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Marie Westwood,[1]* Bram Ramaekers,[2] Shona Lang,[1] Nigel Armstrong,[1] Caro Noake,[1] Shelley de Kock,[1] Manuela Joore,[2] Johan Severens[3] and Jos Kleijnen[4]

[1]Kleijnen Systematic Reviews Ltd, York, UK
[2]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, The Netherlands
[3]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands
[4]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, The Netherlands

*Corresponding author

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This report

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Abstract

ImmunoCAP® ISAC and Microtest for multiplex allergen testing in people with difficult to manage allergic disease: a systematic review and cost analysis

Marie Westwood,[1]* Bram Ramaekers,[2] Shona Lang,[1] Nigel Armstrong,[1] Caro Noake,[1] Shelley de Kock,[1] Manuela Joore,[2] Johan Severens[3] and Jos Kleijnen[4]

[1]Kleijnen Systematic Reviews Ltd, York, UK
[2]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, The Netherlands
[3]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands
[4]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, The Netherlands

*Corresponding author marie@systematic-reviews.com

Background: Allergy is a form of immune-mediated exaggerated sensitivity (hypersensitivity) to a substance that is either inhaled, swallowed, injected or comes into contact with the skin. Foreign substances that provoke allergies are called allergens. It has been claimed that multiplex allergen testing may help in diagnosing the cause of symptoms in patients with an unclear cause of allergy or who are allergic to more than one substance.

Objectives: To evaluate multiplex allergen testing [devices that can measure the presence of multiple immunoglobulin E (IgE) antibodies in a patient's blood at the same time], by assessing (1) clinical effectiveness (allergy symptoms, incidence of acute exacerbations, mortality, adverse events of testing and treatment, health-care presentations or admissions, health-related quality of life); (2) effects on treatment (diet, immunotherapy medications, other potential testing); (3) any additional diagnostic information provided by multiplex allergen testing; and (4) cost-effectiveness (cost of different assessment strategies).

Methods: Fifteen databases were searched from 2005 to April 2015, including MEDLINE (via OvidSp), MEDLINE In-Process Citations, MEDLINE Daily Update, PubMed (National Library of Medicine), EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, Science Citation Index (SCI), Conference Proceedings Citation Index-Science (CPCI-S), BIOSIS Previews, Latin American and Caribbean Health Sciences Literature (LILACS), National Institute for Health Research (NIHR) HTA programme, and the US Food and Drug Administration (FDA); supplementary searches of conference proceedings and trials registries were performed. Review methods followed published guidance from the Cochrane Collaboration and the Centre for Reviews and Dissemination, University of York, UK. The methodological quality of included studies was assessed using appropriate published tools or a review-specific tool designed by the project team. Studies were summarised in a narrative synthesis. Owing to a lack of data on the clinical effectiveness of multiplex allergen testing, no long-term cost-effectiveness model was developed. A conceptual model structure was developed and cost analyses were performed to examine the short-term costs of various possible diagnostic pathways.

Results: Fifteen studies were included in the review. The very limited available data indicated that the addition of multiplex allergen testing [ImmunoCAP® Immuno Solid-phase Allergen Chip (ISAC), Thermo Fisher Scientific/Phadia AB, Uppsala, Sweden] to standard diagnostic work-up can change the clinicians' views on the diagnosis, management and treatment of patients. There was some indication that the use of ImmunoCAP ISAC testing may be useful to guide decisions on the discontinuation of restrictive diets, the content of allergen-specific immunotherapy (SIT) prescriptions, and whether or not patients should receive SIT. However, none of the studies that we identified reported any information on clinical outcomes subsequent to changes in treatment or management. There was some evidence that ImmunoCAP ISAC may be useful for discriminating allergens that are structurally similar and are recognised by the same IgE antibody (cross-immunoreactive). No data were available for Microtest (Microtest Matrices Ltd, London, UK). Detailed cost analyses suggested that multiplex allergen testing would have to result in a substantial reduction of the proportions of patients receiving single IgE testing and oral food challenge tests in order to be cost-saving in the short term.

Conclusions: No recommendations for service provision can be made based on the analyses included in this report. It is suggested that a consensus-based protocol for the use of multiplex allergen testing be developed. The clinical effectiveness and cost-effectiveness of the proposed protocol should then be assessed by comparing long-term clinical and quality of life outcomes and resource use in patients managed using the protocol with those managed using a standard diagnostic pathway.

Study registration: This study is registered as PROSPERO CRD42015019739.

Funding: This project was a Diagnostic Assessment Report commissioned by the NIHR HTA programme on behalf of the National Institute for Health and Care Excellence.

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Glossary

Allergen A substance that causes an allergic reaction.

Antibody A large Y-shaped protein, also known as an immunoglobulin, which is used by the immune system to identify pathogens.

Cost-effectiveness analysis An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Cross-immunoreactive An antibody which can interact or bind with more than one antigen.

Cross-sensitisation The process of producing a specific IgE antibody from one of several homologous allergens.

False negative Incorrect negative test result – number of diseased persons with a negative test result.

