Diagnosis

Ovid MEDLINE(R) <1950 to January Week 2 2010>

1 exp Food hypersensitivity/ (11458)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6891)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or egg* or peanut* or nut* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana*)).ti,ab. (4518)

4 or/1-3 (15119)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2396979)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1356759)

7 5 or 6 (2774216)

8 Medical history taking/ or Physical examination/ or "Diagnostic Techniques and Procedures"/ or "Sensitivity and Specificity"/ (247715)

9 ((physical or medical) adj3 (examin* or assess*)).ti,ab. (51616)

10 ((medical or parent* or famil* or genetic) adj3 histor*).ti,ab. (51941)

11 ((food* or patient* or parent*) adj3 (diar* or record* or chart*)).ti,ab. (60288)

12 Patch Tests/ or passive cutaneous anaphylaxis/ (10442)

13 ((skin prick or skin-prick or skinprick or patch* or atop* or fresh food* or commercial extract*) adj3 (test* or assess*)).ti,ab. (11515)

14 (SPT or passive cutaneous anaphyla*).ti,ab. (3415)

15 ((serum specific or IgE or immunoglobulin E or radioallergosorbent or allerg*) adj3 (test* or assess*)).ti,ab. (8685)

16 (Microarray* adj3 (food allergen* or diagnos* or assay* or chip based)).ti,ab. (882)

17 (RAST or CAP-RAST or ELISA or ImmunoCAP or Immulite 2000 or Turbo-MP or UniCAP or Fluorescence enzyme immunoassay* or FEIA or Recombinant allergen* or purified native allergen* or Component resolved diagnos* or component-resolved diagnos* or CRD or ISAC).ti,ab. (83864)

18 ((Food* or diet*) adj3 (eliminat* or exclu*)).ti,ab. (1991)

19 (((food* or allergen*) adj3 (challenge* or provoc*)) or DBPCFC).ti,ab. (4000)

20 Endoscopy/ (33344)

21 (endoscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop* or OGD or EGD).ti,ab. (102587)

22 ((Vega or leucocytotoxic* or ALCAT or Neutron or Nutron or IgG or immunoglobulin G or Provocation-neutralisation or pulse) adj3 (test* or assess*)).ti,ab. (4191)

23 (kinesiolog* or hair analys* or Bio-Electronic Regulatory Medicine or BER or Miller technique).ti,ab. (2718)

24 or/8-23 (609302)

25 4 and 7 and 24 (2810)

26 Animals/ not Humans/ (3331323)

27 25 not 26 (2789)

28 limit 27 to english language (2332)

Referral

Ovid MEDLINE(R) <1950 to January Week 5 2010>

1 exp Food hypersensitivity/ (10003)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6449)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or infant formula or baby formula or egg* or peanut* or nut* or seed* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana* or corn or strawberr* or celery or rice or red meat or buckwheat or apple* or pear* or peach* or jackfruit or gluten)).ti,ab. (4536)

4 or/1-3 (13017)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (918757)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (983230)

7 5 or 6 (1400615)

8 Pruritus/ (27974)

9 Burning Mouth Syndrome/ (305)

10 ((itch* or burn* or swell* or swollen or pruritis or tight* or inflamm* or irritat*) adj3 (mouth or oral or nose or nasal or nostril* or tongue or lip* or ear* or pharynx or uvula or throat)).ti,ab. (12395)

11 (glossalgia or chelilitis).ti,ab. (11)

12 ((oral or pollen food or pollen-food or exercise-induced food or exercise induced food) adj3 (allerg* or syndrome*)).ti,ab. (1212)

13 Rhinitis/ (7986)

14 rhinitis.ti,ab. (13450)

15 ((inflamm* or runny or irritat* or drip* or congest*) adj3 (nose or nasal or nostril*)).ti,ab. (2640)

16 Conjunctivitis, Allergic/ (1935)

17 (conjunctivitis or rhinoconjunctivitis).ti,ab. (6629)

18 Asthma/ or status asthmaticus/ (85187)

19 (asthma* or wheez* or cough* or (shortness adj1 breath) or (tight* adj3 chest)).ti,ab. (100892)

20 Urticaria/ (13865)

21 Angioedema/ (7054)

22 (urticaria or angioedema or angio-oedema or hives).ti,ab. (9980)

23 Eczema/ (8518)

24 Dermatitis/ (9122)

25 dermatitis herpetiformis/ (1506)

26 (eczema or dermatitis).ti,ab. (33370)

27 ((skin or cutaneous) adj3 (disease* or inflamm* or irritat* or swell* or itch* or condition*)).ti,ab. (23071)

28 exp Diarrhea/ (91819)

29 Vomiting/ (73238)

30 (nause* or diarrhoea or diarrhea or vomit* or sick*).ti,ab. (110879)

31 Abdominal Pain/ (45927)

32 ((abdomin* or stomach or gastrointestin* or GI) adj3 (ache or aching or pain* or cramp* or anaphyla*)).ti,ab. (27074)

33 exp Gastroenteritis/ (7449)

34 eosinophilia/ (12384)

35 (oesophagiti* or esophagiti* or gastroenteriti* or gastriti* or proctiti* or enteropath* or enteriti* or enterocoliti*).ti,ab. (46838)

36 exp Gastroesophageal Reflux/ (20352)

37 ((gastroesophageal or gastroesophageal or gastro-oesophageal or gastro-esophageal or gastro oesophageal or gastro esophageal) adj3 reflux).ti,ab. (12904)

38 (GERD or GORD).ti,ab. (4050)

39 Constipation/ (30152)

40 constipat*.ti,ab. (10361)

41 Celiac Disease/ (9656)

42 ((coeliac or celiac) adj3 (disease or sprue or syndrome*)).ti,ab. (8292)

43 Hemosiderosis/ (1039)

44 ("heiner syndrome" or haemosiderosis* or hemosiderosis* or "chronic pulmonary disease").ti,ab. (1426)

45 "failure to thrive".ti,ab. (2669)

46 or/8-45 (547422)

47 exp primary health care/ (46982)

48 ("primary care" or "primary health care").ti,ab. (44006)

49 Family Practice/ (23938)

50 Physicians, Family/ (32498)

51 Community health nursing/ (214)

52 Patient care team/ (90555)

53 (family practi* or family doctor* or family physician* or gp* or GPwSI or GPSI or PwSI or general practi* or nurs* or health visit*).ti,ab. (181069)

54 ambulatory care facilities/ or outpatient clinics, hospital/ (11524)

55 ((secondary or tertiary or specialist or allerg* or dermatolog* or pediatric or paediatric or immunolog* or hospital* or outpatient* or out-patient* or ambulatory or multidisciplinary or multi-disciplinary or interdisciplinary or inter-disciplinary) adj3 (care or team* or unit* or clinic* or centre* or center* or service*)).ti,ab. (137673)

56 (consultant* or pediatrician* or paediatrician* or immunologist* or allergist* or dermatologist* or specialist respiratory physician* or gastroenterologist*).ti,ab. (37997)

57 "allergy and immunology"/ (11622)

58 "Referral and Consultation"/ (29335)

59 (referral or "second opinion").ti,ab. (34210)

60 Case management/ or Critical pathways/ (2419)

61 ((clinical or critical or care or integrated) adj3 pathway*).ti,ab. (5074)

62 or/47-60 (510282)

63 4 and 7 and 46 and 62 (562)

64 limit 63 to english language (442)

65 Animals/ not Humans/ (19162)

66 64 not 65 (442)

Patient information

Ovid MEDLINE(R) <1950 to February Week 4 2010>

1 exp Food hypersensitivity/ (11545)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6958)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or egg* or peanut* or nut* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana*)).ti,ab. (4557)

4 or/1-3 (15234)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2414071)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1368878)

7 5 or 6 (2795007)

8 4 and 7 (7630)

9 Animals/ not Humans/ (3355096)

10 8 not 9 (7536)

11 Qualitative Research/ (8148)

12 Nursing Methodology Research/ (12981)

13 exp Interviews as topic/ (35673)

14 Questionnaires/ (207131)

15 Narration/ (3114)

16 Health Care Surveys/ (16308)

17 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. (610023)

18 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj3 analys$) or theoretical sampl$ or purposive sampl$).tw. (23054)

19 (hermeneutic$ or heidegger$ or husserl$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. (5200)

20 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$).tw. (165)

21 or/11-20 (709017)

22 exp Patients/px (13517)

23 exp Parents/px (22952)

24 exp Family/px (44706)

25 Caregivers/px (8558)

26 Stress, Psychological/ (64917)

27 Adaptation, psychological/ (58654)

28 Emotions/ (30076)

29 Anxiety/ (39754)

30 Fear/ (17426)

31 exp Consumer Satisfaction/ (57355)

32 or/22-31 (283068)

33 21 or 32 (907226)

34 10 and 33 (715)

35 limit 34 to english (631)

Review of reviews

Ovid MEDLINE(R) <1950 to March Week 4 2010>

1 exp Food hypersensitivity/ (11583)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6990)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or infant formula or baby formula or egg* or peanut* or nut* or seed* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana* or corn or strawberr* or celery or rice or red meat or buckwheat or apple* or pear* or peach* or jackfruit or gluten)).ti,ab. (5313)

4 or/1-3 (15704)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2422065)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1374417)

7 5 or 6 (2804580)

8 Pruritus/ (6952)

9 Burning Mouth Syndrome/ (561)

10 ((itch* or burn* or swell* or swollen or pruritis or tight* or inflamm* or irritat*) adj3 (mouth or oral or nose or nasal or nostril* or tongue or lip* or ear* or pharynx or uvula or throat)).ti,ab. (13866)

11 (glossalgia or chelilitis).ti,ab. (48)

12 ((oral or pollen food or pollen-food or exercise-induced food or exercise induced food) adj3 (allerg* or syndrome*)).ti,ab. (1395)

13 Rhinitis/ (6614)

14 Rhinitis, Allergic, Seasonal/ (10544)

15 (Hayfever or hay fever or hay-fever or ((season* or allerg*) adj3 rhiniti*) or (pollen* adj2 allerg*) or pollinos*).ti,ab. (14348)

16 rhinitis.ti,ab. (14718)

17 ((inflamm* or runny or irritat* or drip* or congest*) adj3 (nose or nasal or nostril*)).ti,ab. (2719)

18 Conjunctivitis, Allergic/ (2201)

19 (conjunctivitis or rhinoconjunctivitis).ti,ab. (8049)

20 Asthma/ or status asthmaticus/ (88662)

21 (asthma* or wheez* or cough* or (shortness adj1 breath) or (tight* adj3 chest)).ti,ab. (117490)

22 Urticaria/ (8175)

23 Angioedema/ (3595)

24 (urticaria or angioedema or angio-oedema or hives).ti,ab. (10618)

25 Eczema/ (7575)

26 Dermatitis/ (6477)

27 dermatitis herpetiformis/ (2269)

28 (eczema or dermatitis).ti,ab. (37859)

29 ((skin or cutaneous) adj3 (disease* or inflamm* or irritat* or swell* or itch* or condition*)).ti,ab. (25879)

30 exp Diarrhea/ (38235)

31 Vomiting/ (16658)

32 (nause* or diarrhoea or diarrhea or vomit* or sick*).ti,ab. (141890)

33 Abdominal Pain/ (10095)

34 ((abdomin* or stomach or gastrointestin* or GI) adj3 (ache or aching or pain* or cramp* or anaphyla*)).ti,ab. (30039)

35 exp Gastroenteritis/ (128475)

36 eosinophilia/ (10644)

37 (oesophagiti* or esophagiti* or gastroenteriti* or gastriti* or proctiti* or enteropath* or enteriti* or enterocoliti*).ti,ab. (64597)

38 exp Gastroesophageal Reflux/ (17932)

39 ((gastroesophageal or gastroesophageal or gastro-oesophageal or gastro-esophageal or gastro oesophageal or gastro esophageal) adj3 reflux).ti,ab. (13682)

40 (GERD or GORD).ti,ab. (4021)

41 Constipation/ (8418)

42 constipat*.ti,ab. (11079)

43 Celiac Disease/ (12460)

44 ((coeliac or celiac) adj3 (disease or sprue or syndrome*)).ti,ab. (9818)

45 Hemosiderosis/ (2061)

46 ("heiner syndrome" or haemosiderosis* or hemosiderosis* or "chronic pulmonary disease").ti,ab. (2465)

47 "failure to thrive".ti,ab. (3082)

48 or/8-47 (617306)

49 Meta-Analysis.pt. (23594)

50 Meta-Analysis as Topic/ (9973)

51 Review.pt. (1507038)

52 exp Review Literature as Topic/ (4706)

53 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (28357)

54 (review$ or overview$).ti. (198692)

55 (systematic$ adj4 (review$ or overview$)).tw. (23668)

56 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (2268)

57 ((studies or trial$) adj1 (review$ or overview$)).tw. (5084)

58 (integrat$ adj2 (research or review$ or literature)).tw. (2114)

59 (pool$ adj1 (analy$ or data)).tw. (5421)

60 (handsearch$ or (hand adj2 search$)).tw. (3201)

61 (manual$ adj2 search$).tw. (1731)

62 or/49-61 (1621950)

63 4 and 7 and 48 and 62 (755)

64 Animals/ not Humans/ (3363922)

65 63 not 64 (754)

66 limit 65 to english language (576)

Economic search

The following sources were searched to identify economic evaluations and quality of life data featuring the Barrett's Oesophagus patient population.

- Health Economic Evaluations Database – HEED (Wiley)
- NHS Economic Evaluation Database – NHS EED (Wiley and CRD website)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Ovid MEDLINE(R) <1950 to February Week 2 2010>

1 exp Food hypersensitivity/ (11520)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6935)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or infant formula or baby formula or egg* or peanut* or nut* or seed* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana* or corn or strawberr* or celery or rice or red meat or buckwheat or apple* or pear* or peach* or jackfruit or gluten)).ti,ab. (5276)

4 or/1-3 (15604)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2407842)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1364495)

7 5 or 6 (2787487)

8 Economics/ use mesz (25702)

9 exp "Costs and Cost Analysis"/ (146654)

10 Economics, Dental/ (1787)

11 exp Economics, Hospital/ (16270)

12 exp Economics, Medical/ (12852)

13 Economics, Nursing/ (3800)

14 Economics, Pharmaceutical/ (2077)

15 Budgets/ (8136)

16 exp Models, Economic/ (6944)

17 Markov Chains/ (6065)

18 Monte Carlo Method/ (13281)

19 Decision Trees/ (7024)

20 econom$.tw. (110417)

21 cba.tw. (7733)

22 cea.tw. (12989)

23 cua.tw. (625)

24 markov$.tw. (7099)

25 (monte adj carlo).tw. (13743)

26 (decision adj2 (tree$ or analys$)).tw. (5410)

27 (cost or costs or costing$ or costly or costed).tw. (216095)

28 (price$ or pricing$).tw. (17104)

29 budget$.tw. (13291)

30 expenditure$.tw. (25803)

31 (value adj2 (money or monetary)).tw. (804)

32 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2229)

33 or/8-32 (485568)

34 "Quality of Life"/ use mesz (79428)

35 quality of life.tw. (86740)

36 "Value of Life"/ use mesz (5062)

37 Quality-Adjusted Life Years/ use mesz (4171)

38 quality adjusted life.tw. (3221)

39 (qaly$ or qald$ or qale$ or qtime$).tw. (2670)

40 disability adjusted life.tw. (583)

41 daly$.tw. (634)

42 Health Status Indicators/ use mesz (14451)

43 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (9413)

44 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (788)

45 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (1312)

46 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (18)

47 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (289)

48 (euroqol or euro qol or eq5d or eq 5d).tw. (1719)

49 (qol or hql or hqol or hrqol).tw. (13648)

50 (hye or hyes).tw. (49)

51 health$ year$ equivalent$.tw. (36)

52 utilit$.tw. (74099)

53 (hui or hui1 or hui2 or hui3).tw. (552)

54 disutili$.tw. (113)

55 rosser.tw. (63)

56 quality of wellbeing.tw. (2)

57 quality of well-being.tw. (255)

58 qwb.tw. (130)

59 willingness to pay.tw. (1195)

60 standard gamble$.tw. (522)

61 time trade off.tw. (479)

62 time tradeoff.tw. (168)

63 tto.tw. (356)

64 or/34-63 (210965)

65 33 or 64 (667901)

66 4 and 7 and 65 (229)

67 limit 66 to english language (200)

Appendix 1.3.1

Clinical Question 1

What elements should allergy focused clinical history taking, physical examination and patient/parent food diaries include in order to effectively diagnose and assess food allergy (IgE, non-IgE-mediated or mixed) in children?