False positive Incorrect positive test result – number of non-diseased persons with a positive test result.

Homologous allergens Allergen molecules with very similar molecular structures.

Immunoglobulin E A type of antibody that is found in mammals and which mediates allergic responses.

Immunoreactive Interaction between an allergen and an antibody.

Index test The test whose performance is being evaluated.

Meta-analysis Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Opportunity costs The cost of forgone outcomes that could have been achieved through alternative investments.

Publication bias Bias arising from the preferential publication of studies with statistically significant results.

Quality-adjusted life-year A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.

Quality of life An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.

Receiver operating characteristic curve A graph that illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.

Reference standard The best currently available method for diagnosing the target condition. The index test is compared against this to allow calculation of estimates of accuracy.

Sensitisation The process of producing a specific immunoglobulin E antibody from exposure to a specific allergen.

Sensitivity Proportion of people with the target disorder who have a positive test result.

Specificity Proportion of people without the target disorder who have a negative test result.

True negative Correct negative test result – number of non-diseased persons with a negative test result.

True positive Correct positive test result – number of diseased persons with a positive test result.

List of abbreviations

AAAAI	American Academy of Allergy, Asthma and Immunology
AAD	American Academy of Dermatology
AE	adverse event
BAD	British Association of Dermatologists
BSACI	British Society for Allergy & Clinical Immunology
CASP	Critical Appraisal Skills Programme
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-Effectiveness Analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CPCI-S	Conference Proceedings Citation Index – Science
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DBPCFC	double-blind placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
EQ-5D	European Quality of Life-5 Dimensions
FAAM	Food Allergy and Anaphylaxis Meeting
FDA	US Food and Drug Administration
HDM	house dust mite
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICTRP	International Clinical Trials Registry Platform
IgE	immunoglobulin E
ISAC	Immuno Solid-phase Allergen Chip
ISMA	International Symposium on Molecular Allergology
ISRCTN	International Standard Randomised Controlled Trial Number
ISU	International Standard Unit
ISU-E	International Standard Unit for immunoglobulin E
LILACS	Latin American and Caribbean Health Sciences
LTP	lipid transfer protein
MCT	mast cell tryptase
NA	not applicable
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NLM	National Library of Medicine
NR	not reported
OFC	oral food challenge
PROQOLID	Patient-Reported Outcome and Quality Of Life Instruments Database
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
ROC	receiver operating characteristic
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SCI	Science Citation Index
sIgE	single specific IgE
SIT	allergen-specific immunotherapy
SPT	skin prick test
VAS	visual analogue scale
WHO	World Health Organization

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Allergy is a form of exaggerated sensitivity (hypersensitivity) to a substance that is either inhaled, swallowed, injected or comes into contact with the skin, involving the immune system. Substances that provoke allergies are called allergens (e.g. pollens, house dust mite, fungal spores, insect sting, animal hair, foods and chemicals found at home and work).

Most allergic reactions happen when chemicals in the body called immunoglobulin E (IgE) antibodies bind to an allergen and are then taken up by specialist cells in the immune system. The body responds by triggering allergy symptoms (e.g. rash or skin irritation, wheezing, watering eyes, nose irritation or stomach upset). In extreme cases, a severe allergic reaction (anaphylaxis) can result in difficulties in breathing and circulation, and can even cause death.

This project aimed to evaluate devices that can measure levels of many different IgE antibodies in a patient's blood at the same time (multiplex allergen testing). It has been claimed that these devices may help in diagnosing the cause of symptoms in patients with an unclear cause of allergy or who are allergic to more than one substance.

We found a small number of studies which indicated that multiplex allergen testing can change the clinicians' views on the cause of allergy symptoms and treatment options. However, none of the studies reported information on what happened to patients' allergy symptoms after changes to treatment. Therefore, we do not yet know how using multiplex allergen testing might affect people's experience of allergic disease.

Scientific summary

Background

Multiplex allergen tests are molecular diagnostic tests, in the form of a glass slide, which can simultaneously test for the presence of multiple antibodies in blood samples (up to 51 allergen sources). Multiplex allergen testing is likely to be used in secondary care settings or specialist tertiary care centres, as an addition to allergen challenge testing and in addition to, or in place of, single immunoglobulin E (IgE) antibody testing. Multiplex tests may be useful for investigating people with difficult to manage allergic disease: people who are allergic to two or more allergens and/or have allergies to unknown sources. In the UK it is estimated that 10 million patients have two or more allergies.

Objectives

The overall aim of this project was to summarise the evidence available to inform estimates of the clinical effectiveness and cost-effectiveness of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease, in secondary or tertiary UK care settings. We defined the following research objectives to address this aim:

1. To assess the effects on clinical outcomes (e.g. allergy symptoms, incidence of acute exacerbations) of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease.
2. To assess the effects on treatment (e.g. restriction diets, immunotherapy, number of allergen challenge tests required) of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease.
3. To assess the accuracy of multiplex allergen testing in predicting clinical reactivity and to investigate whether or not multiplex allergen testing can provide diagnostic information additional to that provided by current standard care in the UK [clinical history, skin prick tests (SPTs), single IgE testing].
4. To assess the cost-effectiveness of adding multiplex allergen testing to the investigation of people difficult to manage allergic disease in secondary or tertiary care settings.

Methods

Assessment of clinical effectiveness

Fifteen databases, including MEDLINE (via OvidSp), MEDLINE In-Process Citations, MEDLINE Daily Update, PubMed (National Library of Medicine), EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, Science Citation Index (SCI), Conference Proceedings Citation Index-Science (CPCI-S), BIOSIS Previews, Latin American and Caribbean Health Sciences Literature (LILACS), National Institute for Health Research (NIHR) HTA programme, and the US Food and Drug Administration (FDA), were searched from 2005 to April 2015 for terms relating to ImmunoCAP®, Microtest (Microtest Matrices Ltd, London, UK) or allergy microarray tests. Additional searching was performed for grey literature, three trial registries and seven conference proceedings. Risk of bias was assessed using QUADAS-2, The Critical Appraisal Skills Programme (CASP) cohort risk-of-bias tool, or a review-specific tool designed by the authors, as appropriate. Search results were screened for relevance independently by two reviewers. Studies were included if they were of adults or children with allergy who received a multiplex allergen test [ImmunoCAP® Immuno Solid-phase Allergen Chip (ISAC) Thermo Fisher Scientific/Phadia AB, Uppsala, Sweden, or Microtest] in comparison with standard pathways of care. Full text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. Results were summarised narratively.

Assessment of cost-effectiveness

MEDLINE, MEDLINE In-Process and Daily Update, EMBASE, EconLit, IDEAS via Research Papers in Economics and NHS Economic Evaluation Database were searched for full cost-effectiveness analysis of multiplex allergen testing from 2005 to May 2015. Included studies are appraised using a quality checklist based on Drummond (Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods For The Economic Evaluation Of Health Care Programmes*. 3rd edn. Oxford: Oxford University Press; 2005).

Owing to a lack of data on the clinical effectiveness of multiplex allergen testing, no long-term cost-effectiveness model was developed. A conceptual model structure was developed, literature on utility scores was reviewed, and cost analyses were performed to examine the short-term costs of various possible diagnostic pathways.

Results

Clinical effectiveness

A total of 8619 records were identified from searching and screened for inclusion. Fifteen studies were included in the review. No studies were identified of people with difficult to manage allergic disease in the UK. All studies evaluated versions of ImmunoCAP ISAC: none was identified for Microtest. ImmunoCAP ISAC 112 is the most recent version of the ImmunoCAP ISAC array (the number refers to the number of tests per array). None of the included studies was classified as having a low risk of bias.

No studies were identified which investigated clinical outcomes.

Two studies ($n = 97$) investigated the use of ImmunoCAP ISAC to guide decisions on the discontinuation of restrictive diets in children with food allergies. Both studies reported that the results from ImmunoCAP ISAC were used to reintroduce foods, but details were unclear.

Two studies ($n = 373$) assessed clinicians' views on whether or not ImmunoCAP ISAC provided information useful in the management of patients. Clinicians judged that ImmunoCAP ISAC 103 provided new information useful in the management of the patient in 91–95% of cases. Added value was defined as the ability to discriminate allergens that were cross-immunoreactive rather than those that were responsible for sensitisation, or the ability to impact upon accuracy of diagnosis or allergen-specific immunotherapy (SIT) prescription that was not possible using standard diagnostic work-up.

Two studies ($n = 459$) investigated the effect on SIT prescriptions of adding ImmunoCAP ISAC testing to the standard diagnostic work-up of people with respiratory allergy. Clinicians judged that for 27–54% of patients changes were made to SIT prescriptions after ImmunoCAP ISAC 103 or ImmunoCAP ISAC 96 testing.

Two studies ($n = 428$) investigated the effect on diagnostic classification of adding ImmunoCAP ISAC 103 testing to the standard diagnostic work-up of people with allergic disease. In one study of idiopathic anaphylaxis, the addition of ImmunoCAP ISAC 103 led to the identification of new sensitisations with strong associations with anaphylaxis in 20% of participants, and in 32% additional sensitisations were identified which were not associated with anaphylaxis. A second study found that the addition of ImmunoCAP ISAC 103 testing resulted in increases in the numbers of people classified as 'polysensitised with suspected cross-reactivity' and the number of people diagnosed with both inhalant and food allergies, as well as facilitating a diagnosis for eight previously unclassifiable patients.

One study ($n = 9$) assessed the relationship between change in IgE levels (measured by ImmunoCAP) before and after a 3-year course of SIT, and the clinicians' evaluation of the benefit of SIT. The median specific IgE levels decreased and this change correlated with clinical benefit of SIT. Single tests for specific IgE measurements did not show a decrease.