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Hand et al 2004 (3166)	Case control study	Tree nuts and peanuts	93 children from the age of 3years with peanut and tree nut sensitivity	Skin prick test and IgE	No oral food challenge	Demographic details, family history of atopy (ingestion of nuts by mothers during pregnancy and lactation) Symptoms graded as follows. Mild: vomiting, abdominal pain, irritability, pruritus urticaria. Moderate: facial oedema (lip and mouth swelling. Severe laryngeal oedema, cyanosis, wheeze, collapse, syncopy anaphylaxis	Not recorded	The authors suggested that the use of DBPCFC raises concerns in clinicians due to possible adverse events and patient resistance to such testing. SPT is an almost painless procedure, was well

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
								tolerated in the very young and gave a very good correlation with clinical history. They concluded that the findings emphasize the importance of good clinical history taking in conjunction with confirmatory SPT and/or specific IgE in the diagnosis and

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
								management of nut allergy
Orhan et al 2009 (4844)	Cross sectional study	Hens egg, beef, cow's milk, fish, tomato, hazelnut, kiwi, black pepper, peanut, corn, walnut, potato,	3500 children 6 to 9 year old urban schoolchildren	Skin prick test	Double Blind Placebo Controlled Food Challenge	Standard questionnaire. Demographics (age and sex), adverse reaction to food within 2hoursof consumption. Symptoms from a list of 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(swallowing/speaking difficulty)	Not recorded	Authors reported that questionnaire was validated. The most frequently reported clinical manifestations were cutaneous 75.6%, gastrointestinal 56.4%, nasal 37.2%, bronchial 32.0%, and

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
						cardiovascular (palpitations/tachycardia, hypotension) and other(sweating, pallor, fainting, loss of consciousness) symptoms. Specify foods that caused reaction		ocular 22.4%. 75.6% children reported a reaction that involved more than one organ system. The rate of IgE reported FA was significantly higher than clinically confirmed FA by means of DBPCFC (or 7.46 CI(4.67-12.01) p<0.0001). Although DBPCFC is considered

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
								the gold standard for diagnosis of FA its positive predictive value has been suggested to be around 90% in patients with peanut allergy. Therefore a cautionary approach should be adopted particularly in patients with a negative FC but with a consistent history and positive SPT

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Kucukosmanoglu et al 2008 (150)	Observational study	Cow's milk	1015 infants between 8 and 18months	Skin prick test	Open food challenge	Questionnaire was via face to face interview of parent. Information sort included history of wheezing, atopic dermatitis, breastfeeding, age of initiation of complementary food, CM intake Family history of atopic diseases were also queried	Not recorded	Information in questionnaire helped authors to group infants into whether those with atopic dermatitis and a history of skin rash were more likely to be cow's milk allergic

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Hill D.J. et al 2004 (3155)	Observational study	Cow milk, egg, peanuts	487 infants from birth	Skin prick test	Open food challenge	Questionnaires administered by trained allergy nurse completed by telephone interview at 4 weekly intervals. Information included infant feeding, the introduction of solid foods, the development of atopic dermatitis and other infant illnesses, contact with health care professionals and medication history. Presence of pets and exposure to environmental allergen exposure, parental smoking and presence of gas heating. Severity of atopic dermatitis was quantified by dividing those subjects into quartiles according to nurse recorded topical steroid use as defined by length of use in days. Gp	Work supported by Victorian Department of Human services, Royal Children's Hospital	In general there was an increase in the proportion of infants with parent reported adverse reactions to specific foods as the severity of atopic dermatitis increased from Gp 0 to4 (19/346 vs 2/36 vs 1/35 vs 3/35 vs 9/35 p= 0.004) Those subjects with IgE-mediated food allergy

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
						0 no atopic dermatitis <8 days steroid treatment in the first 12 months (346). Gp1: 8-14 days steroid treatment (36). Gp 2: 15-28 days of steroid treatment (35). Gp 3: 29-73 days steroid treatment in the first 12 months (n=35). Gp 4: 74-232 days of steroid treatment in the first 12 month of life		were more likely to have reported reactions to ingested foods than those without IgE-mediated food allergy; relative risk 3.2 (95% CI:1.5-6.7) The authors noted that as the severity of atopic dermatitis increased so did the frequency of IgE-mediated food allergy and

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
								reported adverse food reactions.

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Roehr et al 2004 (3161)	Observational cross sectional study	Cow's milk, hens egg wheat fish carrot and soy	patients age up to 18 years of age	Skin prick test	Double blind placebo controlled food challenge	Questions about connections between food ingestion and itching, eczema urticaria, angio-oedema, rhinitis, asthma, gastro intestinal symptoms, headache and other symptoms. The degree of clinical reactions, age of onset of reaction, current dietary habits and/or other methods of treatment were elicited. Patients' history, possible risk factors such as smoking, atopic disorders and treatment and the general attitude towards food safety were included. Upon response to the questionnaire, individuals were contacted by telephone and interviewed using a structured questionnaire. Depending on the	German ministry of health supported study and Pharmacia provided kits.	The two stepped approach used in clinical history taking allowed to control for over and under representation secondary to recall errors or ill beliefs of FA/NAFH. Through this screening process, a third of the presumed food reactions were excluded

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
						patients history a thorough medical history and physical examination including cutaneous, respiratory, cardiovascular, and GI symptoms was obtained.		prior to the physical examination and testing on the grounds of lacking reproducibility of symptoms.
Dean et al 2007 (323)	Population based cohort study	Peanuts, eggs milk	543 children from birth to 3years of age	Skin prick test	Double blind placebo food challenge	Clinical history using standardized questionnaire on family structure, family history of atopy, smoking habits, pet ownership, reported symptoms of atopy and physician diagnosed symptoms	Not recorded	There was no significant association between sensitization and sibship (p=0.28) or family history of smoking (p=1.000) There was also no association

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
								between sensitization and any reported family history of atopy. However there was a significant association between maternal atopy (considered on its own) and sensitization .

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Skolnick et al 2001(3575)	Observational study	Peanuts	Children 4 years and older	Puncture skin tests, specific IgE tests	Double blind placebo food challenge	Clinical history by way of questionnaire including age of onset of peanut allergy, the characteristics of all prior peanut reactions, and any other food allergies and their resolution or lack of resolution and any history of other atopic diseases.	Not recorded	Patients were determined to have peanut allergy if they had a history of an acute reaction to peanut ingestion and positive results to a skin test or challenge or in some cases positive results to a RAST or a skin test without ever ingesting peanuts

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Asarnoj et al 2009 (4460)	Population-based cohort study	Peanut s allergy	4089 children born between 1994 and 1996 and followed up at 1,2,4 and 8 years via questionnaires on symptoms of allergic diseases and key exposures.	IgE	No reference test.	Information at 4 years of age: After 2 years of age, Has your child experienced any problems from eating peanuts such as vomiting, diarrhoea, eczema, urticaria/itching rash, swollen lips/eyes itchy, blocked or runny nose or asthma? Information at 8 years of age: Is your child allergic to peanuts? If yes, symptoms options were nose/eye symptoms, 'mouth itching', breathing difficulties', vomiting/diarrhea, eczema, urticaria or excluded because of early symptoms. Peanuts had to be indicated on at least one of these symptoms. They investigated cross sensitization with birch	Work supported by Swedish asthma and allergy foundation	At 4 years of age the proportion of children reporting symptoms from peanut did not differ among peanut sensitized children with or without concomitant sensitization to pollen. At 8 years of age 76% of the children sensitized to peanut but not to birch pollen reported symptoms to peanut, whereas

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
						pollen by asking similar question with regard to birch pollen allergy especially in the month of May.		among children sensitized both to peanut and birch pollen only 46% reported such symptoms p=0.002. They suggested that there is a major risk of misclassifying peanut sensitized individuals as allergic to peanuts

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Von Berg et al 2003 (4933)	Prospective randomized double blind intervention follow up study	Cows milk formula compared with partially hydrolysed and wholly partially formula	2252 children randomized from weaning	Observation of defined symptoms for such as skin lesions, pruritus,	Not recorded	Mothers were asked to document in weekly diaries the kind of milk the infant was fed for the first six months, time of first introduction and kinds of new solid foods and any health problems. Health problems including symptoms related to AD, allergic urticaria, and food allergy manifestation in the GIT were verified by structured interview and by clinical examination. Information on sociodemographic factors, family and living conditions, and smoking habits were documented.	Not recorded	Authors commented that they could demonstrate that the preventive potential of the different formulas depends on the family history of AD

Bibliographic Reference (Ref ID)	Study type	Foods tested	Number of participants /Age Characteristics	Type of Test	Reference Standard	Information retrieved in clinical history and relevant interpretation	Source of Funding	Additional Comments
Simeone et al 2008 (158)	Observational prospective study	Cows milk	Study included 69 constipated study subjects and 69 controls. Participants were between the ages of 6months and 6 years	Skin prick test and specific IgE	Not recorded	A detailed questionnaire was completed for each participant. Details included family and personal history of atopic disease, the presence of allergic symptoms, duration of breastfeeding and age at first introduction of cow's milk protein. Presence of symptoms relating to Cows milk allergy such as vomiting, diarrhoea, abdominal pain, painful defecation and the presence of anal fissures or erythema. A detailed dietary history was also recorded.	Not recorded	Participants were asked to go through a period of elimination and events were recorded in a diary. Study shows detailed clinical history taking could be an integral part of food allergy diagnosis

Review of reviews

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Lack 2008 (Ref ID:73)	Not systematic review-no mention of how articles were selected & no methodology	**Genetic risk factors**: There is some evidence to support a strong genetic contribution to peanut allergy. In the case of peanut allergy, a child has a 7 fold increase in the risk of peanut allergy if he or she has a parent or sibling with peanut allergy. **Other atopic disease**: There is a well-documented link between the presence of early eczema in childhood and the development of food allergy, especially peanut, egg and milk allergies (between 33% and 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. **Exposure to food allergens**: Although conventional wisdom has always been that early exposure to allergenic food proteins during pregnancy or lactation could lead to food allergies, it is stated that the evidence to support food allergen avoidance is currently lacking and there is no compelling evidence that exclusive breast feeding beyond 4 months of age has any effect on reducing atopic disease **Changes in dietary composition**: There are few data to refute or support the dietary fat hypothesis with respect to food allergy, which argues that reduction in consumption of animal fats and corresponding increases in use of margarine and vegetable oils has led to the increase in allergies. There is no data to support the hypothesis that diets high in antioxidants (from fresh fruits and vegetables) are associated with lower rates of food allergy. There is some evidence to support that increases in vitamin D have led to increased allergies and some to support that inadequate vitamin D have led to an increase in allergies. There is controversy relating to the vitamin D excess and deficiency hypotheses which remains unsolved. **The hygiene hypothesis**: There is limited support for the hygiene hypothesis having a role in the development of food allergies, although evidence is stronger for a role in eczema than in food allergy. **Other factors**: Caesarean sections appear to increase risk for the development of food allergies. A recent meta analysis on the relationship between caesarean delivery and atopic outcome found 6 studies that confirmed a mild effect of caesarean delivery, increasing the risk of food allergy or atopy (OR 1.32, CI 1.12-1.55)	Not reported	In summary the author suggests that antigen exposure through inflamed skin or through the gastrointestinal mucosa might be involved in the establishment of allergy and tolerance. It is also suggested that more interventional trials are needed.

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Schuller 2004 (Ref ID:836)	Not systematic review-no mention of how articles were selected & no methodology	**Genetics:** The risk that a particular neonate will develop atopic symptoms during the first two decades of his life is strongly related to the presence of disease in their parents and siblings. **Prenatal:** The interaction of the foetus with the gestation associated environment from the amniotic fluid or nutritional factors at the placental interface may lead to foetal programming and a susceptibility to atopic disease development. **Postnatal:** Elevated umbilical cord IgE was thought to be a specific marker of later atopic disease, but has not been proven to be a sensitive marker of disease development. It has also been documented that IFN-γ at birth is further decreased in infants who are at risk of atopic disease. **Other environmental risk factors**: including increased risk for sensitisation in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth. Also lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood. Endotoxin exposure is a possible element of atopy prevention in early life. Prenatal or perinatal bacterial infections should also be considered risk factors for modulation of atopy. **Feeding:** It has been postulated that maternal secretory IgA may protect against the development of atopic disease in infants.	Not reported	

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Cochrane et al 2009	Published as part of Europrevall project. No methodology	**Other atopic disease**: Family history of atopy is a strong risk factor for the development of atopic diseases as shown in several studies. Having one atopic disease is a risk factor for developing another atopic disease. The sequential appearance of atopic disease is unlikely to be because one disease causes the other but rather that certain individuals are prone to manifest these atopic disorders under the influence of environmental factors within a particular time-frame. **Genetics:** There are studies that show that the prevalence of allergic disease in first degree relatives of affected individuals was significantly higher than in relatives of unaffected individuals. A literature research indicates a wealth of studies related to asthma but nearly none to food-related allergy disorders. **The gut immune system:** Although no data are available so far on the role of gut-derived dendritic cells in humans, there is some support from a mouse model of food allergy that a reduced production of IL-12 by dendritic cells may play a pivotal role in the development of food allergy in humans as well. Changes to the microflora of the gut may alter the immunological responses in the gut. Other changes to the gut's transport of foods and proteins, such as changes to the M-cells might change susceptibility. Nutritional or pharmacological co-factors may also be important for example broad spectrum antibiotics (changing the bacterial ecosystem) and vitamin D (suppressing normal gut Th1 development). **Allergen exposure**: Whether a person becomes sensitised to an allergen depend on the timing and dose of the allergen as well as the route of exposure. **Acidity of the gut**: It has been speculated that the relatively high pH in the stomach of infants may make them more susceptible to sensitisation by ingested allergens. **Breastfeeding and diet:** The influence of mode of birth (c-section) on the subsequent development of food allergy is still unknown and there are currently no published data on antibiotic use as a risk factor for food allergy.	Funded by the EU through the EuroPrevall project.	The aetiology of food allergy poses specific problems which have been hard to investigate but for which answers are needed. Several hypotheses have been proposed but have little information currently to support them.

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Koplin et al 2008	Systematic review searching MEDLINE and PubMed. 4 papers were included.	Review found evidence that children delivered by caesarean section have an increased rate of sensitisation to food allergens compared with those delivered by vaginal birth (Eggesbo 2003 parent reported food allergy OR 3.2, CI 1.4-7.3 and objectively diagnosed egg allergy OR 1.6, CI 0.5-5.1, Renz-Polster 2005 diagnosis of food allergy OR 1.34, CI 0.54-3.29.) In addition, there is evidence from one study that symptoms of food allergy occur more commonly among children who are born by caesarean section. This study also suggests that this association is stronger in children born to allergic mothers although the evidence for the related findings was modest (OR 4.1, CI 0.9-19, p=0.08). Wide confidence intervals of the relevant estimates including for the interaction term suggest that this is probably related to the inadequate power of the study. Although potential confounding factors may exist that could explain the observed increase in food allergy among children born by caesarean section, three out of four studies included in the analysis controlled for factors that differed between children born by caesarean section compared with children born by vaginal birth.	Not reported	Overall, there is evidence that delivery by caesarean section increases the risk of sensitisation to food allergens but further large studies, ideally using food challenges to establish a diagnosis of food allergy, are needed to confirm whether the same relationship exists between mode of delivery and confirmed food allergy.

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Chapman et al 2006	Food allergy: A practice parameter-guideline developed by the Joint Task Force on Practice Parameters. Each summary statement is supported by graded references.	**Summary statement 31:** The rate of observed food allergy in children born to families with parental asthma was approximately 4-fold higher than expected when compared with an unselected population. Although currently no genetic tests are available to identify persons at risk of food allergy, a family history of atopy, or food allergy in particular, appears to be the best current screening test. In regard to food allergy, numerous possible environmental risk factors have been investigated with variable and often controversial results. Factors under consideration include maternal diet during pregnancy and breastfeeding, age at solid food exposure, age at introduction to allergenic foods, exposure to indoor and outdoor allergens, birth order, race/ethnicity, caesarean section, maternal age and others. For example soy feeding formula feeding (OR 2 to 6) and complaint of rash consistent with atopic dermatitis (OR 2.6 to 5.2) were independently associated with development of peanut allergy. **Summary statement 32**: Food allergy prevention strategies include breastfeeding, maternal dietary restrictions during breastfeeding, delayed introduction of solid foods, delayed introduction of particular allergenic foods and the use of supplemental infant formulae that are hypoallergenic or of reduced allergenicity. The effectiveness of these strategies for safeguarding against the development of food allergies has not been established.	Not reported	

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Bahna 2003	Data sources include reviews and original articles & classic textbooks. No mention of how articles were selected & no methodology.	**Gastrointestinal manifestation:** The most common GI symptoms are vomiting, colic, and diarrhoea, reflecting hypermotility. However constipation during infancy can be a manifestation of food hypersensitivity. Gastro-esophageal reflux and eosinophilic esophagitis during childhood may be related to food allergy. **Dermatologic manifestation:** Several studies have demonstrated a role of FA in one third to one half of childhood atopic dermatitis. Foods are among the common causes of acute urticaria/angioedema. In chronic urticaria, however, food or food additives are rarely implicated. Food induced erythematous, papular or urticarial contact rashes have been observed in some children. Immediate contact urticaria to food is relatively common and can be localised, generalised or associated with other system involvement. Rare cases of food-induced vasculitis have been reported. Food induced fixed skin eruption has been reported in a few patients. **Respiratory manifestation:** Chronic serious otitis media may develop secondary to chronic rhinitis and Eustachian tube dysfunction. Food induced asthma is more common in young children, particularly in association with atopic dermatitis. Heiner syndrome is a chronic pulmonary disease caused by food hypersensitivity, primarily to cow's milk during infancy. Hypersensitivity pneumonitis to inhaled soybean flour has been reported in one subject. **Systemic anaphylaxis:** When multiple systems are involved in food hypersensitivity the reaction can be life-threatening, particularly when hypotension is combined with respiratory tract obstruction. Asthmatic children are at a particularly high risk, and the reaction may occur by exposure to minute quantities of the offending food that can be hidden in another ingested food or through skin contact or inhalation. In some cases the reaction only occurred when the person exercised within a few hours of eating the food (food dependent, exercise induced anaphylaxis). **Rare miscellaneous manifestations:** Some rare manifestations seem to be reasonably well documented including headache or migraine, irritability or sleepiness in infants, arthropathy, nephropathy and thrombocytopenia.	Not reported.	

Review of reviews

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Lack 2008 (Ref ID:73)	Not systematic review-no mention of how articles were selected & no methodology	**Genetic risk factors**: There is some evidence to support a strong genetic contribution to peanut allergy. In the case of peanut allergy, a child has a 7 fold increase in the risk of peanut allergy if he or she has a parent or sibling with peanut allergy. **Other atopic disease**: There is a well-documented link between the presence of early eczema in childhood and the development of food allergy, especially peanut, egg and milk allergies (between 33% and 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. **Exposure to food allergens**: Although conventional wisdom has always been that early exposure to allergenic food proteins during pregnancy or lactation could lead to food allergies, it is stated that the evidence to support food allergen avoidance is currently lacking and there is no compelling evidence that exclusive breast feeding beyond 4 months of age has any effect on reducing atopic disease **Changes in dietary composition**: There are few data to refute or support the dietary fat hypothesis with respect to food allergy, which argues that reduction in consumption of animal fats and corresponding increases in use of margarine and vegetable oils has led to the increase in allergies. There is no data to support the hypothesis that diets high in antioxidants (from fresh fruits and vegetables) are associated with lower rates of food allergy. There is some evidence to support that increases in vitamin D have led to increased allergies and some to support that inadequate vitamin D have led to an increase in allergies. There is controversy relating to the vitamin D excess and deficiency hypotheses which remains unsolved. **The hygiene hypothesis**: There is limited support for the hygiene hypothesis having a role in the development of food allergies, although evidence is stronger for a role in eczema than in food allergy. **Other factors**: Caesarean sections appear to increase risk for the development of food allergies. A recent meta analysis on the relationship between caesarean delivery and atopic outcome found 6 studies that confirmed a mild effect of caesarean delivery, increasing the risk of food allergy or atopy (OR 1.32, CI 1.12-1.55)	Not reported	In summary the author suggests that antigen exposure through inflamed skin or through the gastrointestinal mucosa might be involved in the establishment of allergy and tolerance. It is also suggested that more interventional trials are needed.