Eight studies investigated diagnostic accuracy; none was conducted in people with difficult to manage allergic disease. ImmunoCAP ISAC 112 was not investigated; however, ImmunoCAP ISAC 103, 89, 50 out of 51 were investigated. The diagnostic performance of ImmunoCAP ISAC in comparison with either single IgE or SPT varied considerably between studies, according to the allergens investigated and the way in which ISAC testing was applied. In general, individual components of ImmunoCAP ISAC tended to have high specificity, but low sensitivity, relative to whole-allergen single IgE tests or SPTs for the prediction of allergic response. The studies did not provide any information on the specificity of the whole ImmunoCAP ISAC panel.

Assessment of cost-effectiveness

Four economic analyses and 14 health-related quality of life studies were included in the literature review. The systematic review component of this assessment found no data on the clinical consequences of adding multiplex allergen testing to current clinical practice; therefore, a long-term economic model to inform health policy decision-making was not possible. Therefore, the assessment aimed to inform research decisions and support future model-based economic evaluations.

All cost-effectiveness studies showed an increased effectiveness when using ImmunoCAP ISAC and the majority showed cost savings when using ImmunoCAP ISAC. The methods and assumptions used were largely unclear and the credibility of the assessments was questionable; therefore, these findings should be interpreted with extreme caution.

The evidence on utility values for allergic conditions in the UK population was limited.

Test costs for ImmunoCAP ISAC and Microtest were estimated to be £219.51 and £156.85, respectively. For SPT, single IgE and the food challenge test these were £62.29, £136.37 and £570.00, respectively. A speculative analysis indicated that multiplex allergen testing would have to result in a substantial reduction of the proportions of patients receiving single IgE testing and food challenge tests in order to be cost-saving in the short term. Analyses to compare the effect of replacing single IgE with multiplex testing were difficult to perform because of lack of information regarding where the multiplex test would sit in the care pathway.

Conclusions

No recommendations for service provision can be made based on the analyses included in this report. The clinical effectiveness and cost-effectiveness of using multiplex allergen testing in the investigation of people with difficult to manage allergic disease have yet to be adequately investigated. It is suggested that a consensus-based protocol for the use of multiplex allergen testing be developed. The clinical effectiveness and cost-effectiveness of the proposed protocol should then be assessed by comparing long-term clinical and quality of life outcomes and resource use in patients managed using the protocol with those managed using a standard diagnostic pathway.

Study registration

This study is registered as PROSPERO CRD42015019739.

Funding

This project was a Diagnostic Assessment Report commissioned by the NIHR HTA programme on behalf of the National Institute for Health and Care Excellence.

Chapter 1 Objective

The overall aim of this project was to summarise the evidence available to inform estimates of the clinical effectiveness and cost-effectiveness of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease, in secondary or tertiary care settings. Multiplex allergen testing may replace some single immunoglobulin E (IgE) testing, but, where the multiplex testing panel does not include all of the suspected allergens, additional single specific IgE (sIgE) tests may be needed.

We defined the following research objectives to address this aim:

- To assess the effects on clinical outcomes [e.g. allergy symptoms, incidence of acute exacerbations, mortality, adverse events (AEs) of testing and treatment, health-care presentations or admissions, health-related quality of life (HRQoL)] of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease.
- To assess the effects on treatment (e.g. restriction diets, immunotherapy, use of other medications such as corticosteroids, number of allergen challenge tests required) of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease.
- To assess the accuracy of multiplex allergen testing in predicting clinical reactivity (response to allergen challenge testing or response to immunotherapy) and to investigate whether or not multiplex allergen testing can provide diagnostic information additional to that provided by current standard care in the UK (clinical history, skin prick tests) and single IgE testing or a combination of these approaches).
- To assess the cost-effectiveness of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease in secondary or tertiary care settings.
- This report contains reference to confidential information provided as part of the National Institute for Health and Care Excellence (NICE) appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 2 Background and definition of the decision problem(s)

Population

The indication for this assessment is to evaluate the clinical effectiveness and cost-effectiveness of using multiplex allergen testing [ImmunoCAP® Immuno-Solid phase Allergy Chip (ISAC) (Thermo Fisher Scientific/ Phadia AB, Uppsala, Sweden) or Microtest (Microtest Matrices Ltd, London, UK)] as an adjunct to current clinical investigations in people with allergy that is difficult to manage (defined as people who are allergic to two or more allergens and/or have allergies to unknown sources).

Multiplex allergen testing is likely to be used in secondary care settings or specialist tertiary care centres, as an addition to allergen challenge testing and in addition to, or in place of, some sIgE antibody testing. Multiplex allergen testing may replace some IgE testing, but where the multiplex testing panel does not include all of the suspected allergens, additional sIgE tests may be needed.

Allergy is a term used to describe immune-mediated hypersensitivity to external stimuli (allergens). Immune-mediated hypersensitivity reactions are divided into two categories: IgE-mediated reactions and non-IgE-mediated reactions. IgE antibodies are normally present in very small amounts in the body, but levels are raised in allergic disease. IgE-mediated immune reactions, also called type 1 hypersensitivity reactions, are typically rapid in onset and can involve extreme acute symptoms as in anaphylaxis or prolonged symptoms (e.g. urticaria or eczema). In an IgE-mediated reaction IgE binds to allergen molecules, which are then taken up by receptors on the surface cells of the immune system, causing the release of biologically active agents and consequent response: vasodilation (widening of blood vessels); increased capillary permeability; mucus hypersecretion; smooth muscle contraction; and tissue inflammation.