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Schuller 2004 (Ref ID:836)	Not systematic review-no mention of how articles were selected & no methodology	**Genetics:** The risk that a particular neonate will develop atopic symptoms during the first two decades of his life is strongly related to the presence of disease in their parents and siblings. **Prenatal:** The interaction of the foetus with the gestation associated environment from the amniotic fluid or nutritional factors at the placental interface may lead to foetal programming and a susceptibility to atopic disease development. **Postnatal:** Elevated umbilical cord IgE was thought to be a specific marker of later atopic disease, but has not been proven to be a sensitive marker of disease development. It has also been documented that IFN-γ at birth is further decreased in infants who are at risk of atopic disease. **Other environmental risk factors**: including increased risk for sensitisation in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth. Also lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood. Endotoxin exposure is a possible element of atopy prevention in early life. Prenatal or perinatal bacterial infections should also be considered risk factors for modulation of atopy. **Feeding:** It has been postulated that maternal secretory IgA may protect against the development of atopic disease in infants.	Not reported	

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Cochrane et al 2009	Published as part of Europrevall project. No methodology	**Other atopic disease**: Family history of atopy is a strong risk factor for the development of atopic diseases as shown in several studies. Having one atopic disease is a risk factor for developing another atopic disease. The sequential appearance of atopic disease is unlikely to be because one disease causes the other but rather that certain individuals are prone to manifest these atopic disorders under the influence of environmental factors within a particular time-frame. **Genetics:** There are studies that show that the prevalence of allergic disease in first degree relatives of affected individuals was significantly higher than in relatives of unaffected individuals. A literature research indicates a wealth of studies related to asthma but nearly none to food-related allergy disorders. **The gut immune system:** Although no data are available so far on the role of gut-derived dendritic cells in humans, there is some support from a mouse model of food allergy that a reduced production of IL-12 by dendritic cells may play a pivotal role in the development of food allergy in humans as well. Changes to the microflora of the gut may alter the immunological responses in the gut. Other changes to the gut's transport of foods and proteins, such as changes to the M-cells might change susceptibility. Nutritional or pharmacological co-factors may also be important for example broad spectrum antibiotics (changing the bacterial ecosystem) and vitamin D (suppressing normal gut Th1 development). **Allergen exposure**: Whether a person becomes sensitised to an allergen depend on the timing and dose of the allergen as well as the route of exposure. **Acidity of the gut**: It has been speculated that the relatively high pH in the stomach of infants may make them more susceptible to sensitisation by ingested allergens. **Breastfeeding and diet:** The influence of mode of birth (c-section) on the subsequent development of food allergy is still unknown and there are currently no published data on antibiotic use as a risk factor for food allergy.	Funded by the EU through the EuroPrevall project.	The aetiology of food allergy poses specific problems which have been hard to investigate but for which answers are needed. Several hypotheses have been proposed but have little information currently to support them.

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Koplin et al 2008	Systematic review searching MEDLINE and PubMed. 4 papers were included.	Review found evidence that children delivered by caesarean section have an increased rate of sensitisation to food allergens compared with those delivered by vaginal birth (Eggesbo 2003 parent reported food allergy OR 3.2, CI 1.4-7.3 and objectively diagnosed egg allergy OR 1.6, CI 0.5-5.1, Renz-Polster 2005 diagnosis of food allergy OR 1.34, CI 0.54-3.29.) In addition, there is evidence from one study that symptoms of food allergy occur more commonly among children who are born by caesarean section. This study also suggests that this association is stronger in children born to allergic mothers although the evidence for the related findings was modest (OR 4.1, CI 0.9-19, p=0.08). Wide confidence intervals of the relevant estimates including for the interaction term suggest that this is probably related to the inadequate power of the study. Although potential confounding factors may exist that could explain the observed increase in food allergy among children born by caesarean section, three out of four studies included in the analysis controlled for factors that differed between children born by caesarean section compared with children born by vaginal birth.	Not reported	Overall, there is evidence that delivery by caesarean section increases the risk of sensitisation to food allergens but further large studies, ideally using food challenges to establish a diagnosis of food allergy, are needed to confirm whether the same relationship exists between mode of delivery and confirmed food allergy.

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Chapman et al 2006	Food allergy: A practice parameter-guideline developed by the Joint Task Force on Practice Parameters. Each summary statement is supported by graded references.	**Summary statement 31:** The rate of observed food allergy in children born to families with parental asthma was approximately 4-fold higher than expected when compared with an unselected population. Although currently no genetic tests are available to identify persons at risk of food allergy, a family history of atopy, or food allergy in particular, appears to be the best current screening test. In regard to food allergy, numerous possible environmental risk factors have been investigated with variable and often controversial results. Factors under consideration include maternal diet during pregnancy and breastfeeding, age at solid food exposure, age at introduction to allergenic foods, exposure to indoor and outdoor allergens, birth order, race/ethnicity, caesarean section, maternal age and others. For example soy feeding formula feeding (OR 2 to 6) and complaint of rash consistent with atopic dermatitis (OR 2.6 to 5.2) were independently associated with development of peanut allergy. **Summary statement 32**: Food allergy prevention strategies include breastfeeding, maternal dietary restrictions during breastfeeding, delayed introduction of solid foods, delayed introduction of particular allergenic foods and the use of supplemental infant formulae that are hypoallergenic or of reduced allergenicity. The effectiveness of these strategies for safeguarding against the development of food allergies has not been established.	Not reported	

Bibliography (Ref ID)	Details of review	Risk factors	Source of funding	Comments
Bahna 2003	Data sources include reviews and original articles & classic textbooks. No mention of how articles were selected & no methodology.	**Gastrointestinal manifestation:** The most common GI symptoms are vomiting, colic, and diarrhoea, reflecting hypermotility. However constipation during infancy can be a manifestation of food hypersensitivity. Gastro-esophageal reflux and eosinophilic esophagitis during childhood may be related to food allergy. **Dermatologic manifestation:** Several studies have demonstrated a role of FA in one third to one half of childhood atopic dermatitis. Foods are among the common causes of acute urticaria/angioedema. In chronic urticaria, however, food or food additives are rarely implicated. Food induced erythematous, papular or urticarial contact rashes have been observed in some children. Immediate contact urticaria to food is relatively common and can be localised, generalised or associated with other system involvement. Rare cases of food-induced vasculitis have been reported. Food induced fixed skin eruption has been reported in a few patients. **Respiratory manifestation:** Chronic serious otitis media may develop secondary to chronic rhinitis and Eustachian tube dysfunction. Food induced asthma is more common in young children, particularly in association with atopic dermatitis. Heiner syndrome is a chronic pulmonary disease caused by food hypersensitivity, primarily to cow's milk during infancy. Hypersensitivity pneumonitis to inhaled soybean flour has been reported in one subject. **Systemic anaphylaxis:** When multiple systems are involved in food hypersensitivity the reaction can be life-threatening, particularly when hypotension is combined with respiratory tract obstruction. Asthmatic children are at a particularly high risk, and the reaction may occur by exposure to minute quantities of the offending food that can be hidden in another ingested food or through skin contact or inhalation. In some cases the reaction only occurred when the person exercised within a few hours of eating the food (food dependent, exercise induced anaphylaxis). **Rare miscellaneous manifestations:** Some rare manifestations seem to be reasonably well documented including headache or migraine, irritability or sleepiness in infants, arthropathy, nephropathy and thrombocytopenia.	Not reported.	

Appendix 1.3.2

Clinical Question 2

Which diagnostic tools and strategy are most appropriate and accurate to diagnose non-IgE-mediated and mixed IgE-mediated food allergy in children?

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Sant'Anna, A.M.G.A., Rolland, S., Founet, J.C., Yazbeck, S., & Drouin, E. (2004)/ Ref ID: 762	To review the authors experience with eosinophilic esophagitis/ Retrospective chart review.	Review of 12 children with final diagnosis of EE. Each child with EE was matched with 3 controls of same age and same time of exam. Second control group were last 200 pH probe studies from 2001. 9 males, 3 females, median age of presentation=10.8 yrs. Age range: 1-17 years old.	EE: defined histologically as infiltration≥20 eosinophils/HPF. No specific distinctions between IgE and non-IgE reactions.	**Total blood eosinophil count** (peripheral eosinophilia >700 eosinophils/mm³), **total IgE, specific IgE, esophageal pH monitoring**	N/A	Food allergy reported in 8 children (2 cow's milk & dairy, 3 nuts, 3 peanuts). **Peripheral eosinophilia:** documented in 42%, **Total IgE:** elevated 5/7. **Specific IgE:** to casein, lactoglobulin, nuts, soy, peanuts, egg and wheat detected in 6/9. **Symptoms:** Younger children (1-7yrs) presented with abdominal pain, vomiting and failure to thrive while older children (10-17yrs) presented with solid dysphagia and abdominal pain & impaction. **PH probe:** results show none with abnormal acid reflux but did show an alkalinization of the esophagus of variable intensity in all children.	N/A	Not reported.	Food allergy reported in hospital records (challenge not done).	Younger children presented with vomiting and pain, whereas older children presented with solid food dysphagia and impaction. Concomitant atopic disease or FA were reported in 66% of our group. Radiologic evaluation of children with EE usually was normal. The main endoscopic features were white specks on the esophageal mucosa, granula mucosa, eryematous esophagus, esophageal narrowing, esophageal rings & furrowing. Biopsies revealed a median of 65 eos/HPF.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Cavataio, F., Iacono, G., Montalto, G., Soresi, M., Tumminello, M., Campagna, P., Notarbartolo, A., & Carroccio, A. (1996)/ Ref ID: 1611	To suggest the simplest diagnostic procedure for infants under 1 year old with suspected gastroesophageal reflux (GER) and/or hypersensitivity to cow's milk protein (CMPA) and to confirm the utility of PH-metry analysis in distinguishing between infants with GER only and those with GER & CMPA/ cross sectional	140 referred to clinic for suspected GER and/or CMPA. Mean age 6 months, age range 1-12 months, 60 males, 80 females. Clinical symptoms of those with GER + CMPA at diagnosis: regurgitation 70%, vomiting 60%, fits of crying 20%, anorexia 16.7%, growth disorder 13.3%, anaemia 10%, dermatitis 10%, rhinitis 3.3%.	GER: 1) those with endoscopic and histological evidence of esophagitis. 2) Those in whom total reflux percentage time (recorded by 24 hour PH) was above normal limits with respect to age. 3) Those with clear link between observation of clinical symptom and an episode of esophageal reflux recorded during PH monitoring. CMPA: Those improved on elimination diet had DBPCFC 6-8 weeks later. Intestinal biopsy performed before and 24 hrs after challenge. **Positive result:** if same symptoms reappeared within 24hrs after challenge or intestinal biopsy normal before challenge and abnormal after. Diagnosis of CMPA based on challenge results. Diagnosed 4 groups: GER alone (42), GER+CMPA (30), CMPA alone (38), no GER or CMPA (30).	Immunological tests: **SPT** (positive result wheal>control & >one fourth the size of histamine wheal), **serum total IgE** (RAST-pos result: >60 KU/liter), **circulating eosinophils**-pos result >400/mm^3, **serum IgG** (pos result >36% higher than control standard.) **Esophageal endoscopy & 24 hr PH**	**DBPCFC** with intestinal **biopsy** (clinic)	30/72 with GER also had CMPA. **GER + CMPA**: Immunological tests were sig more likely to be positive in this group in comparison to GER alone: SPT (43.3%, χ^2=13.5, p<0.0003), total IgE 33.3%, eosinophils 33.3% (χ^2=13.6, p<0.0002), IgG (90%, χ^2=43.0, p<0.0001). Phasic tracing of PH monitoring was sig more likely in those with CMPA in comparison to those without (p<0.0001).**Follow up after 2 & 4 weeks:** 4/30 in GER + CMPA no improvement (but 3 had allergy other than cow's milk & symptoms improved when these foods were eliminated). In 13/30 milk was reintroduced but in 46% symptoms returned & in 54% no negative reaction.	N/A	Not reported.	N/A	The characteristic phasic tracing of PH monitoring is almost 90% sensitive in identifying children with GER + CMPA (26/30) & 100% specific. The 36% IgG cut off we chose as the value with greatest diagnostic accuracy shows sensitivity and specificity of 90% in diagnosis of GER + CMPA. The presence of a 'phasic' pH-metry and an elevated value in the serum IgG are elements sufficient to identify cases of GER associated with CMPA.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Nielsen, R.G., Fenger, C., Bindslev-Jensen, C., & Husby, S. (2006)/ Ref ID: 578	To assess whether biopsies from the upper GI tract of children with milk sensitive GERD have a specific allergic inflammatory pattern, and to compare two different techniques for measuring inflammatory cells in gastrointestinal biopsies.	42 children referred to tertiary centre for evaluation of GERD (51 initially).	Severe GERD: criteria included endoscopic oesophagitis and/or reflux index. Those with severe GERD completed 4-6 weeks elimination diet before challenge completed. Positive reactions to challenge continued on elimination diet. No specific distinctions between IgE and non-IgE reactions.	**PH monitor, endoscopy, biopsy, immunohistochemistry** to identify mast cells, eosinophils & T cells, **measurement of inflammatory cells** (cast grid vs. counting cells/HPF)	**Open challenge** in children < 3 yrs & DBPCFC in children > 3yrs. (Tertiary centre).	**Diagnosis:** Severe GERD & CMH (10), severe GERD (7) & control (24). **Other results:** Sig difference (p=0.0001) in thickness of basal zone between endoscopically normal (median 10%) and those with endoscopic oesophagitis (median 40%). Sig higher numbers of mast cells, eosinophils and T cells were found in biopsies from infants with endoscopic oesophagitis. No sig differences were found between clinical groups for mast cell, eosinophil and T cell numbers in all biopsies using the two methods. **Follow up:** biopsies in GERD + CMH showed sig increase in numbers of eosinophils in the biopsies from antrum and duoedenum after elimination diet.	N/A	Not reported.		No sig differences seen in numbers of eosinophils, mast cells or T-cells in upper GI tract biopsies from children with CMH + GERD compared with primary GERD and controls. Despite sharing an association with FA, CMH & GERD and eosinophilic oesophagitis are 2 distinct entities.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Nielson, R.G., Bindslev-Jensen, C., Kruse-Andersen, S., & Husby, S. (2004)/ Ref ID: 4917	To examine whether a causal relationship between GERD and CMH could be established in a population of infants and children and to evaluate whether a cow's milk challenge during pH monitoring is useful to identify GERD + CMH sub-group and whether any specific endoscopic or PH findings were characteristic of this group.	18 children with completed diagnostic work-up & GERD diagnosis (51 invited) 21 excluded children used as controls. Median age 104 months, age range 0-15 years. Follow-up conducted 3-4 months for primary GERD group and after continuous elimination diet for GERD + CMH.	CMH: Challenge performed following 4-6 weeks on diet period. 2 hr observation period. Challenge code not broken until 48 hours after challenge. Primary GERD: negative elimination/ challenge. GERD + CMH: positive elimination/ challenge. No specific distinction between IgE and non-IgE reactions although it is noted in discussion that all but one child showed no evidence of a general IgE-mediated reactivity and that skin patch tests could be a potentially useful diagnostic test in patients with non-IgE-mediated reactions, as the reactivity in the skin patch test presumably depends on T-cell mediated reactions.	**Endoscopy, biopsies, 48 h pH monitoring, RAST, SPT**(prick-prick using fresh foods),	**DBPCFC** (>3 yrs) or open challenge (Paediatric university hospital).	GERD + CMH: 59% (10/17). **SPT-** none were positive in primary GERD group, 1 in GERD + CMH (milk, soy, peanut) & 2 in control group (soy=1, milk & egg=1). **Serum IgE**- No differences between groups. **Patch test-** GERD+CMH (5 at 48hrs & 4 at 72hrs). None in primary GERD. **PH-** Children in GERD+CMH group showed sig increased time of esophageal acid exposure compared to primary GERD (p=0.03). **Follow-up PH**- Sig reduction in total recording time (RI) observed in GERD + CMH group after elimination diet period (primary GERD median RI 15.6, and at follow-up 10.7, p=0.05). 3 children (one from GERD+CMH) showed increased RI at challenge beyond level of day-to-day variability. **Endoscopy-** 7 had esophagitis (primary GERD 4, GERD+CMH 2).	N/A	Ronald McDonald House Charities & The Clinical Institute at University of Southern Denmark,	One child excluded due to anorexia nervosa.	An association of CMH and severe GERD was observed not only in infants but also in preschool/school children. Simultaneous food challenge and pH monitoring did not provide additional diagnostic value.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Kalach, N., Soulaines, P., De Boissieu, D., & Dupont, C. (2005)/ Ref ID: 2996	To assess the correlation and safety of ready to use APT in comparison with another APT in the evaluation of cow's milk allergy, together with its usefulness in the diagnosis of CMA as determined by open challenge	41 children with referral to outpatient clinic for FA. Mean age 34.3 months, age range 5-78 months, 18 female, 31 male. Children exhibited min of one symptom of allergy: AD (10.2%), digestive manifestations-loose stools, colic, vomiting, gastroesophageal reflux & failure to thrive (40.8%), and combined manifestations (49%). Exclusions: on exclusion diet, present with skin lesions impeding APT application, Treatment with antihistamines/ steroids for last week.	FA: Open challenge-positive result: disappearance of symptoms on elimination diet & unequivocal adverse reaction to challenge. **Immediate onset reaction:** reaction within 2 hours of challenge. **Delayed onset:** reactions after 2 hrs. Some didn't have challenge and assumed to have FA: history of severe unequivocal adverse reaction to ingestion of CM with positive IgE, SPT or both & having completely recovered with elimination diet. Cite evidence to suggest that in the absence of immediate reactions, delayed onset reactions, most of the time related to non-IgE mechanism. Conclusions state that late onset reactions were non-IgE-mediated.	**Specific IgE:** (RAST)-positive result: ≥ 0.35 KU/L. **SPT**: (fresh milk). Positive result: >3mm than control. **2 x APT:** (Finn Chamber) & ready to use (Diallertest). Occlusion time 48 hrs, read 20 mins and 24 hrs after removal (72hrs). Classified as: negative irritation, significant erythema & erythema with eczema or edema. Positive result: at 72 hrs APT exhibited stronger reaction than negative control.	**Open oral food challenge** (started in hospital for those with risk of anaphylaxis and/or positive IgE and/or SPT or at home in case of delayed symptoms and negative IgE and SPT.) Outpatient basis.	10.2% positive IgE, 2% positive SPT. **Diallertest:** APT positive in 44.8%, **Finn Chamber**: APT (comparator) positive in 26.5% at 72 hrs. **Food challenge**: Positive challenge in 60.9% (25). Of these 15 carried out at home & 4 in hospital. **Other results**: Overall 56% were delayed reactions, 16% immediate reactions, 28% history of severe reaction at enrolment. 29 children presented with eczema (either isolated or combined with digestive manifestations) and 13 had positive challenge. **Diallertest:** sensitivity 76% (CI 59.2-92.7), specificity 93.8% (81.9-100). **Finn Chamber:** sensitivity 44% (24.5-63.4), specificity 93.8% (81.9-100). Sig diff between sensitivity of two APT types (p=0.02).	**Diallertest:** PPV 95% (85.4-100), NPV 71.4% (52-90.7). Test accuracy: 82.9% (71.3-94.5). **Finn Chamber**: PPV 91.7% (76-100), NPV 51.7% (33.5-69.8). Test accuracy: 63.4% (48.6-78.1). Sig diff between test accuracy of two APT types (p=0.05).	Pharmaceutical firm DBV-Technologies	Funding from makers of Diallertest.	In conclusion, in a population of children with non IgE-mediated late onset reactions (digestive and eczematous) and with reference to open oral food challenge, the ready to use APT exhibited sig higher sensitivity (76% vs 44%) and test accuracy (82.9% vs 63.4%) in comparison to Finn Chambers APT, with both techniques exhibiting high spec & PPV and being devoid of any side effects.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Iacono, G., Carroccio, A., Cavataio, F., Montalto, D., Lorello, D., Kazmierska, I., Soresi, M., & Campo, M. (1995)/ Ref ID: 1644	To report our experience in using a new immunoenzymatic commercial kit for assaying IgG antibetalactoglobulin, in an attempt to indicate the antibody levels useful for a correct diagnosis of CMPA	301 infants referred to gastroenterology clinic suffering from predominantly GI symptoms & suspected CMPA. Median age 5 months, age range 1 month to 6 years, 180 male, 121 female. IgG also assayed on 218 healthy controls matched for age. Exclusion: breast fed infants.	CMPA: Those who had improved symptoms on elimination diet challenged after 4-6 weeks. Also given intestinal biopsy before and 24hrs after DBPCFC. **Positive result:** if same symptoms reappeared within 24 hrs of DBPCFC, if biopsy normal before and abnormal (partial atrophy & presence of eosinophils) after challenge. No specific distinction between IgE and non-IgE-mediated reactions.	**IgG anti-betalactoglobulin**: (Betalactotest) & other examinations including: **total serum & specific IgE** (RAST), **oesophageal pH-metry**, **oesophago-gastrduodenoscopy & colonoscopy**.	Intestinal **biopsy** & **DBPCFC** (in hospital)	205 with CMPA & 96 with other GI pathologies. Based on clinical presentation CMPA1 (82 with regurgitation, vomiting, retarded growth), CMPA2 (108 with diarrhoea, retarded growth, anorexia, proctitis) & CMPA3 (41 with constipation, abdominal pain, colic). **IgG test**: IgG values were sig higher in children with CMPA in comparison to those with other GI disease ($p<0.0001$) and healthy controls ($p<0.0001$). Using low cut off of 36% elicited highest diagnostic accuracy in comparison to high cut off of 48% (sensitivity 89%, specificity 85%). **Comparison of CMPA with matched GI controls**: CMPA1 low cut off (sensitivity 90%, specificity 81%) vs high cut off (sens 78%, spec 94%). CMPA2 low cut off (sens 83%, spec 93%) vs high cut off (sens 75%, spec 93%). CMPA3 low cut off (sens 96%, spec 97%) vs high cut off (sens 91%, spec 100%).	N/A	Not reported.	N/A	IgG anti-betalactoglobulin are present in all infants. The higher the cut off value of the IgG, the better the specificity of the test and the lower the sensitivity. In CMPA children, the distribution of IgG values was sig diff to healthy controls and children with other GI disease. Test value> 48% is highly specific in distinguishing between CMPA children and those with other disease with similar clinical symptoms (exception of coeliac disease).