Non-IgE-mediated reactions are less well understood and are mediated by other components of the immune system. They are typically delayed in onset, and occur 4–28 hours after exposure.

This assessment will focus on IgE-mediated hypersensitivity.

Sensitisation describes the process at the start of the immune response. Exposure to an allergen [e.g. house dust mite (HDM) or pollen] initiates a complex set of cellular events within the human body, leading to the production of a specific IgE antibody to a specific allergen. At this point there is no clinical reaction (rash, sneezing). Upon re-exposure, the allergen can bind to the specific antibody that orchestrates the immune system to initiate a more aggressive and rapid response, resulting in an inflammatory response with clinical symptoms. However, many 'sensitised' individuals do not experience clinical reactions upon subsequent exposure to allergen, a situation known as tolerance.

The term polysensitisation usually refers to sensitisation to two or more allergen sources, and the term paucisensitisation has been used to describe sensitisation to between two and four allergens. Clinical reactivity can be difficult to diagnose in polysensitised patients because of problems distinguishing between sensitisation to cross-reactive allergens. Cross-reactivity occurs when the molecular structure/shape of two different antigens is very similar and the antibody recognises the two different antigens as the same antigen; for example, an IgE antibody that recognises and causes an allergic reaction to Bet v 1 in birch pollen can also trigger an allergic response to Cor a1 in hazelnut. In nature there are many molecules with similar molecular structures/shapes and this translates into the clinic as an obstacle when trying to identify all potential allergens that might cause an allergic reaction in a given patient. Currently, patients undergo allergy testing to identify the allergens to which they are sensitive. This is based on skin prick testing or

identifying the presence of individual antibodies in the bloodstream using single IgE tests. For both methods, it is difficult to identify multiple cross-reactive allergens for patients who appear to be polysensitised or have difficult to diagnose allergic disease. It has been claimed that multiplex allergen testing may provide improved information about the sensitisation profile in polysensitised patients. This assessment will summarise the available data on information provided by multiplex allergen testing, which is additional to that obtained from single IgE tests and/or skin prick or allergen challenge tests.

It is difficult to obtain reliable statistics on allergy prevalence in the UK. The charity Allergy UK states, on its website, that there are an estimated 21 million adults in the UK who have at least one allergy and that an estimated 10 million of these have two or more allergies;[1] however, these figures appear to be taken from a 2010 report on allergy and allergy remedies from the market research company Mintel. Data from the QRESEARCH project, a database containing the psuedoanonymised health records of over 13 million people, from 950 UK general practices,[2] can provide some information on the prevalence of allergy symptoms and diagnoses seen in primary care and on changing patterns over time. At the end of 2005, QRESEARCH data indicated that approximately one in nine people had a recorded diagnosis of 'any allergic disease' (including asthma, hay fever, eczema, anaphylaxis or peanut allergy); this figure represented a 27.7% increase over a 4-year period.[3] Increases in the incidence of eczema and allergic rhinitis were reported for the same time period; the age- and sex-standardised incidence of eczema was 9.58 per 1000 patient-years in 2001, rising to 13.58 per 1000 patient-years in 2005,[4] with the corresponding figures for allergic rhinitis being 5.57 per 1000 patient-years and 7.41 per 1000 patient-years, respectively.[5] QRESEARCH data also indicate that the incidence of multiple allergic disorders is increasing. The age- and sex-standardised incidence of multiple allergic disorders was 4.72 per 1000 patient-years in 2001, rising to 6.28 per 1000 patient-years in 2005.[6] Alongside data on increasing incidence of allergic disease, QRESEARCH reports also record increases in the number of allergy-related prescriptions and general practice consultations, which are indicative of an increasing burden upon the UK NHS.[4–6] There are no QRESEARCH publications that specifically report on food allergy. NICE Clinical Guideline 116[7] (food allergy in children and young people) reports an estimated prevalence for self-reported food allergy of between 3% and 35% for individual foods. However, the guideline also notes that only 25–40% of self-reported food allergy is confirmed by oral food challenge (OFC) testing.[7]

Allergic disease can present as a severe, life-threatening reaction (anaphylaxis). The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network have recommended that anaphylaxis be defined as 'a serious allergic reaction that is rapid in onset and may cause death' and is likely to be the diagnosis when there is involvement of skin or mucosal tissue (e.g. hives, angioedema) and airway compromise (wheezing, dyspnoea) and/or reduced blood pressure or associated symptoms (hypotonia, syncope), along with a temporal relationship (minutes to several hours) to a potential causative agent.[8] There are limited data on the incidence of anaphylaxis in the UK. Hospital Episode Statistics record 'allergy (including anaphylaxis)' as the primary diagnosis associated with Accident and Emergency attendance for around 70,000 cases (approximately 0.4% of all reports) in both 2013 and 2014; however, no separate statistics are recorded for anaphylaxis.[9] A 2010 study,[10] based on the Health Improvement Network database, estimated the UK incidence of anaphylaxis at 21.3 [95% confidence interval (CI) 17.6 to 25.4] per 100,000 patient-years. This study included 382 cases of anaphylaxis and the causes were listed as drug (27%); food (24%); insect (12%); latex (0.8%); idiopathic (27%); and no information (10%).[10] NICE Clinical Guideline 134[11,12] (anaphylaxis assessment) reports an estimate of 20 UK deaths per year from anaphylaxis from a study conducted in 2000. A study published in 2015,[13] which analysed data from 1992 to 2012, shows that mortality has not risen, despite an increase in hospitalisations.

Where data are available, this assessment will focus on studies conducted in the people with allergy that is difficult to manage. If data are lacking for this population, studies conducted in patients with specific allergic disease (e.g. peanut allergy) will not be excluded and all potential clinical applications of multiplex allergen testing will be considered.

Intervention technologies

ImmunoCAP Immuno-Solid phase Allergy Chip

The ImmunoCAP ISAC is a miniaturised immunoassay platform (multiple allergen components immobilised on a slide) that is intended to assess the presence of multiple antibodies in a single blood test. IgE antibodies from the patient's blood sample bind to the immobilised allergen components on the slide, and allergen-bound IgE antibodies are then detected using fluorescence-labelled anti-IgE antibodies. Slides are read using a separate microarray scanner and image analysis software. Using these technologies may provide more detailed information about individual sensitisation profiles than single IgE testing. ImmunoCAP ISAC is intended for use in complex allergy cases, such as those with inconsistent case histories/unsatisfactory response to treatment, those who are polysensitised and patients with idiopathic anaphylaxis. These are people with severe or unclear allergic disease who test positive to a range of allergens but in whom the true cause of symptoms can be difficult to identify. It is claimed that using the ImmunoCAP ISAC test could improve health outcomes by improving allergy management, more appropriately targeting specific immunotherapy, and reducing the number of investigative diagnostic tests. These improvements could also lead to potential savings to the NHS from reducing the number of tests and avoiding the use of unnecessary immunotherapy.

ImmunoCAP ISAC 112 is a molecular diagnostic test that can simultaneously test for IgE antibodies to 112 components from 51 allergen sources. The ISAC is a miniaturised immunoassay platform that uses a single sample (30 μl) of serum, plasma or capillary blood to test for IgE antibodies to multiple allergens. ImmunoCAP ISAC is a two-step assay. IgE antibodies from the patient sample bind to immobilised allergen components spotted in triplets on polymer-coated slides. Each slide contains four microarrays, giving results for four samples per slide. The results are measured using a biochip scanner [confocal laser scanning devices, in particular the CapitalBio LuxScan 10k microarray scanner (Capitalbio, San Diego, CA, USA), are recommended] and evaluated using proprietary software produced by the same company, Phadia Microarray Image Analysis software (MIA) (Phadia AB, Uppsala, Sweden). ImmunoCAP ISAC is a semi-quantitative test and results are reported in International Standard Units (ISUs), giving indications of specific IgE antibody levels; the operating range is 0.3–100 ISU for IgE (ISU-E). This range approximately corresponds to a concentration range of 0.3–100 kilo international units of allergen-specific-antibody per unit volume of sample (kUA/l) of IgE (1 kUA/l is equal to 2.4 ng/ml). The assay takes a total of 4 hours, including sample processing and incubation time.

Microtest

The Microtest Instrument is a CE (Conformité Européenne)-marked automated immunoassay platform that uses microarrays to simultaneously test for 26 allergen components. It is designed for processing and reading protein microarrays of allergens printed in the biochips. The Microtest instrument can simultaneously process up to five Microtest biochips, each containing a different serum sample, in each run. The process is fully automated. When the test is completed, the Microtest Instrument uses a fluorimeter to read the microarrays and the results are semi-quantitative, reported on an allergy risk scale of 0–4. The user can print or export the reports as appropriate. Microtest is intended for use in any patient (infants, children and adults) presenting with allergy symptoms.

Table 1 summarises the key characteristics of the multiplex allergen tests ImmunoCAP ISAC and Microtest, compared with comparator tests that are currently used in the standard diagnostic work-up of patients with difficult to manage allergic disease.