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Ford, R.P.K., Hill, D.J., & Hosking, C.S. (1983)/ Ref ID: 2177	To present data supporting the concept that there are important differences in the clinical patterns of cow's milk hypersensitivity	72 children with CM hypersensitivity (predominantly GI manifestations). Mean age 18 months, age range 3 months to 10 years 7 months, followed up for periods between 3 months and 4 yrs. Children with cutaneous reactions (angioedema, rash, urticaria, eczema) predominantly immediate onset (46%) (p=0.0001) & those with GI symptoms (vomiting, diarrhoea, colic, abdominal pain) had mainly delayed onset reactions (54%) (p=0.008).	Elimination diet for min of 1 week (usually 4 weeks) prior to challenge. DBPCFC: first single blind in hospital. **Positive result:** severe symptoms on single blind challenge, severe symptoms during DBPCFC, min 2 symptoms over and above those on placebo days. Open challenge: observation for ≥4 hrs. If no or mild symptoms sent home with increasing amounts to be taken at home. Symptoms recorded in diary. Continued for 4 weeks or until symptoms developed. Both definite and probable hypersensitivity considered to have milk hypersensitivity. **Immediate symptoms:** within 1 hr of ingestion, **delayed symptoms**: after 1 hr. Conclude that evidence suggests that immediate onset reactions mediated by IgE as these children had SPT+ & RAST responses indicating specific IgE sensitisation. Delayed onset group did not	**SPT**: (Bencard allergens). Positive result: ≥3mm.	**DBPCFC or open challenge** (both started in hospital)	Those with delayed symptoms less likely to have pos milk SPT (p=0.0001) and pos milk RAST (p=0.017) in comparison to those with immediate reactions. Those with positive SPT (40%) usually had cutaneous symptoms (p=0.002) while negative SPT usually had GI symptoms (p=0.006), less likely to have positive milk RAST (p=0.0001) & raised IgE (p=0.023) in comparison to positive SPT. Positive correlation between time of onset of clinical reaction and result of milk prick test (r=0.28, p=0.011 when controlled for GI symptoms, cutaneous symptoms & atopy).	N/A	National Health and Medical Council (Australia) and Canterbury Medical Research Foundation (New Zealand).	N/A	Found immediate onset reactions and delayed onset reactions. The latter occurring after 1 hr, usually with GI symptoms and negative prick tests. They had correspondingly negative RAST results to milk.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Fogg, M.I., Brown-Whitehorn, T.A., Pawlowski, N.A., & Spergel, J.M. (2006)/ Ref ID: 506	To determine whether the APT is able to predict the results of the OFC in children with suspected food protein-induced enterocolitis syndrome (FPIES)	19 children with suspected FPIES. Mean age 15.6 months, age range 5-30 months, 10 male, 9 female. 2 children had atopic dermatitis (AD). Exclusion: evidence of IgE-mediated reaction (pos SPT), presence of skin disorders other than AD, severe diffuse AD with no surface area for APT, use of oral immunosuppressant medicines that may affect results, use of oral medicines that may affect interpretation of challenge (e.g. antimotility agents, anti-inflammatory medicines & β-blockers.)	Suspected FPIES based on clinical criteria proposed by Sicherer (2000). FPIES: Confirmed using non-blinded food challenge. Elimination diet of foods positive in APT. Observed 4 hrs-those tolerated in hospital sent home with food reintroduction plan. **Negative result**: If no symptoms on reintroduction. **Positive result:** If GI symptoms with no other cause developed during reintroduction. Telephone follow-up performed to ascertain results of follow-up. Assumption that FPIES is non-IgE-mediated and SPT or in vitro tests for specific IgE not useful as they are negative. Confirmed diagnosis based on challenge results.	**APT**: (Finn Chambers-removed 48 hrs, read 72 hrs). Results: + erythema, ++ erythema & papules, +++ erythema & vesicles.	**Non-blinded oral food challenge** (in allergy clinic).	Sensitivity= 100%, specificity= 71%.	PPV=75%, NPV=100%	Not reported.	APT not standardised test. As FPIES usually outgrown before 36 months, it's likely that several children lost reactivity to suspected food in interval between onset of disease and study. No follow-up.	We will recommend APT for children who have a suggestive clinical history for FPIES. If APT is negative, an oral food challenge will be performed as there is strong possibility that the child is either not sensitive to food or has outgrown sensitivity, this is supported by NPV of 100% in this study. If APT is positive, challenge will be delayed until 1 yr after most recent reaction.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Zapatero Remon, L., Alonso Lebrero, E., Martin, Fernandez, E., & Martinez Molero, M.I. (2005)/ Ref ID: 595	To study 14 infants with FPIES due to fish protein and report the clinical characteristics of these children and their clinical course	14 children referred for GI symptoms following ingestion of fish. Age range 9-12 months, 6 males, 8 females.	FPIES: based on clinical criteria and in 9 children on oral food challenge. Challenge involved observation for 3 hours. State that FPIES is form of cell-mediated, non-IgE associated food hypersensitivity.	**SPT**-positive result: ≥3mm greater than control. **APT** (Curatest)-occlusion 48 hrs, read 30mins after removal & after 96 hrs. **Serum specific IgE:** (CAP System)-positive result ≥0.35KU/L.	**Open oral food challenge** (referred to allergy clinic).	SPT with commercial extracts to fish and prick-prick with boiled fish negative in all cases. **IgE**: negative in all but one case (positive to hake). **APT**: positive in 3/8. **Oral challenges:** performed in 9 and all positive. Remaining 5 didn't undergo challenge as they referred various evocative episodes of FPIES. **Follow-up:** After elimination diet of 3-4 yrs, undertook follow-up FC. 4 became tolerant, 3 tolerate one single fish, 5 continue elimination diets, 2 had positive rechallenge so continue diet.	N/A	Not reported.	APT not done in all children.	Our report confirms previous observations that measurements of food allergen specific IgE antibodies (SPT or serum levels) are typically negative.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Fiocchi, A., Besana, R., Ryden, A.C., Terracciano, L., Andreotti, M., Arrigoni, S., & Martelli, A. (2004). Ref ID: 737	To evaluate a blood test, Phadiatop Infant, for differentiating the capability of IgE-mediated disease in young children with recurrent wheezing, eczema, or both/ cross sectional.	147 children with recurrent wheezing, eczema or both referred for allergy evaluation by primary care physician. Mean age 2 years, 68% male. Results presented by age groups: <2yrs, ≥2yrs & all ages.	Clinical evaluation made by single allergist at each centre. **Preliminary diagnosis:** IgE-mediated symptoms, no such symptoms or inconclusive diagnosis (no clear relationship with allergic reactions). This was based on case history & physical examination. **Final diagnosis:** IgE-mediated, Non-IgE-mediated or inconclusive (discrepancies among case history, SPT and specific IgE). This was based on preliminary diagnosis and additional SPT & specific IgE. Children with positive IgE and final diagnosis of non-IgE-mediated disease were recalled after 2yrs for re-evaluation of allergic status. Diagnoses differentiated between IgE and non-IgE allergies but not clear how these were diagnosed.	**Skin prick test:** (10 food allergen extracts-cow's milk, α-lactalbumin, casein, egg white, egg yolk, peanut, wheat, cod, soy, tomato). Positive result: ≥3mm. **Specific IgE:** (Pharmacia CAP). Positive result: ≥0.35kU/L.	**Final diagnosis** by allergist (2 allergy centres).	**Preliminary diagnosis:** IgE-mediated allergy (31), not IgE-mediated (40), inconclusive (76). **Final diagnosis**: IgE-mediated (61), not IgE-mediated (78), inconclusive (8). **Symptom distribution:** Overall more children with wheezing (58% vs 39.1%), and eczema (50.7% vs 43.5%) in non-IgE than IgE group. **Sensitivity**: 92% (CI 82-97%), **specificity:** 82% (CI 72-90%). Similar results for children <2yrs, 2-4yrs and for children with wheezing and eczema separately. **Follow-up:** 13/14 diagnosed as non-IgE allergy with positive specific IgE re-evaluated after 2 yrs. 12/13 diagnosed as having IgE-mediated disease (specific IgE antibodies to 1 or several allergens). Positive Phadiatop Infant result accurate in predicting IgE allergy in 92%. One persistently evaluated as being non-allergic.	**PPV:** 80% (CI 69-97%), **NPV:** 93% (CI 84-98%)	Pharmacia Diagnostics AB (makers of Phadiatop Infant)	Food challenge not completed & ref used was allergist's final diagnosis. Limited info on how IgE and non-IgE diagnoses were reached. No statistical calculations for symptoms and triggering factors between IgE and non-IgE allergy.	This study supports the use of Phadiatop Infant in a primary care setting to identify candidates most likely to benefit from referral to an allergist. Furthermore, a positive test result could predict the development of IgE-mediated allergic disease.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Niggeman, B., Reibel, S., & Wahn, U. (2000)/ Ref ID: 3684	To evaluate the diagnostic value of the APT with regard to late phase reactions observed in DBPCFC's with cow's milk, hen's egg, wheat and soybean/	75 children with suspected FA. 34 female, 41 male, median age 2.1 yrs, age range 4 months to 12.5 years. 69 had AD. Total of 209 oral challenges performed on 75 children (54 CM, 41 HE, 23 wheat, 15 soybean).	AD: Diagnosed according to criteria by Sampson (1990) & Seymor et al (1987). Severity assessed according to SCORAD index. FA: DBPCFC-observed up to 48 hrs. **Positive result:** if objective clinical reaction observed such as urticaria, angioedema, wheezing, vomiting, diarrhoea, abdominal pain or exacerbation of eczema. **Early reaction:** symptoms appeared within 2 hrs of highest dose. **Late reaction:** symptoms occurred >2hrs. Acknowledge that immediate reactions can be easily identified and hypothesize that APT may have high predictive capacity for late phase reactions. In their findings they state that T-cells play an important role in AD & FA and this is supported by findings of study.	**SPT**-reactions read at 15 mins, positive result: ≥3mm & no reaction to control. **APT** (Finn Chambers) occlusion time 48hrs, results read 20min & 24 hrs after removal (72hrs). + erythema and slight infiltration, ++ erythema and papules, +++ erythema and vesicles. **Specific IgE**: (FEIA) positive result: ≥0.35 kU/l.	**DBPCFC** (as inpatient).	58% (77/133) of challenges and 2.6% (2/76) placebo were positive. Of 77 positive reactions, 66% with HE, 65% with CM, 48% with wheat, 27% with soybean. 51% showed early clinical reactions while 27% showed late reactions. 22% had combined early and late reactions. All late reactions were exacerbation of eczema & combined reactions included eczematous reactions. **Sensitivity for early reactions:** IgE 95%, SPT 95%, APT 33%. **Specificity for early reactions**: IgE 29%, SPT 70%, APT 95%. **Sensitivity for late reactions:** IgE 71%, SPT 58%, APT 76%. **Specificity for late reactions**: IgE 29%, SPT 70%, APT 95%.	**PPV for early reactions**: IgE 62%, SPT 69%, APT 81%. **NPV for early reactions**: IgE 59%, SPT 95%, APT 67%. **PPV for late reactions:** IgE 37%, SPT 41%, APT 81%. **NPV for late reactions**: IgE 72%, SPT 81%, APT 93%.	Not reported.	N/A	APT seems to be a valuable additional tool in the diagnostic work up of FA in children with AD, especially with regard to late phase reactions. At this time, a positive APT does not make challenge superfluous.

Ref ID	Study aim/ Study type	No of participants/ characteristics	Diagnosis	Type of Test	Reference Standard	Sensitivity and Specificity/ /Modified	PPV or NPV or Modified	Source of Funding	Additional comments	Author's Conclusions
Verini, M., Di Pillo, S., Spagnuolo, A., Cingolanio, A, Consilvio, N.P., Chiarelli, F. (2007)/ Ref ID: 2585	To assess the role of APT in evaluating the correlation with age of allergic sensitisation IgE and non IgE-mediated, against main respiratory, food and contact allergens in children with AD/ cross-sectional.	135 (and 10 controls) outpatients with AD without respiratory symptoms. 79 males, 56 females, mean age 3.7 yrs, age range 1-15 years. Age groups: 1) < 2yrs (50 children). 2) 2-5yrs (40). 3) >5 yrs (45). None of controls showed positive APT.	AD: Diagnosed according to criteria by Hanifin & Rajka. FA: Assessed by SPT, serum specific IgE & APT. **IgE sensitisation**: positive SPT and/or IgE. **Non-IgE sensitisation:** positive APT alone. Differentiate between IgE and non-IgE by test results of SPT, APT and/or serum specific IgE.	**SPT:** (allergen's extract), **specific IgE:** (ImmunoCAP FEIA) positive result: >0.70 KU/L. **APT:** (Curatest) applied for 48 hrs, evaluation after 48 and 72 hrs.	N/A	Overall sensitisation to food allergens 48%. Food allergen sensitisation (SPT, IgE & APT) found in 25.9% for hen's egg protein, 19.9% milk, 18.5% wheat, 14% codfish & 6.8% tomato. **Non-IgE sensitisation:** (APT positive only) found 7.4% for egg, 8.1% milk, 4.4% wheat, 5.2% codfish & 6% tomato. AD improved following elimination diet. **Age specific analyses:** Prevalence of positive food allergen test <2 yrs (64%), 2-5 yrs (50%), >5yrs (26%). Significantly more positive food allergen tests were found in <2's in comparison to 2-5yr age group (p=0.04) and significantly more positive results in 2-5yr group when compared to >5's (p=0.001). Positive APT results found <2 (58%), 2-5yrs (50%), >5yrs (35%). Significantly more positive APTs were found in 2-5yr group compared with >5's (p=0.05).	N/A	Not reported.	No challenge used to confirm FA.	Study showed a higher prevalence of FA in younger groups and of respiratory allergy in older ones. The APT may be helpful in evaluating allergic sensitisation in those children affected with AD with negative SPT and IgE, mainly in children <5 years of age.

Appendix 1.3.3

Clinical Question 3

Which diagnostic tools and strategy are most appropriate and accurate to diagnose IgE-mediated food allergy in children?

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Vierrucci et al 1989. (Ref ID: 4324)	To report experience in diagnosing food allergy in children with AD/ Italy	Egg, milk, peanut, tomato	112 children with AD. Age range 0-5 yrs (median age 4.6 yrs).	**SPT:** positive result ≥3mm than control. **Total IgE:** Using PRIST **Specific IgE:** Using RAST	DBPCFC (59 challenges performed in 35 children on the basis of positive SPT and/or suggestive history of food allergy)	**Sensitivity**: SPT (milk=28%, egg= 100%, tomato=100%, peanut=100%). RAST (milk=35%, egg=62%, tomato=14%, peanut=25%). **Specificity**: SPT (milk=80%, egg=25%, tomato=66%, peanut= 50%). RAST (milk=77%, egg=33%, tomato=50%, peanut=100%).	**PPV:** SPT (milk=66%, egg=60%, tomato=40%, peanut= 83%). RAST (milk=71%, egg=71%, tomato=33%, peanut= 33%). **NPV**: SPT (milk=44%, egg=75%, tomato= 100%, peanut= 50%). RAST (milk=50%, egg=50%, tomato=25%, peanut= 25%).	Italian Consiglio Nazionale delle Ricerche.	

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Niggemann et al 2002. (Ref ID: 1009)	To compare the use of smaller chambers for APT in young children/ Germany.	Cow's milk, hen's egg, wheat, soy	30 children with AD. 17 boys, 13 girls. Age range=3 to 58 months, median=13 months. No other details reported.	**APT:** Using Finn Chambers 12mm and 6mm. **SPT:** Positive reaction ≥3mm without reaction of the negative control.	DBPCFC (55 challenges performed in 30 children)	**Sensitivity:** APT 12mm (CM=60%, HE=71%, soy=100%, wheat=100%). APT 6mm (CM=0, HE=29%, soy=0, wheat=0). SPT (CM=90%, HE=86%, soy=50%, wheat=67%). **Specificity:** APT 12mm (CM=100%, HE=100%, soy= 100%, wheat=89%). APT 6mm (CM=100%, HE= 100%, soy= 100%, wheat=100%). SPT (CM=82%, HE=75%, soy=100%, wheat= 89%).	**PPV:** APT 12mm (CM=100%, HE=100%, soy=100%, wheat=75%). APT 6mm (CM= 0, HE=100%, soy=0, wheat= 0). SPT (CM=82%, HE=86%, soy=100%, wheat=67%). **NPV:** APT 12mm (CM=73%, HE=67%, soy=100%, wheat= 100%). APT 6mm (CM=52%, HE=44%, soy=82%, wheat=75%). SPT (CM=90%, HE=75%, soy=90%, wheat=89%).	Not reported.	Not reported whether all children underwent all testing.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Dieguez et al 2008. (Ref ID: 2629)	To estimate the diagnostic accuracy of the SPT with egg allergens in children with IgE-mediated cow's milk allergy in first known egg exposure/ Spain.	Egg white, OVM	104 milk allergic children who came to the allergy department at Madrid hospital. Milk allergy included those with anaphylactic reaction, clinical history of recent IgE-mediated reaction to milk, both with positive SPT and/or positive specific IgE, although milk oral food challenge was not performed. 54.8% male. 30.4% had at least one atopic parent, 59.4% with AD, 16.3% with asthma. Children given SPT with egg between age of 12 and 15 months old.	**SPT:** Positive reaction ≥3mm	Egg challenge test (all patients received challenge test regardless of SPT results.)	Values recorded are using SPT cut off 3mm. **Sensitivity:** Egg white =94.6%, OVM=66.7%. **Specificity:** Egg white =40%, OVM=85.3%. Values recorded are using optimal decision point (6mm for egg white & 5mm for OVM). **Sensitivity:** Egg white= 81.1%, OVM =58.3%. **Specificity:** Egg white= 72.5%, OVM =97.1%. Author's also recorded ROC curves, AUC & calculated **optimal cut off points** (calculated as maximum sum of sensitivity and specificity): Egg white (AUC=0.83, optimal decision point (odp)=6mm). Yolk (AUC=0.73, odp= 3mm). OVA (AUC=0.55, odp= 3mm). OVM (AUC=0.82, odp= 5mm). OVT (AUC=0.55). Lisozime (AUC=0.60)	Values recorded are using SPT cut off 3mm. **PPV:** Egg white= 59.3%, OVM =82.7%. **NPV:** Egg white= 88.9%, OVM =70.7%. Values recorded are using SPT cut off optimal decision point (6mm for egg white & 5mm for OVM) . **PPV:** Egg white= 73.2%, OVM =95.4%. **NPV:** Egg white= 80.6%, OVM =69.4%.	Sociedad de Pediatria de Madrid y Castilla La Mancha.	

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Saarinen et al 2001. (Ref ID:4951)	To study the usefulness of the SPT, patch test, IgE and eosinophil cationic protein (ECP) in serum as diagnostic tools for CMA/ Finland.	Cow's milk	239 full-term newborn infants with suspected CMA. Mean age of those with positive challenge=6.7 months & mean age of 7.1 months in children with negative challenge.	**SPT, Specific IgE:** Using Cap system. Also measured ECP but results not reported in evidence table. **Patch test:** Using Finn Chamber. Occlusion time=48 hrs with results read 48hrs after removal of cups. Positive result involved marked erythema and erythema with induration.	Open challenge (performed at out-patient clinic in all children).	All values based on SPT cut off ≥3mm, 0.35kU/L for IgE and patch test positive for whole CM and/or CM protein fractions. **Sensitivity:** SPT=61%, IgE=72%, patch test=43%. **Specificity:** SPT=76%, IgE=49%, patch test=72%.	All Values based on SPT cut off ≥3mm, 0.35kU/L for IgE and patch test positive for whole CM and/or CM protein fractions. **PPV:** SPT=71%, IgE=58%, patch test=60%. **NPV:** SPT=67%, IgE=64%, patch test=57%.	Research Fund of Helsinki University Central Hospital, the Finnish Society of Allergology and Immunology, the Finnish Foundation for Allergy Research and the Sigrid Juselius Foundation.	Also reported sensitivity, specificity, PPV & NPV values for SPT thresholds 6 & 8mm, IgE cut off values of 0.7 & 3.5 kU/L, Patch test using whole milk and CM protein fractions separately & values based on symptoms. These are not reported in the evidence table. Also provide values for combined accuracy of all 4 tests using different cut-offs but not included as this also includes ECP.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Caffarelli et al 1995. (Ref ID: 1682)	To investigate the relationship between egg specific IgE and positive SPT and/or RAST which had never previously been ingested/ Italy.	Egg	33 children with food allergy who had never previously ingested egg or egg-containing products. **Patient group:** 21 children (age range 5 months-3yrs 5months) with positive SPT reaction and/or sIgE to egg. **Control group:** 12 patients (age range 11 months-4 yrs 9months) with negative SPT and sIgE reactions to egg.	**SPT:** Positive result ≥3mm after the diameter of the wheal elicited by diluents was subtracted. **Specific IgE (RAST):** Using RAST. Results graded 0 to 4 in accordance with manufacturer's instructions.	DBPCFC (performed in allergy unit and was carried out in all children).	**Sensitivity:** SPT= 92%, RAST=85%, SPT & RAST=92%. **Specificity:** SPT= 57%, RAST=68%, SPT & RAST=57%. There was no significant difference between results of SPT and RAST or SPT plus RAST, in predicting challenge results correctly.	**PPV:** SPT= 61%, RAST=66%, SPT & RAST=61%. **NPV:** SPT= 91%, RAST=86%, SPT & RAST=91%.	Not reported.	Symptoms were separated into immediate and late onset reactions.
Fiocchi et al 2002. (Ref ID: 4936)	To present data about the test performance of beef extracts used in SPT among children with AD reporting immediate hypersensitivity to beef/ Italy.	Beef	34 children with AD and IgE-mediated sensitisation to foods. Age ranged from 1.00-4.41 years (median=2.26 years).	**SPT:** Used commercial (cSPT) and fresh foods (ffSPT). Positive result ≥3.01mm	DBPCFC (all children were tested. 20 children were positive and 14 negative & underwent SPT using commercial and fresh).	**Sensitivity:** cSPT=90%, ffSPT=100%. **Specificity**: cSPT=100%, ffSPT=78.57%.	Authors did not report predictive values. 2 x 2 table calculated: **PPV:** cSPT=100%, ffSPT=87%. **NPV**: cSPT=88%, ffSPT=100%.	Not reported.	Authors did not report predictive values.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Cudowska & Kaczmarski 2005. (Ref ID: 599)	To evaluate the diagnostic accuracy of APT in the detection of food allergy in correlation with SPT, sIgE & positive oral food challenge to milk/ Poland.	Milk	34 children with AD referred to department of paediatrics for evaluation of atopic eczema dermatitis syndrome (AEDS) suspected of food hypersensitivity. Age ranged from 5 months to 16 years. Children divided into 2 age-groups: A) 20 children < 3 years old & B) 14 children >3 years old. 35 boys and 9 girls.	**SPT:** Positive result ≥3mm without reaction of negative control. **APT:** Using Finn Chambers (8mm for children < 3 years & 12mm for children > 3 years). **Total and specific IgE:** Using UniCAP. Detection limit of CAP system is 0.35 kU/L. Positive sIgE result ≥0.7 kU/L.	Oral food challenge (started in hospital and continued in patient's home. Immediate onset reactions defined as those within 2 hours after last dose. Done in all children. Open challenge used in children < 1 year & blinded in older children).	Values based on SPT and sIgE for immediate onset reactions in group A and APT in patients with delayed onset reactions in group A and B. **Sensitivity:** SPT/sIgE group A=100%, APT (group A=80%, group B=80%). **Specificity:** SPT/sIgE group A=94%, APT (group A=70%, group B=89%). Values based on combined SPT, APT and sIgE. **Sensitivity:** Group A=92%, group B=80%. **Specificity:** Group A=71%, Group B=89%.	Values based on immediate & delayed onset reactions **PPV:** SPT/sIgE group A=75%, APT (group A=73%, group B=80%). **NPV:** SPT/sIgE group A=0%, APT (group A=22%, group B=11%). Values based on combined SPT, APT and sIgE. **PPV:** Group A=85%, group B=80%. **NPV:** Group A=17%, Group B=11%.	Not reported.	Also tested other food allergens but sensitivity/ specificity values only reported for milk. Also reported likelihood ratios but these are not reported in evidence table.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Hill et al 2004. (Ref ID: 3153)	To present the results of studies on the diagnostic value of SPT and food specific IgE/ Australia.	Cow's milk, egg, peanut	Prospective study of 467 children referred from high risk population for investigation of food allergy. Median age= 3 years.	SPT	Oral food challenge (555 challenges performed in 467 children-classified as positive, negative or inconclusive)	Authors present diagnostic accuracy of age specific SPT wheal in children. Data presented are for SPT threshold 3mm. **Sensitivity for children ≥2 years:** CM =79%, egg =87%, & peanut=95%. **Sensitivity for children <2 years:** CM =58%, egg =79%, & peanut=100%. **Specificity for children ≥2 years:** CM =73%, egg =67%, & peanut=72%. **Specificity for children <2 years:** CM =91%, egg =75%, & peanut=67%. Authors also report 100% diagnostic SPT cut off levels (levels representing 100% specificity). **For children ≥2 years:** CM ≥8mm, egg≥7mm, peanut≥8mm. **For children <2 years:** CM ≥6mm, egg≥5mm, peanut≥4mm.	Data presented are for SPT threshold 3mm. **PPV ≥2 years:** CM =75%, egg =93%, & peanut=91% **PPV <2 years:** CM =79%, egg =92%, & peanut=94% . **NPV ≥2 years:** CM =77%, egg =50%, & peanut=81% . **NPV <2 years:** CM =78%, egg =50%, & peanut=100 %.	Not reported.	Also report sensitivity, specificity, PPV & NPV values for SPT wheal diameter 0mm, ≥6mm, ≥8mm (for CM and peanut) and 0mm, ≥6mm, ≥7mm for egg- these are not reported in evidence table.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Hansen et al 2004. (Ref ID:752)	To determine whether SAFT or APT could increase the diagnostic accuracy in detecting egg allergy/ Denmark	Hen's egg (undiluted fresh whole egg extract used in SPT & SAFT. APT used 100%, 50% & 25% dilution).	**Allergy group**: 10 clinically egg-allergic children (all but 4 tested by challenge) with AD. Age range 10 months-8.4yrs (mean 3.4yrs). **Control group:** 10 egg-tolerant children without AD. Age range 3.6-10.5 yrs (mean 5.8yrs). All tests performed serially in all children (APT, SPT & SAFT).	**SPT:** Positive result ≥3mm than neg control. **SAFT (Skin Application Food Test):** (12mm Finn Chambers). 1=no reaction, 2= erythema, 3=erythema & oedema within chamber, 4=erythema & oedema also outside chamber. Positive result ≥3. **APT:** (12mm Finn Chambers). Positive, doubtful or negative result. Doubtful reaction (mild erythema with no infiltration) regarded as negative.	DBPCFC or OFC (those in allergy group had previous result 2-24 months prior to study).	All values based on SAFT cut-off of ≥3 at 15mins (erythema= negative) and when APT was doubtful it was classified as a negative result. APT used 50% dilutions interpreted after 72 hours. **Sensitivity:** SPT=100%, SAFT =40% & APT=60%. **Specificity**: SPT=85%, SAFT=100% & APT= 95%. **Reproducibility of tests**:1 reacted to negative control in APT, 6 discordant results in duplicate application seen among children concerning SAFT & 4 in APT.	**PPV:** SPT=77%, SAFT=100% & APT=75%. **NPV:** SPT=100%, SAFT=86% & APT=90%.	Not reported.	Results were also reported for SAFT cut-off ≥2 and when a doubtful APT result was classified as a positive result- these are not reported in the evidence table. Results also available for SAFT (30mins) & APT (concentration 25 & 100% at 48 & 72hrs).

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Sampson 1998. (Ref ID:3817)	To evaluate the predictive values of food-specific IgE/ USA	Egg, milk, peanut, soy, wheat & fish.	200 children with AD and sometimes other symptoms (asthma, allergic rhinitis). No other details reported.	**Skin test (ST):** (positive result ≥ 3mm) & **Specific IgE:** (CAP FEIA). Positive result ≥0.35 kU/l	DBPCFC or convincing history of anaphylaxis.	**Sensitivity:** Skin Test (egg=98%, milk=96%, peanut=90%, soy=76%, wheat=90%, fish=90%). IgE (egg= 98%, milk=100%, peanut= 97%, soy= 94%, wheat=96%, fish= 94%). **Specificity:** Skin Test (egg= 53%, milk=51%, peanut= 29%, soy=47%, wheat= 51%, fish= 57%). IgE (egg= 45%, milk=30%, peanut= 38%, soy= 25%, wheat=20%, fish= 65%). **Cut-off values** (determined by calculating the 95% predictive values):Egg 6 kU/l, milk 32 kU/l, peanut 15 kU/l, fish 20 kU/l, soy 65 kU/l, wheat 100 kU/l.	All values based on prevalence of FA as 100%. **PPV:** ST (egg= 85%, milk= 66%, peanut= 55%, soy= 35%, wheat=35%, fish=77%). IgE (egg= 84%, milk=57%, peanut=78% , soy=21%, wheat=14%, fish=49%). **NPV:** ST (egg=90%, milk=93%, peanut=75% , soy=84%, wheat=94%, fish=80%). IgE (egg= 88%, milk= 100%, peanut=85% , soy=95%, wheat=97%, fish=97%).	Not reported.	Results were also reported for PPV and NPV values based on FA prevalence of 10% which reflect the situation of a normalised population in which only 10% presented with true food allergy- however these figures are not reported in the evidence table.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Eigenmann &Sampson 1998. (Ref ID: 3821)	To compare different SPT recording methods with the outcome of the oral food challenge/	Egg, milk, peanut, soy, wheat	250 children with AD with suspected IgE-mediated allergies were admitted to the Clinical Research Center for evaluation of food allergy. No details of participants given as characteristics have been previously described.	**SPT:** 2 techniques used to measure wheal size (mean diameter & electronic scanner).	DBPCFC or convincing history of recent anaphylactic reaction (all negative results confirmed by feeding food openly in usual proportion under observation.)	All values reported using ≥3mm as positive SPT result. **Sensitivity:** Egg=100%, milk=94%, peanut= 80%, soy=60%, wheat=81%. **Specificity:** Egg=61%, milk=46%, peanut=47%, soy= 53%, wheat=64%.	**PPV:** Egg=85%, milk=69%, peanut=61% , soy=55%, wheat=68%. **NPV:** Egg= 100%, milk=86%, peanut=69% , soy=58%, wheat=78%.	Swiss National Research Foundation, the Eugenio Litta Foundation, National Institutes of Allergy and Infectious Diseases, the Division of Research Resources, National Institutes of Health.	Reported values for 2 different techniques used to measure SPT wheal but results reported in evidence table relate to wheal by diameter ≥3mm (most commonly used method).