There are a number of poorly understood factors that influence whether or not clinical symptoms manifest at a certain IgE level, including inhibitory allergen-specific antibodies of non-IgE subclass. Furthermore, other factors, for example age, patient population, concomitant exposure to other allergens, other clinical conditions such as infections, etc., can also affect the degree of symptoms which may occur following allergen exposure. Thus it is not possible to establish general cut-off values valid for all patients at all times. However, when combined with clinical history, the results of multiplex allergen testing may aid the clinician

TABLE 1 Test characteristics

	ISAC 112	Microtest	Skin prick	Specific IgE	OFC
Time to perform assay/test	3.45 hours for immunoassay + time to scan + time to interpret results + time to consult with patient	5 minutes to load samples and reagents ~ 4 hours to run Microtest machine and generate results + time to consult with patient	15–20 minutes	3.45 hours for immunoassay + time to interpret results + time to consult with patient	Up to 5 hours
No. of allergens tested	51 allergens per chip (4 chips per slide) 4 patient samples can be analysed at once of 51 allergens each	26 allergens per chip 5 chips can be run at once 5 patient samples can be run at once of 26 allergens each	3–25	1 (variable but up to 650 allergens available on Phadia website)	1
Staff required	Trained laboratory professionals and physicians	Any trained operator (laboratory professionals not required)	Trained practitioners (for assay and resuscitation) will do the test and give the result	Trained laboratory professionals and physicians	Trained practitioners (for test and resuscitation)
Method summary	1. Standard immunoassay is performed using kit. Serum or plasma samples are applied to one of four chips on a microscope slide 2. An image scanner is used to identify fluorescently labelled samples, one slide at a time 3. Scanned images are analysed 4. Clinical results are reported back to patient	1. Microtest chips are loaded 2. Microtest reagents are loaded and the Microtest instrument started 3. Samples are loaded 4. A report of results is generated automatically from computer	1. Usually carried out on the inner forearm (but also thigh or back for babies or areas clear of eczema/topical creams) 2. The test allergens are selected following consultation with clinician and clinical history 3. The skin is coded with a marker pen to identify the allergens to be tested. Tests should be 2 cm apart 4. A drop of the allergen (extract) solution is placed on the skin 5. The skin is then pricked through the drop using the tip of a lancet – this should not be painful and should not bleed 6. Results are analysed and given back to patient	1. Standard immunoassay is performed using kit. Serum or plasma samples are applied 2. Results generated by automated analyser 3. Clinical results are reported back to patient	1. Challenge is started by rubbing lip with food item 2. If there is no reaction the patient is exposed to an increasing amount of the food or liquid at regular intervals, aiming for a target amount 3. At each stage 15–20 minutes is allowed to make sure there is no reaction 4. The test is stopped if there is a significant reaction

	ISAC 112	Microtest	Skin prick	Specific IgE	OFC
Controls conducted	Internal positive and negative controls For each component analysed there are three dots and two must be positive to record a positive result Calibration curves must be generated from samples in the kit plus a chip, at least every 30 days	Internal positive and negative controls. These adjust a stored calibration curve (from international standards)	Positive and negative control	Positive and negative controls	None
Quantitative results	Semi-quantitative: 0 < 0.3 ISU-E 1 ≥ 0.3 = < 1 (low) 2 ≥ 1 = < 15 (moderate) 3 ≥ 15 (high)	Semi-quantitative: 0 < 0.35 kU/l 1 0.35–1 kU/l (low) 2 1.01–15 kU/l (moderate) 3 ≥ 15 kU/l (high)			None
Special considerations	Not recommended for investigation of isolated venom allergies, as these patients may have very low levels of IgE, below the detection limit of ImmunoCAP ISAC		Not for use if patient taking antihistamines Emergency equipment must be available (antihistamine, adrenaline, hydrocortisone)	Immunohistochemical kits and imaging equipment and likely to be variable, between different hospital sites	Stop antihistamine medicines Challenge tests are always undertaken in hospital under close medical supervision where resuscitation equipment and emergency medication are available in case a severe reaction occurs

continued

TABLE 1 Test characteristics (*continued*)

	ISAC 112	Microtest	Skin prick	Specific IgE	OFC
Equipment required	ImmunoCAP ISAC 112 IgE kit Laser scanner Computer to run analyser software	Microtest allergy biochip Microtest allergy cartridges and reagents Microtest instrument Computer and analysis software	SPT kit	Specific IgE kit Automated analyser	None
References	PHADIA_ISAC-DfU_IgE – Extracted English version.pdf[a] 45_Phadia_MIA_User_manual_v1.2_EN.pdf[a] immunocap_isac_112_technical-brochure.pdf[a]	Microtest Users Manual 2015.pdf[a] Microtest Instructions for Use MAN-IFU-SYS-01–03.pdf[a]	www.allergyuk.org/diagnosis–testing-of-allergy/skin-testing (accessed 30 August 2016) www.bsaci.org/_literature_121183/Paediatric_skin_prick_testing_guideline (accessed 30 August 2016)	www.phadia.com/en-GB/5/Products/ImmunoCAP-Assays/1/ (accessed 30 August 2016)	www.allergyuk.org/diagnosis–testing-of-allergy/allergy-challenge (accessed 30 August 2016) www.northumbria.nhs.uk/sites/default/files/images/Oral_Food_Challenge_Test.PDF (accessed 30 August 2016) www.ruh.nhs.uk/patients/patients_leaflets/paediatrics/PAE041_Allergy_food_Challenge_tests.pdf (accessed 30 August 2016)

kU/l, kilo International Unit per litre; SPT, skin prick test.
a Instructions for use/technical information supplied, to the National Institute for Health and Care Excellence, by the manufacturer.

in the diagnosis of allergy. Multiplex allergen testing should always be used in conjunction with allergy-focused clinical history and may be used in addition to, or in place of, single IgE antibody tests and/or skin prick testing.