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Rance et al 2002. (Ref ID:4944)	To develop a new strategy combining SPT's and specific IgE for diagnosing peanut allergy, while reducing the need for DBPCFC's/ France	Peanut	363 children with suspected food hypersensitivity. Median age 4 years (range 0.1-15.9 years) & 67.5% had family history of atopic disease. They were later categorised as allergic (age range=1.0-15yrs, median age=4.4yrs) or non-allergic (age range=0.1-15.9yrs, median=3.7yrs) depending on results of challenge.	**SPT:** using commercial & fresh extracts. Positive result ≥3mm than neg control & at least 50% greater than positive control. **Specific IgE:** using CAP FEIA. Positive result ≥0.35 kU/L.	DBPCFC (performed in all children)	All values reported using SPT cut off ≥3mm & IgE ≥0.35 **Sensitivity:** SPT= 100% (CI 97.9-100), IgE=96.6% (CI 92.7-99.0). **Specificity:** SPT=66.1% (CI 58.8-72.9), IgE=62.4% (CI 55.0-69.3). Authors also present **ROC curve analysis:** IgE threshold ≥57kU/L resulted in 100% specificity and PPV. The SPT thresholds required to exclude false negative and false positive results were 3 and 16mm respectively. **AUC:** Raw extract= 0.90, commercial extract =0.79.	**PPV:** SPT=73.7% (CI 67.7-79.2), IgE=71.0% (CI 64.8-76.6). **NPV:** SPT=100% (CI 97.5-100), IgE=95.1% (CI 89.6-98.2)	Not reported.	Based on ROC curve analysis diagnostic accuracy values were also reported for SPT cut off ≥16mm and specific IgE≥ 57kU/L & combined use (positive diagnosis if at least one of the 2 tests was positive-i.e. SPT≥16mm or specific IgE≥ 57) but these are not reported in evidence table.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Roehr et al 2001 (Ref ID: 3674)	To evaluate whether a combination of allergologic tests could improve the prognostic value of the individual tests for positive food challenge results/ Germany	Cow's milk (CM), hen's egg (HE), wheat, soy	98 children with AD with suspected food allergy who were admitted to author's wards. 51 boys, 47 girls with age range 2 months-11.2 years (median age=13 months). 61 had mild AD, 27 moderate AD & 10 with severe AD.	**SPT:** Using fresh foods. Positive reaction ≥3mm without reaction of negative control. **APT:** Using Finn Chambers. Positive result if erythema with infiltration occurred. Results read at 48hrs & 72hrs. **Specific IgE:** Using CAP FEIA.	DBPCFC .All children had DBPCFC, SPT, APT and IgE. (173 challenges were conducted in 98 children).	Values for performance of single tests APT, SPT and specific IgE. **Sensitivity:** IgE (CM=84%, HE=96%, wheat=67%, soy=75%). SPT (CM=78%, HE=89%, wheat=67%, soy=50%). APT (CM=47%, HE=57%, wheat=89%, soy=75%). **Specificity:** IgE (CM=38%, HE=36%, wheat=47%, soy=52%). SPT (CM=69%, HE=57%, wheat=53%, soy=90%). APT (CM=96%, HE=93%, wheat=94%, APT=86%). Authors also reported sensitivity and specificity values for different combinations of tests. A=IgE & SPT, B=APT & IgE, C=APT & SPT, D=APT & SPT & IgE.	**PPV:** IgE (CM=70%, HE=75%, wheat=57%, soy=23%). SPT (CM=81%, HE=81%, wheat=60%, soy=50%). APT (CM=95%, HE=94%, wheat=94%, soy=50%). **NPV:** IgE (CM=59%, HE=83%, wheat=57%, soy=92%). SPT (CM=64%, HE=73%, wheat=60%, soy=90%). APT (CM=51%, HE=52%, wheat=89%, soy=95%).	Not reported.	Also reported sensitivity, specificity, PPV & NPV values for different combinations of tests and late and early phase reactions which are not reported in evidence table.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Celik-Bilgili et al 2005. (Ref ID: 692)	To evaluate the role of specific IgE in predicting the outcome of oral food challenges and to determine threshold concentrations that could render DBPCFC unnecessary/ Germany	Cow's milk, hen's egg, soy, wheat	501 children who were admitted to the author's ward with suspicion of food related symptoms. Age range=1 month-16.1 years (median=13 months). 60% boys and 88% with AD. 204 with mild AD, 116 with moderate AD, 56 with severe AD & 64 with no clinical symptoms of AD at time of challenge.	**Specific IgE:** using CAP FEIA. Positive result ≥0.35 kU/L.	Challenge (728 DBPCFC, 264 open challenges in children <1 year and history of immediate type reactions. All children were challenged & given IgE). 992 challenges performed in 501 children.	**Sensitivity of IgE for food challenge:** CM=83%, HE=97%, wheat=79%, soy= 69%. **Specificity of IgE for food challenge:** CM=53%, HE=51%, wheat= 38%, soy=50%. Also used logistic regression model proposed by Sampson to calculate **predicted probabilities** for showing a positive oral food challenge at a given specific IgE value. **For children <1 yr:** CM (90% cut off=25.8kU/L), HE (90%=4.2, 95%=10.9, 99%=88.6kU/L) & no calculated values for wheat or soy. **For children <1 yr:** HE (90%=6.7, 95%=13.2, 99%=58.2kU/L) & no calculated values for CM, wheat or soy.	**PPV:** CM=63%, HE=80%, wheat=41%, soy=22%. **NPV:** CM=76%, HE=89%, wheat=77%, soy=88%.	Not reported.	Authors also presented ROC curves which showed a tendency towards a relationship between specific IgE values and percentages of positive challenges. In the case of CM and HE, challenges were positive from CAP >50.0kU/L. For wheat and soy there was no clear relationship.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Breuer et al 2004. (Ref ID: 803)	To investigate the importance of food for the induction of late eczematous reactions in children with AD and to correlate the clinical outcome to the results of specific IgE determinations and APTs/ Germany.	Cow's milk, hen's egg, wheat, soy	64 children aged 1-10 years (median 2 yrs) with mild-severe AD who visited the Department of Dermatology as outpatients. APT was performed in 41/64 children-23 had eczematous lesions on their back or refused.	**Total and specific IgE:** Using CAP RAST FEIA. Positive result ≥0.35 kU/L. **APT:** Using 12mm Finn Chambers. Positive result if erythema occurred with infiltration. Erythema without infiltration was considered irritative reaction.	DBPCFC (performed in all children).	Values based on type of reaction: **Sensitivity:** Any reaction (specific IgE=76%, APT=70%). Immediate reactions (IgE=77%, APT= 67%). Eczematous reactions (IgE=68%, APT=67%). **Specificity**: Any reaction (IgE=63%, APT=41%). Immediate reactions (IgE=60%, APT= 38%). Eczematous reactions (IgE=50%, APT =38%. Values based on age: **Sensitivity**: <2 yrs= 86%, ≥2yrs=70%. **Specificity**: <2 yrs= 74%, ≥2yrs=57%.	Values based on type of reaction: **PPV**: Any reaction (IgE=64%, APT=45%). Immediate reactions (IgE=57%, APT= 38%). Eczematous reactions (IgE=33%, APT=24%). **NPV:** Any reaction (IgE=75%, APT=67%). Immediate reactions (IgE=79%, APT= 67%). Eczematous reactions (IgE=81%, APT =79%. Values based on age: **PPV:** <2 yrs= 75%, ≥2yrs=56%. **NPV:** <2 yrs= 95%, ≥2yrs=71%.	Not reported.	Authors don't provide sensitivity, specificity, PPV or NPV values based on foods tested.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Dieguez et al 2009. (Ref ID:2480)	To assess the accuracy of a SPT and specific IgE to egg allergens in order to determine persistent egg allergy in IgE-mediated allergic children/ Spain.	Egg (white, yolk, OVA, lysozyme, OVM, OVT.)	157 children aged 1-16 years (median age= 2.5yrs). 66.9% of children diagnosed with AD, 19.7% had allergic rhinitis or asthma, 22.9% had non-allergic asthma. 63.6% had other food allergies confirmed by positive SPT, positive IgE & when necessary oral challenge). 61% were male.	**SPT:** Positive reaction ≥3mm. **Total and specific IgE:** Using CAP FEIA.	DBPCFC (performed in all children. Follow-up performed after 1 month-children with negative challenge were in tolerant group while those with positive results were in persistent allergic group).	Tolerant group= 57 children, persistent egg allergy=100 children. All values are based on SPT cut off of 3mm & IgE cut off of 0.35 kU/L. **Sensitivity:** SPT (egg white=86%, OVM=59%). IgE (egg white=86.7%, yolk=55.4%, OVA= 86.7%, OVM=65.5%). **Specificity:** SPT (egg white=42.9%, OVM=74.1%). IgE (egg white=39.6%, yolk=92.3%, OVA= 47.1%, OVM=78.4%). Authors also reported ROC curves of SPT and IgE to egg allergens. **Area under the curve (AUC):** for SPT (egg white=0.79, OVA=0.78, OVM=0.71, yolk=0.64, OVA=0.63, lysozyme=0.56, OVT=0.54) and IgE (egg white=0.77, OVM=0.74, yolk= 0.74).	All values are based on SPT cut off of 3mm & IgE cut off of 0.35 kU/L. **PPV:** SPT (egg white= 72.9%, OVM =80.8%). IgE (egg white =70.9%, yolk=92%, OVA=72.7%, OVM=83.8%). **NPV:** SPT (egg white= 63.2%, OVM =49.4%). IgE (egg white= 63.6%, yolk =56.5%, OVA=68.6%, OVM=57.1%).	Fondo para la Investigacion Sanitaria & Premio de Investigacion del Instituto de Estudios del Huevo 2006.	Results also reported values for alternative SPT cut off values (e.g. 5, 7 & 9mm) and IgE cut off values (e.g. 1, 1.5 & 25kU/L) these are not reported in the evidence table. Reported AUC values for SPT-OVA has been reported twice in paper.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Verstege et al 2005. (Ref ID: 4903)	To evaluate the diagnostic capacity of SPT in predicting the outcome of oral food challenges and to determine decision points for wheal size and skin index (SI) that could render DBPCFC unnecessary/ Germany.	Cow's milk, hen's egg, wheat, soy	385 children referred to Department of Pediatric Pneumology and Immunology at German children's hospital with suspected food-dependent symptoms. Children's ages ranged from 3 months-14.5 years (median 22 months). 58% boys, 42% girls. 335 children had AD: 168 with mild AD, 87 with moderate AD & 41 with severe AD.	**SPT:** Positive test ≥3mm and SI >0.6 (SI is ration of allergen wheal diameter divided by wheal size of histamine).	Oral food challenge (552 DBPCFC & 183 open challenge if children <1 year of age and with history of immediate type reactions.	**Sensitivity:** HE=93%, CM=85%, wheat=65%, soy=21%. **Specificity:** HE=59%, CM=75%, wheat=77%, soy=88%. Authors also reported ROC curves. **AUC** for wheal sizes showed acceptable values for CM (0.82), HE (0.83), wheat (0.75). The values for SI were comparable: CM (0.83), HE (0.85), wheat (0.74). For soy the relationship between sensitivity and specificity in ROC curves was poor and AUC not statistically significant. Logistic regression proposed by Sampson also used to calculate predicted probabilities illustrating the likelihood of patients with a given weal size to generate a positive food challenge.	**PPV:** HE=80%, CM=76%, wheat=52%, soy=29%. **NPV:** HE=83%, CM=83%, wheat=85%, soy=83%. **Predictive probabilities:** All values for 99% cut off. HE (<1 yr=15.4, >1 yr=18.3, all children=17.8) & CM ((<1 yr=13.5, all children=17.3). No values available for wheat and soy.	Not reported.	Also report 90 & 95% predictive probabilities which are not reported in evidence table.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Mehl et al 2006. (Ref ID:2857)	To study the utility of APT in the diagnostic work up of food allergy/ Germany.	Cow's milk, hen's egg, wheat, soy	437 children with suspected food allergy referred to author's department. Age ranged from 3 months-14 years (median= 13 months). 60% boys. 391 (90%) had history of AD, 43% of these patients had mild AD, 25% with moderate AD, 12% with severe AD & 20% had no AD at time of challenge.	**SPT, APT:** Using Finn Chambers. Positive result if there was erythema with infiltration or papules. **sIgE:** Positive result ≥0.35kU/L	Oral food challenge (performed based on medical history, and/or pos SPT, and/or pos IgE. 77% were DBPCFC. Open challenges carried out in children <1 year with history of immediate type reactions) Total of 873 challenges analysed in 437 children.	**Sensitivity:** sIgE (CM=87%, HE=96%, wheat=82%, soy=65%). SPT (CM=85%, HE=93%, wheat=75%, soy=29%). APT (CM=31%, HE=41%, wheat=27%, soy=23%). **Specificity:** sIgE (CM=49%, HE=48%, wheat=34%, soy=50%). SPT (CM=70%, HE=54%, wheat=64%, soy=85%). APT (CM=95%, HE=87%, wheat=89%, soy=86%). Author's also calculated decision points for sIgE and SPT. **Decision points:** sIgE (95% HE=15.9, 99% HE=75.5 kU/L). SPT (95% CM= 13.8mm, 99% CM=20mm, 95% HE=14mm, 99% HE=20mm).	**PPV:** sIgE (CM=62%, HE=79%, wheat=41%, soy=22%). SPT (CM=73%, HE=79%, wheat=49%, soy=33%). APT (CM=86%, HE=86%, wheat=58%, soy=30%). **NPV:** sIgE (CM=79%, HE=85%, wheat=77%, soy=86%). SPT (CM=83%, HE=81%, wheat=85%, soy=82%). APT (CM=60%, HE=43%, wheat=69%, soy=82%).	Not reported.	Results also reported sensitivity, specificity, PPV & NPV values based on combination of sIgE, SPT & APT-these results are not reported in evidence table. Also reported decision points for children with positive and negative APT.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Ando et al 2008. (Ref ID: 190)	To evaluate the clinical usefulness and added diagnostic value of IgE antibodies to egg white, ovalbumin & ovomucoid in children with egg allergy/	Egg white, ovalbumin, ovomucoid	108 children with suspected egg allergy referred to author's clinic. Children ranged in age from 14 months to 13 years (median=34.5 months) and had mostly AD, asthma and in a few cases GI symptoms and anaphylaxis. Children were divided into 3 groups: A) 38 positive challenge results for heated and raw egg white. B) 29 with positive reactions to raw egg white but negative when heated. C) 41 with negative reactions to both raw & heated egg white.	**Specific and total IgE:** Using ImmunoCAP.	DBPCFC (all children tested).	All values reported are for IgE cut off 0.35kU/L for raw egg white. **Sensitivity:** egg white=97%, ovalbumin=97%, ovomucoid=87%. **Specificity**: egg white=29%, ovalbumin=32%, ovomucoid=41%. All values reported are for IgE cut off 0.35kU/L for heated egg white. **Sensitivity:** egg white=100%, ovalbumin=100%, ovomucoid=97%. **Specificity**: egg white=20%, ovalbumin=21%, ovomucoid=36%. Authors also reported positive and negative decision points based on at least 95% clinical specificity. **95% Negative & positive decision points for raw egg**: Egg white (0.60, 7.38kU/L), ovalbumin (0.79, 9.84kU/L), ovomucoid (positive only=5.21kU/L).	All values reported are for IgE cut off 0.35kU/L for raw egg white. **PPV:** egg white =69%, ovalbumin =70%, ovomucoid= 71%. **NPV**: egg white =86%, ovalbumin =87%, ovomucoid= 65%. All values reported for raw egg white. **PPV:** egg white =40%, ovalbumin =41%, ovomucoid= 45%. **NPV**: egg white =100%, ovalbumin =100%, ovomucoid= 96%.	Health and Labour Science Research Grants from Ministry of Health, Labour and Welfare of Japan.	Also reported sensitivity, specificity, PPV & NPV values for optimal cut off, positive and negative decision points-these are not reported in evidence table. Negative and positive decision points for heated egg also not reported in evidence table.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Sampson & Ho 1997. (Ref ID: 1494)	To determine the efficacy of the CAP system in the diagnosis of IgE-mediated food allergy in a group of children and adolescents referred for evaluation of AD/ USA	Egg, milk, peanut, soy, wheat, fish	196 children and adolescents with AD (randomly selected from 300). Approx 50% had asthma and allergic rhinitis & 90% with family history of atopic disease. Age ranged from 0.6-17.9 years (mean= 5.2 yrs). 117 boys and 79 girls.	**Total and specific IgE:** Using CAP FEIA. Cut-off of 0.35 kU/L used. **SPT:** Positive result ≥3mm than the negative control.	DBPCFC (all negative results were confirmed using open challenge. DBPCFCs not performed when a patient with evidence of food-specific IgE antibody had a convincing history of a severe allergic reaction to food). 494 DBPCFCs performed in 196 children.	Values for SPT are compared to DBPCFC and for IgE are based on positive DBPCFC results and convincing histories of allergic reactions. **Sensitivity:** SPT (egg=98%, milk=96%, peanut=90%, soy=76%, wheat= 90%, fish=90%). IgE (egg=98%, milk= 100%, peanut=97%, soy=94%, wheat= 96%, fish=94%). **Specificity:** SPT (egg=53%, milk=51%, peanut=29%, soy=47%, wheat= 51%, fish=57%). IgE (egg=45%, milk= 30%, peanut=38%, soy=25%, wheat= 20%, fish=65%). Also report optimal decision points (ODP) selected from ROC curve. Values are based on study population. **ODP when using IgE (CAP):** egg=3.4 kU/L, milk=5.8, peanut= 10.7, soy=5.0, wheat=8.1, fish=1.8.	Values based on study population. **PPV:** SPT (egg=85%, milk=66%, peanut=55% , soy=35%, wheat= 35%, fish=77%). IgE (egg=84%, milk= 57%, peanut=78% , soy=21%, wheat= 14%, fish=49%). **NPV:** SPT (egg=90%, milk=93%, peanut=75% , soy=84%, wheat= 94%, fish=80%). IgE (egg=88%, milk= 100%, peanut=85% , soy=95%, wheat= 97%, fish=97%).	Not reported	Most positive responses to egg, milk, soy & wheat based on challenge but 43% peanut & 33% fish diagnoses based on convincing history. Also reported predictive values based on hypothetical normalised population (10% prevalence of food allergy)- not reported in table. Also report diagnostic accuracy values for ODP (not reported) and additionally report 90% and 95% PPV & NPV values for IgE. 95% PPV (Egg=6, milk=32, peanut=15, fish= 20kU/L).

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Sampson 2001. (Ref ID: 3560)	To determine the utility of 95% predictive decision points in the prospective evaluation of food allergy/ USA.	Egg, milk, peanut, fish, soybean, wheat	100 children and adolescents referred to paediatric allergy clinic for suspected IgE food hypersensitivity. Age ranged from 3 months-14 years (median=3.8 years). Male/female=62: 38. 61% had AD, approx 50% had asthma & 90% came from atopic families. Validation study of Sampson & Ho 1997 predictive decision points.	**SPT:** Positive result ≥3mm or larger than that produced by negative control. **Specific IgE:** Using CAP FEIA. Considered definitely allergic if IgE ≥95% predictive decision points established in previous study. Considered possibly allergic if IgE<95% predictive decision points. Considered non-allergic if <0.35 kU/L.	Food challenge (single blind or open in children with positive SPT or IgE who were not suspected to have food allergy. Suspected food hypersensitivity confirmed using DBPCFC.)	Values based on 95% predictive decision points established in the retrospective study Sampson & Ho 1997. **Sensitivity:** Egg= 64% (at 6kU/L), milk=34% (at 32kU/L), peanut=57% (at 15kU/L), Fish=25% (at 20kU/L), soybean=24% (at 65kU/L), wheat=13% (at 100kU/L). **Specificity:** Egg= 90% (at 6kU/L), milk=100% (at 32kU/L), peanut=100% (at 15kU/L), Fish=100% (at 20kU/L), soybean=99% (at 65kU/L), wheat=100% (at 100kU/L).	Values based on 95% predictive decision points established in the retrospective study. **PPV:** Egg= 96% (at 6kU/L), milk=100% (at 32kU/L), peanut= 100% (at 15kU/L), Fish=100% (at 20kU/L), soybean= 86% (at 65kU/L), wheat=100% (at 100kU/L). **NPV:** Egg= 39%, milk=44%, peanut= 36%, Fish=89%, soybean= 78%, wheat= 76%.	Pharmacia/ Upjohn Diagnostics, National Institutes of Allergy and Infectious Disease, National Institutes of Health.	Also reported 90% diagnostic decision points (which were generated in retrospective study) but are not reported in evidence table. Also present recommended interpretation of food allergen specific IgE levels in the diagnosis of food allergy (not reported in evidence table).

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Nolan et al 2007. (Ref ID: 2794)	To investigate whether SPT with a commercial extractor fresh food adds additional information to FEIA in discriminating allergic and tolerant children/ Australia.	Peanut	51 children from pediatric allergy clinics agreed to undergo challenge testing. Median age was 6.3 years (range 3.7-14.8 years).	Previous SPT and FEIA results were obtained from patient file when available. **SPT:** Recorded maximum diameter of wheal and perpendicular maximum diameter. Mean diameter calculated as an average of 2 values.	Open oral food challenge (tolerant if child completed challenge without reacting and remained tolerant at follow-up clinic 2-4 weeks later. There were total of 51 challenges 19 were positive, 27 negative & 5 indeterminate).	**Sensitivity:** 6mm=89%, 7mm=83%. **Specificity:** 6mm=93%, 7mm=97%. Author's also used **ROC curve analysis:** The SPT substrate that best predicted challenge outcome was commercial extract. Using largest diameter (AUC=0.937) was marginally better than mean diameter (AUC=0.930) but not statistically significant. Both raw (AUC=0.887) and roasted peanut extracts (AUC=0.913) correlated strongly with the commercial extract (r=0.85, r=0.83 respectively). Although AUC for fresh foods was lower than commercial extract, this was not statistically significant.	**PPV:** 6mm=89%, 7mm=93%. **NPV:** 6mm=93%.	Not reported.	Values based on cut off of ≥6mm as the largest diameter or 5.5mm as mean diameter for commercial extract and largest diameter of ≥7mm. Authors didn't report NPV for 7mm.

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Heine et al 2006. (Ref ID: 534)	To evaluate the diagnostic properties of single APT skin signs in relation to the outcome of controlled food challenges in order to validate the reading of the APT/ Germany.	Cow's milk, hen's egg, wheat, soy	87 children with AD and suspected food allergy. Age ranged from 0.5-13.5 years (mean=2.4 years). 57 were male.	**APT:** Using Finn Chambers 12 mm. Skin changes graded for erythema (none, mild, moderate or severe), induration (none, minor within Finn Chamber or extensive beyond Finn Chamber), papule formation (none, 1-3, 4-6, 7+), vesiculation (present, absent) & crescendo (increase in severity of patch test reading at 48 and 72 hours).	DBPCFC (performed in all children)	Values based on crescendo phenomenon, alone and in combination with single APT signs at 72 hours. **Sensitivity:** Crescendo=11%, moderate erythema plus crescendo=5%, induration plus crescendo= 4%, papules (7+) plus crescendo=5%. **Specificity:** Crescendo=93%, moderate erythema plus crescendo=99%, induration plus crescendo= 98%, papules (7+) plus crescendo=98%.	**PPV:** Crescendo= 57%, moderate erythema plus crescendo= 80%, induration plus crescendo= 60%, papules (7+) plus crescendo= 67%. **NPV:** Crescendo= 56%, moderate erythema plus crescendo= 56%, induration plus crescendo= 55%, papules (7+) plus crescendo= 55%.	Not reported.	Also report diagnostic accuracy values of combined APT skin signs which are not reported in evidence table. No analyses based on food tested (focus on APT signs).

Bibliography Reference (Ref ID)	Study aim/ Country of participants	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Knight et al 2006. (Ref ID: 2926)	To determine whether the size of SPT to egg white adds diagnostic utility for children with low egg white specific IgE antibody levels/ USA.	Egg	74 children who were typically selected for oral food challenge based on low egg white specific IgE (≤2.5) and lack of known recent egg associated allergic reactions. Those who passed OFC (age range 1.9-14.6 years, mean age=5.1 yrs, 66% male, 90% other food allergies, 55% asthma, 79% eczema, 55% allergic rhinitis, 3% OAS). Those who failed OFC (age range 2.1-13.6 years, mean age=5.7 yrs, 58% male, 91% other food allergies, 71% asthma, 89% eczema, 82% allergic rhinitis, 4% OAS).	**SPT:** Using commercial extract. **Specific IgE:** Using CAP. Cut-off of 0.35 kU/L used.	Oral food challenge (68/ 78 were DBPCFC).	Authors do not report sensitivity and specificity values. 2 x 2 table for SPT produced using 'passing OFC' as negative result & 'failing OFC' as positive result. Calculated **sensitivity** SPT=93%, **specificity** SPT=31%.	Calculated **PPV**=68%, **NPV**=75%.	National Institutes of Health & American Academy of Allergy, Asthma and Immunology Clinical Fellowship award.	Difficult to interpret what passing and failing an OFC means in terms of positive/ negative results.

Appendix 1.3.4

JAMA Review

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Canani 2007 (375)	To evaluate the diagnostic accuracy of APT for diagnosing FA related gastrointestinal disease, both alone and with SPT and specific IgE	Cow's milk, hen's egg and wheat	60 children referred to tertiary clinic for suspected FA-related gastrointestinal symptoms. Children ranged in age from 3 to 48 months, 63% were male and 53% had a positive family history for atopic disorders.	**Specific IgE:** using CAP-RAST positive result ≥0.35kU/L. **SPT**: using fresh foods. **APT:** using Finn chambers and commercial kit (Euromedical)	Open food challenge	**Sensitivity:** cow's milk (IgE=22.5%, SPT=45.1%, APT fresh= 64.5%, APT commercial= 6.45%). Hen's egg (IgE=31.5%, SPT=57.8%, APT fresh= 84.2%, APT commercial= 5.26%). **Specificity:** cow's milk (IgE=73.9%, SPT=69.5%, APT fresh= 95.8%, APT commercial= 95.6%). Hen's egg (IgE=66.6%, SPT=66.6%, APT fresh= 100%, APT commercial= 100%).	**PPV:** Cow's milk (IgE=53.8%, SPT=66.6%, APT fresh= 95.2%, APT commercial= 66.6%). Hen's egg (IgE=66.7%, SPT=78.5%, APT fresh= 100%, APT commercial= 100%). **NPV:** Cow's milk (IgE=41.6%, SPT=51.2%, APT fresh= 67.4%, APT commercial= 43.1%). Hen's egg (IgE=31.5%, SPT=42.8%, APT fresh=75%, APT commercial= 33.3%).	Not reported	Authors concluded that APT is a reliable, safe and useful diagnostic tool with which to evaluate suspected FA-related GI symptoms in childhood and infancy, and that APT with fresh foods has a higher diagnostic accuracy than APT with freeze dried extracts. Also suggest that APT use should be standardised.

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Osterballe 2004 (763)	To investigate the clinical relevance of APT in predicting hypersensitivity to hen's egg or cow's milk compared to SPT, histamine release (HR) and specific IgE in an unselected population	Cow's milk and hen's egg	Oral challenge was performed in 22 children from a cohort of 495 unselected children aged 3 years. Food hypersensitivity (FHS) was defined as self-reported FHS from questionnaire or positive outcome on one of test procedures.	**Specific IgE:** using Magic Lite positive result ≥1.43SU/ml .**SPT**: using prick-prick. Positive result ≥3mm **APT:** using Finn chambers 8mm cups. **HR:** using glass fiber based histamine assay. Positive result≥10 ng/ml.	Open oral challenge	**Sensitivity:** Hen's egg (APT=40%, SPT=88%, HR=71%, IgE=75%), cow's milk (APT=0%, SPT=67%, HR=67%, IgE=50%). **Specificity:** Hen's egg (APT=99%, SPT=99%, HR=96%, IgE=89%), cow's milk (APT=99%, SPT=100%, HR=94%, IgE=98%).	**PPV:** Hen's egg (APT=39%, SPT=59%, HR=22%, IgE=10%), cow's milk (APT=0%, SPT=45%, HR=6%, IgE=14%). **NPV:** Hen's egg (APT=99%, SPT=99%, HR=99%, IgE=99%), cow's milk (APT=99%, SPT=99%, HR=99%, IgE=99%).	Danish Ministry of Food, Agriculture and Fisheries	Authors concluded that APT could not predict hypersensitivity not predicted by SPT, HR or IgE. Thus APT cannot be recommended in daily practice for the diagnosis of FHS of hen's egg and cow's milk in children aged 3 years old.

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Garcia-Ara 2001 (3583)	To find the optimal cut-off values for specific IgE antibody levels that discriminate between allergic and tolerant infants by using cow's milk and its principle proteins as allergens	Milk	161 children consecutively selected over a 4 year period from an allergy service. Age ranged from 1 to 12 months. 50% had a positive family background of atopy and 23% had atopic dermatitis.	**SPT:** using extract. Positive result ≥3mm. **Total and specific IgE:** positive result≥0.35 kU/L.	Open food challenge	**Sensitivity:** SPT=72%, IgE=84% **Specificity:** SPT=62%, IgE=56%	**PPV:** SPT=60%, IgE=61% **NPV:** SPT=73%, IgE=81%	Not reported	Also use specific milk proteins (not reported in evidence table).
De Boissieu 2003 (950)	To provide an approach to the accuracy of the APT in the diagnosis of cow's milk allergy in patients with digestive symptoms	Cow's milk	35 children aged 2 to 57 months referred for diagnosis of nonspecific persistent digestive symptoms. 15 were female and 20 male.	**IgE:** using CAP-RAST. **SPT**: positive result≥ 3mm. **APT:** using Finn Chambers	Open challenge or DBPCFC	**Sensitivity:** APT=79% **Specificity:** APT=91%	N/A	Not reported	Authors reported good sensitivity and specificity values for milk APT in patients with cow's milk allergy but standardisation is needed.

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Monti 2002 (999)	To compare the outcome of an oral food challenge with never ingested egg and results of SPTs and RASTs	Egg (albumen and yolk)	107 children referred to atopic dermatitis (AD) service. Their age ranged from 1 to 19 months, 66 males and 41 females.	**SPT:** using commercial extracts. **Specific IgE:** using CAP RAST. Results classified as negative, borderline, positive, highly positive, very highly positive or extremely highly positive.	Food challenge	**Sensitivity:** (at 3mm threshold) SPT albumen =87.5%, SPT yolk=66.6%. **Specificity:** SPT albumen =85.7%, SPT yolk=88.6%.	**PPV:** (at 3mm threshold) SPT albumen =92.6%, SPT yolk=92.3%. **NPV:** SPT albumen =77%, SPT yolk=56.3%.	Not reported	

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Jarvinen 2003 (3303)	To determine the concurrent occurrence of cereal allergy among children with challenge proven cow's milk allergy who have residual symptoms during elimination diet.	Wheat (using cereal)	90 children aged between 2.5 to 36 months referred to university hospital due to AD. There were 59 males and 31 females.	**SPT:** using commercial extracts, positive result ≥3mm and at least half size of histamine induced wheal. **APT:** using Finn Chambers	Open food challenge	**Sensitivity:** prick=23%, patch=100%. **Specificity:** prick=67%, patch=79%	**PPV:** prick=100%, patch=32%. **NPV:** prick=90%, patch=46%	Not reported	The authors concluded that patch testing with cereals aids in diagnosing cereal allergy in small children, especially when used together with SPT.

Appendix 1.3.5

Clinical Question 4

At which stage in the diagnostic process should children with symptoms of IgE, non IgE or mixed mediated food allergy be referred to secondary/specialist care?

Bibliography (Ref ID)	Study type	Food	Symptoms or risk factors for referral	Source of funding	Comments
Allen et al 2009 (Ref ID: 452)	Review article (expert panel perspective)	Cow's milk	Recommendations for further referral in difficult-to-manage clinical scenarios of suspected Cow's Milk Protein Allergy (CMPA). • Referral if trial of cow's milk elimination fails (haematemesis, chronic diarrhoea, persistent vomiting, persistent rectal bleeding, iron deficiency anaemia & severe eczema). Urgent referrals for: • anaphylaxis, • Food Protein Induced Enterocolitis Syndrome (FPIES) • severe failure to thrive, • hypoproteinaemia/ protein losing enteropathy	Not reported	Doesn't mention where patients should be referred to or from.
Robinson & Smart 2008 (Ref ID: 1034)	Review article	Not specific	Referral to an allergy specialist should be considered in any child with history of: • suspected IgE-mediated food allergy • suspected non-IgE-mediated food allergy • asthma that required a preventer therapy to assess the possible role of environmental allergens • allergic rhinoconjunctivitis that has not responded to maximal therapy • atopic dermatitis where there has been a poor response to topical management or where dietary precipitants are suspected	Not reported	Not specific to food allergy as considers all allergic diseases

Bibliography (Ref ID)	Study type	Food	Symptoms or risk factors for referral	Source of funding	Comments
Allen 2007 (Ref ID: 1037)	Review	Cow's milk	Recommend referral to specialist in a vomiting infant with suspected CMA who has failure to thrive or bloody diarrhoea. Infants with evidence of immediate reactions to CMA suggestive of IgE-mediated food allergy should be urgently referred to pediatric specialist for SPT.	Not reported	Doesn't mention where patients referred from
Vandenplas et al 2007 (Ref ID: 514)	Guideline (based on consensus)	Cow's milk	For children who have been exclusively breast fed, refer to paediatrician specialist based on suspicion of severe CMPA and one of more of following symptoms: • Gastrointestinal: failure to thrive because of diarrhoea or regurgitation/ vomiting; refusal to feed, moderate to large amounts of blood in stool with decreased haemoglobin, protein losing enteropathy • Dermatological: failure to thrive and severe atopic dermatitis For children who have been formula fed, refer to paediatrician specialist based on suspicion of severe CMPA and one of more of following symptoms: • Gastrointestinal: failure to thrive because of diarrhoea and/or regurgitation/ vomiting and/or refusal to feed, iron deficient anaemia, protein losing enteropathy, endoscopic /histologically confirmed enteropathy or severe ulcerative colitis • Dermatological: exudative or severe atopic dermatitis with hypoalbuminaemia-anaemia or failure to thrive or iron deficiency anaemia • Respiratory: acute laryngoedema or bronchial obstruction with difficulty breathing • Systemic reactions: (anaphylactic shock needs immediate referral to hospital for management)	SHS/ Nutricia	

Bibliography (Ref ID)	Study type	Food	Symptoms or risk factors for referral	Source of funding	Comments
Kaila et al 2008	Finnish Guideline by Finnish Medical Society Duodecim	Not specific	Indications for referral to specialist care: • infant with widespread eczema or worsening symptoms • infant with difficult or perplexing symptoms and parents are convinced of food allergy • failure to thrive • diet is limited by parent to dangerously few foods • an older child needs to be referred if the diet threatens to become too limited	Not reported	
Leung and Schatz 2006	Consultation and referral guideline by American Academy of Allergy, Asthma and Immunology	Not specific	Guideline is aimed at patients and healthcare professionals and set out when referral to an allergist-immunologist could be helpful. For food allergy, referrals may be helpful for: • people who have limited their diet on basis of perceived adverse reactions to foods • people with a diagnosed food allergy • atopic families with or expecting a newborn who are interested in identifying risks for and preventing allergy • people who have experience allergic symptoms in association with food exposure • people who experience an itchy mouth from raw fruit and vegetables • Infants with GORD or older individuals with recalcitrant reflux symptoms • Infants with gastrointestinal symptoms including vomiting, diarrhoea (particularly with blood), poor growth etc • people with known eosinophilic inflammation of the gut	Not reported	Most of the disorders affecting infants cannot be identified with simple screening tests. Older individuals might have reflux symptoms and possibly dysphagia caused by eosinophilic esophagitis, a disorder that is also commonly food responsive.

Appendix 1.3.6

Clinical Question 5

What information should children with suspected food allergy and their parents/carers receive during the diagnostic process?

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
Lever et al 1998 (Ref ID: 4987)	Randomised Control Trial (RCT) to investigate the effect of advice on excluding eggs from the diet of young children with evidence of egg sensitivity and atopic eczema.	55 (out of 300) children with atopic eczema referred for suspected food allergy. Mean age of presentation 11.3 months in diet group and 17.2 months in control group. All received specific IgE at	(1) Parents of children in the diet group were advised to exclude all foods containing eggs for 4 weeks and were given lists of food known to contain eggs and of egg-free foods. They were also helped with interpreting labels on food. (2) Parents of children in the control group were	**Changes in eczema:** Assessed in two ways (1) estimating the area affected by eczema (% of total skin area) and (2) severity score in arbitrary units (0-3) which assessed 6 clinical features at initial presentation, study entry and after the trial. Changes were also analysed correcting for a child's entry value. **Results:** **(1) Surface area affected:** During the trial it was found that more children in the diet group showed improvement: 25 (89%) compared to controls 16 (59%). The reduction in mean area affected was significantly greater in the diet group than controls ($t=2.08$, $p=0.04$). In relation to initial entry scores, generally children from diet group improved more than controls and this tended to be greatest in children with the largest affected area at outset. Non-significant linear regression slopes between control and diet group ($p=0.13$) may have been influenced by 2 children; one control whose eczema cleared almost completely during trial and a diet child with marked involvement showing	Not reported	Detailed dietary histories were taken from the parents of 62 children & were randomised by dietitian to diet group or control group. During the 4 week trial treatment continued	Study suggests that children with atopic eczema and sensitivity to eggs benefit from a regime in which parents are advised by a dietitian to exclude eggs and egg

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
		presentation. All children received DBPCFC after the trial to confirm egg allergy-7 had a negative challenge result.	given no specific advice on avoidance of any particular item of food.	no improvement. **(2) Severity scores:** During the trial similar changes were seen in severity scores and improvement was greater in diet group (t=1.99, p=0.05). In relation to initial entry scores, there were no significant difference in slopes between diet and control groups (p=0.22) although the mean change in severity in the diet group from 33.9 to 24.0 was significantly greater (p=0.04) than that in controls (36.7 to 33.7).		unchanged in both groups. 7 children had negative challenges.	products from their child's diet.

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
Hu et al 2007(Ref ID: 151)	Qualitative study using in-depth semi-structured interviews and focus groups to examine the patient information needs and preferences of parents regarding food allergy	84 parents of children presenting for evaluation of food allergy recruited from pediatric allergy clinics or a national consumer organisation. Age ranged from 23 to 55 years.	Thematic categories were developed from transcribed interviews and focus groups using the constant comparative method	**Phases in information needs:** parents described 3 distinct phases in information seeking; on initial diagnosis, at follow-up and at milestones. When food allergy was first diagnosed the majority of parents requested that more information be given at the first visit, with only 2 parents stating that they were given too much information. **Information content needs:** parents described 2 aspects of information content. The first concerned the reasoning behind the doctor's judgements about their allergy. The second type of information concerned basic medical facts and practical advice related to daily management. **Core areas identified by parents**: What is and what is not anaphylaxis, recognising symptoms of allergic reactions, the timescale of reactions, how accidental exposures occur and how to manage risky situations, what to feed your child (rather than what to avoid), practical allergen avoidance: label reading, shopping, cooking, eating out etc, when and how to give auto injector, how to educate extended family, carers and adults who may give child food, risks and benefits of skin testing and oral challenges, interpretation of results, when follow-up is required and why, where more information can be found, how to educate your child & background information about allergy. **Preferences for information delivery:** Information format was one aspect of this theme. Written take home information was strongly preferred as it was difficult to recall details of food ingredients and products but was not a substitute for talking to a healthcare professional. Parents also spoke highly of videos which they found essential for educating their child. They also preferred to receive more trustworthy information from their doctor and found nurse led education sessions valuable. Other aspects included clinic procedures and accessibility & doctor-parent-child relationship.	Australian Allergy Foundation & the National Health and Medical Research Council of Australia	Thematic categories were validated by 6 expert reviewers from allergy and non-allergy specialist, general practice, sociology, consumer and lay background.	Patients prefer information to be delivered in a variety of formats, and in an accessible, ongoing, parent and child-centred manner. These findings may assist development of more effective educational strategies.

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
Mikkelsen et al 2005 (Ref ID:290)	Questionnaire survey was used to develop a suitable form of group education for families suffering from cow's milk allergy/ intolerance and to evaluate this intervention immediately after participation and 3 years later	84 families of children diagnosed or suspected to have cow's milk allergy in the primary healthcare system in Sweden who were prescribed a milk free diet. The children's age ranged from 3 months to 5 years.	Milk allergy school: At group sessions participants were encouraged to narrate how the allergy was diagnosed, for how long they had been pursuing a milk free diet and what they experienced as major problems in their new situation. The dietitian provided information, answered questions, corrected eventual misconceptions and kept discussions on track. Sessions also included practical exercises such as reading ingredient labels & parents were also given written instructions on how to follow an elimination diet and booklets of recipes	**Post session evaluation:** 72% of participants indicated at the end of the course that they were satisfied with the content and presentation of information received. 27% felt their need for information had only been partially met. At 3 year follow-up the participant's responses showed more positive attitudes including satisfaction with the information received in most cases (88%) and partial satisfaction in only 9 cases (12%). 56% preferred to get information both individually and in group, 13% considered it sufficient to attend a milk allergy school and 8% would have preferred individual information. **Positive and negative aspects**: Positive aspects of the milk allergy school included qualities of the given information and support (38%), the encounter with other parents in the same situation (35%) or both features (14%). The most common negative aspect was that the composition of the group was heterogeneous according to age and/or symptoms of the children (11%) as well as level of knowledge among participants. Other negative aspects (14%) include the premises and lack of follow-up.	The Swedish Asthma and Allergy Foundation	No control group were used.	The milk allergy school seems to satisfy most families need for information and support to manage the milk-free diet

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
Barnett 2005 (Ref ID: 265)	Use an online questionnaire to determine whether community-pharmacist provided food allergy education and auto-injectable epinephrine training is needed.	1887 recently joined members of the Food Allergy and Anaphylaxis Network (FANN). 4.9% were food allergic individuals & 95.1% were parents or caregivers who answered on behalf of food-allergic individual. Mean age of food-allergic individuals was 5.74 years and had been diagnosed for mean 3.26 years but recall was required	Online questionnaire consisted of 35 items. Demographics and past education and training associated with food allergy and use of auto-injectable epinephrine were explored in 26 questions that used forced choice and open ended responses.	**Education and training provided by prescriber**: 1.4% reported education and training provided by family practitioner. 6 categories of information: general information about food allergy, information about signs of allergic reaction, training in use of epi-pen, information on specific foods to avoid, drug information of epinephrine and day-to-day management information of food allergy. 23% of respondents reported comprehensive information and training, 16.3% reported no information or training, and 60.7% reported incomplete information covering some of the 6 categories. **Initial prescription for auto-injectable epinephrine**: 94% were dispensed in community pharmacy and 0.4% in physician's office. 73.6% received both patient insert and drug information leaflet, 23.8% received only the patient insert, 2% received only drug information leaflet and 0.6% received neither. **Education and training provided by pharmacist**: 86.6% recalled that no oral counselling was offered, 13.4% recalled drug information about epinephrine, 13.3% received training in use of epi-pen, 2.3% received information about signs of allergic reaction, 1.1% about specific foods to avoid, 1% received general information about food allergy and 0.9% had management advice. **Attitudes towards pharmacist provided education:** The mean overall attitude was 3.47 on the 5-point likert scale representing an attitude between neutral and favourable. Stronger attitudes were presented with respect to 4 statements-respondents disagreed with the statements 'A pharmacist that tried to talk with me about food allergies would be wasting my time' (2.32) and 'that only thing that	Not reported	Recall of initial diagnosis may not be accurate.	Community pharmacists should consider working collaboratively with paediatricians and allergists who do not provide education and training at the time of initial prescription order is written for auto-injectable epinephrine.

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
		related to initial diagnosis of food allergy.		pharmacists should do for the food allergic is fill their prescriptions' (2.23). Respondents agreed with the statements 'When I pick up an epi-pen, the pharmacist should counsel me without asking me or waiting for me to ask' (3.64) and 'I would welcome the chance to update my knowledge and skills about food allergy by talking with a pharmacist' (3.64).			
Gillespie et al 2007 (Ref ID: 181)	Phenomenological study to develop a narrative description of detailing the central underlying meaning of the mother's lived experience of parenting a child at risk of Food Induced Anaphylaxis (FIA)	6 mothers of children aged 6 to 12 years old considered at risk of FIA who were required to carry epinephrine. Mother's were recruited from private pediatric allergist's office and from a parent support group.	Semi-structured interviews were used to aid mothers in describing what it was like for them to have a child with a life threatening food allergy.	The essence or meta-theme of the mother's experiences is described as 'living with risk' and is supported by 5 themes including relying on resources. **Relying on resources:** The main resources were identified as personal, help from others and information sources. Within 'help from others' physicians played an important role. Allergists especially were valued for their expert knowledge, as well as some physicians for their supportive manner. How physicians treated the child was important, and mothers praised child-focused encounters. Within 'information resources' all mothers were active in finding information from sources such as the internet. They believed that physicians should clearly indicate not only the seriousness of the allergy at diagnosis but also the fact that it could be managed; in addition physicians should provide reliable information that would help protect the child. They did not all believe that they had received enough information from their physicians and did not know what to ask at first. Some mother's suggested it would be helpful to have a nurse available for teaching, counselling, contact and follow-up after the original appointment. Referral to other parents understanding daily problems was also suggested.	One author supported by Winnipeg Health Sciences Centre Foundation & the other by a Canadian Cancer Society Research Scientist award and a Manitoba Health Research Council		This study has shown that mothers need support, information and knowledge that people in contact with their child are informed about FIA. Clear information must be given early, with reassurance of the child's prognosis for a healthy life but

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
					Establishment award.		acknowledging that challenges will be faced. Printed resources should include what needs to be avoided, the importance and 'how to' of reading labels, how to contact companies and how to deal with problems.

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
Arvola et al 2000 (Ref ID: 1218)	Questionnaires used to describe the problems that parents experience in the care of their high risk atopic infant and their expectation of healthcare professional.	81 breast fed infants with atopic eczema (AE) who were admitted to the Department of Pediatrics at University hospital in Finland. AE had developed during breast feeding at a mean age of 2 months. Mean age at enrolment was 5 months (range 1.5-15	Intervention team comprised of a pediatric nurse and 2 paediatricians with expertise in food allergy, who consulted regularly with a dietitian and a dermatologist. Foods suspected to cause allergic symptoms (on basis of clinical history, specific IgE and SPT results) were eliminated from the diet and substituted with nutritionally equal foods for 9 months. During study visits patients were clinically examined	The questionnaire before intervention related to: diet of infant and mother at onset of AE symptoms, problems in care before diagnostic and therapeutic intervention, the advice received in primary healthcare and whether this advice was beneficial & expectations from diagnostic and therapeutic evaluation. The questionnaire after the intervention related to: Parent's perception of the care received by intervention team, problems concerning care of the infant during intervention, usefulness of advice received & the realisation of expectations from intervention. **Problems in managing infant:** Before intervention 88% found care of atopic infant more demanding than healthy child with severe AE, pruritus, restlessness, sleep loss, difficulties in skin treatment and adherence to strict diet being perceived as most important problems. 53% had consulted a GP and remainder had consulted a nurse for advice. Advice included follow-up (16% of cases) and topical treatment (29%) which parents considered inadequate, whereas elimination of specific food (32%) and diagnostic evaluation (17%) were felt to be necessary. After intervention 92% of parents considered care of atopic infant more demanding than healthy child although	Medical Research Fund of Tampere University Hospital and the Academy of Finland	No control group without intervention	The present data support a comprehensive team approach to the care of atopic infants and their parents.

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
		months). 56% found to have a challenge confirmed allergy during study.	and severity of AE was scored (SCORAD method). Parents also interviewed regarding recent symptoms and were given new list of foods to introduce if no symptoms appeared. Compliance to recommendations were assessed by monitoring growth. Pediatric nurse gave practical advice on elimination diets and was available for enquiries relating to care of infant. Challenge was conducted one month after cessation of breast feeding.	problems in management of infant had significantly diminished. **Expectations from intervention:** Parents expected, in order of importance: alleviation of AE symptoms, practical advice on skin treatment and elimination diet, accurate diagnosis of food allergies and follow-up of nutritional state. **Perceptions of intervention:** 92% considered help and advice from intervention team to be sufficient in care of their atopic infant. The expectations with regard to alleviation of symptoms were moderately or well fulfilled in 98% of cases, advice on skin treatment and elimination diet in 100%, allergy diagnosis in 94% and follow-up of growth and nutrition in 100% of cases. Parents criticised busy schedule of paediatricians, the dermatologist and the dietitian and hoped for improvement between exchange of information between them. They appreciated the individual doctor-patient relationship, permanence of medical staff, continuous follow-up and the child and family centred care provided by the pediatric nurse.			

<table>
<tr><th>Bibliography (Ref ID)</th><th>Research question/ study design</th><th>Population</th><th>Intervention</th><th>Outcomes</th><th>Source of funding</th><th>Comments</th><th>Authors conclusion</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Weber et al 2007 (Ref ID: 144)</td><td>Questionnaires and interviews used to investigate how well parents of children on cow's milk free diets perform at recognising whether or not expressions describe and foods contain</td><td>24 parents of children on cow's milk free diets and control group of 23 parents of children with no need for any type of exclusion diet. Mean age of study group 30.9 years and 32.7 years in control group.</td><td><u>Dietary guidance:</u>
In study group 71% had been instructed to exclude cow's milk and by-products and 29% to exclude cow's milk, by-products and soy. Of these 80% had received instruction on how to read product labels and 38% received instructions on words associated with cow's milk.</td><td>Data collected by questionnaire applied in 4 stages: personal details of child's guardian, economic classification, questions about dietary guidance given when elimination diet was prescribed and whether participant was capable of identifying whether 10 commercial foods were free of cow's milk (5 with cow's milk and 5 without).

<u>Results:</u> Table of median products correctly identified for each group
<table><tr><td>Correct ID</td><td>Study group</td><td>Control group</td><td>p-value</td></tr><tr><td>With milk</td><td>4.0</td><td>3.0</td><td>0.005</td></tr><tr><td>Without milk</td><td>3.0</td><td>2.0</td><td>0.079</td></tr><tr><td>Total</td><td>6.0</td><td>5.0</td><td>0.008</td></tr></table>Table shows median products correctly identified is higher in study group. For popular expressions of whole milk, powdered milk, skimmed milk and semi-skimmed milk there were non-</td><td>Not reported</td><td>Intervention assessed (i.e. dietary guidance) was provided previously and measured using questionnaire. No specific analysis on association between previous dietary</td><td>The capacity of parents to correctly identify products with and without cow's milk and by-products is not completely satisfactory. Strategies should be developed to improve</td></tr>
</table>

Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Source of funding	Comments	Authors conclusion
	cow's milk proteins.		Those in control group had not received any instruction on elimination diets.	significant differences of correct identification between groups. For technical expressions in study and control group respectively, the following percentages were observed of recognition of dairy products (71% and 45%, p=0.06, cow's milk protein (71% and 9%, p=0.001), traces of milk (54% and 9%, p=0.001) and milk formulation (42% and 13%, p=0.03). Recognition of scientific expressions did not exhibit statistical differences for casein (25% vs. 4%), lactalbumin (17% vs. 4%) or lactoglobulin (8% vs. 4%) but did for caseinate (21% vs. 0%, p=0.03). Only 3 individuals correctly identified all 10 products- all these were from the study group and had received professional instructions on how to identify foods that are and are not permitted in exclusion diet.		guidance and correct identification of cow's milk containing products.	effectiveness of guidance on implementing elimination diets.

Appendix 1.3.7

Alternative Tests

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Fundin g	Additional Comments

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Funding	Additional Comments
Moneret-Vautrin 1999 (3805)	To assess if flow cytometric analysis of basophil activation could be applied to food allergy diagnosis and if this method paralleled LTC4 release	Several (no specific details given)	**Food allergic group:** 27 individuals with 19 male and 8 female. 21 were <15 years, 5 were 15-40 years and 1 was 40+ years. **Control group:** 24 individuals with 10 male and 14 female. 7 were <15 years,10 were 15-40 years and 7 were 40+ years. 10 were atopic.	Basophil Activation Test (BAT) and LTC4 release test (LRT) using direct stimulation and passive sensitisation of basophils taken from blood donors	Food challenge (OFC or DBPCFC)	Values were calculated using extracted 2 X 2 tables. **Sensitivity:** BAT (direct stimulation= 80%, passive sensitisation= 48%) and LRT (direct stimulation= 85%, passive sensitisation= 52%). **Specificity:** BAT (direct stimulation= 100%, passive sensitisation= 94%) and LRT (direct stimulation= 100%, passive sensitisation= 100%).	Not calculated	Not reported	Adults are included in this study however the majority in the food allergic group are children. Authors conclude that the results presented are in favour of the reliability of BAT and LRT for the diagnosis of food allergy.
Osterballe et al 2004	To investigate the clinical	Cow's milk, hen's	455 children aged 3 years old. 74 had atopic	Histamine release from	Open food challenge	**Sensitivity:** HE=71%, CM=67%.	**PPV:** HE=22%, CM=6%.	Danish Ministry of Food,	Children were also tested with

Bibliography Reference (Ref ID)	Study aim	Foods tested for	Number, Age and Characteristics of participants/	Type of Test	Reference standard	Sensitivity/ Specificity	Positive/ Negative predictive values	Source of Fundin g	Additional Comments
	relevance of APT in predicting hypersensiti vity to cow's milk and hen's egg in unselected children	egg	dermatitis	basophils		**Specificity:** HE=96%, CM=94%.	**NPV:** HE=99%, CM=99%.	Agricult ure and Fisherie s	APT, IgE and SPT.