Comparator

The comparator for this assessment will be current standard care, which should always include allergy-focused clinical history and can additionally involve tests of IgE antibody status (single IgE antibody testing), tests of clinical reactivity such as skin prick testing or allergen challenge testing, or a combination of these approaches.

Single immunoglobulin E testing

Allergen-specific IgE antibody assays are designed to detect and quantify circulating IgE antibodies to one allergen. The choice of which antibodies to test for is based on the clinical history of the patient, and several single IgE tests and/or a stepwise strategy which tests for the most likely causative agents first may be required.

The single IgE test process involves incubation of a blood sample with specific IgE antibodies. Allergen-specific IgE in the patient's sample binds to the allergen, and unbound antibodies and excess sample are then removed by washing. Anti-IgE antibody, labelled to enable detection (e.g. fluorescently labelled anti-IgE antibody), is then added. The amount of bound allergen-specific IgE is calculated via a standard calibration curve, which is linked to the World Health Organization (WHO) IgE standard and reported in arbitrary mass units (kUA/l).

Higher levels of IgE are considered to be associated with allergy, but the amount of IgE is not predictive of the severity of reaction. Not all patients with a positive specific IgE test will have clinically manifest allergic reaction when exposed to that allergen. Unlike IgE antibody testing, skin prick tests (SPTs) and allergen challenge tests can provide direct information about clinical reactivity to a given allergen.

Skin prick testing

Skin prick testing is a method used to assist in the diagnosis of IgE-mediated allergic disease in patients with rhinoconjunctivitis, asthma, urticaria, anaphylaxis, atopic eczema or gastrointestinal symptoms that are suspected (based on clinical history) to be caused by type 1 (immediate) allergic reaction. It provides evidence for sensitisation in the form of reaction to allergenic stimulus.

The test involves putting a drop of liquid allergen onto the skin, followed by a gentle pin prick through the drop. SPT interpretation utilises the presence and degree of skin reactivity as a marker for sensitisation. When relevant allergens are introduced into the skin, an IgE-mediated immune response occurs. This produces a 'weal and flare' response, which can be quantified. Many different allergens can be tested simultaneously because the resultant reaction to a specific allergen is localised to the immediate area of the SPT.

One potential advantage of SPTs compared with in vitro measurement of IgE antibodies is that the test can be interpreted within 15–20 minutes after the reagent is applied to the skin, and therefore results can potentially be given to the patient in the same consultation. SPT results provide evidence of IgE in skin-resident mast cells which may, but does not always, correlate with clinical reactivity. SPTs can also be utilised to test less common allergens, (e.g. medications, and fresh fruits and vegetables) where no specific IgE antibody assays are available. As with any test, the results of SPTs must be interpreted in the context of medical history, clinical symptoms and, where appropriate, other test results. It has been suggested that skin prick testing is an inexpensive option. However, whilst the test materials may be relatively inexpensive, any estimation of costs should consider the staff time needed to perform these tests in an appropriate and safe health-care setting.

Skin prick testing has the following limitations:

- Skin reactivity might be affected by previous ingestion of antihistamines or other drugs.
- Children may not tolerate multiple skin needle pricks.
- Prior or coexisting dermatological conditions, such as eczema, may preclude the performance of skin tests.
- The potency of antigen extracts needs to be maintained.
- Systemic reactions, although very rare, may occur.
- SPTs alone are not sufficient as a confirmatory test.

Allergen challenge testing

Oral food challenges or inhalant challenges are indicated where there is a discrepancy between clinical history and other test results, and can be useful in establishing the identity of specific triggers. The most rigorous method for allergen challenge tests is double blinded and placebo controlled, thus requiring two separate visits. Therefore, single (patient)-blind and open challenges are more frequently performed because only one visit is required. An open challenge describes a challenge in which the patient can recognise the target trigger and there is no attempt at blinding; this is the least time-intensive type of challenge test, but may produce less reliable results as there is the potential for the result to be influenced by either the patient's anxiety about a particular trigger and/or the health-care professional's expectations. The general methodology of any challenge test is to administer the trigger in gradually increasing doses in a medical setting. Allergen challenge tests should be performed in a setting that is fully equipped for emergency treatment if an episode of anaphylaxis occurs.

Care pathway

There are a number of National Institute for Health and Care Excellence (NICE) guidelines that consider elements of the diagnosis, management and treatment of allergy.[7,11,14,15]

Diagnosis

Clinical guidelines consistently emphasise the importance of obtaining a clinical history and asking specific, allergy-focused questions.[7,15,16] NICE Clinical Guideline 116[7] (food allergy in children and young people) states that this can be done by general practitioners or other primary health-care professionals with the appropriate competencies. According to the guidelines, the following should be included when taking a clinical history:

- Any personal history of atopic disease (asthma, eczema or allergic rhinitis).
- Any individual and family history of atopic disease (such as asthma, eczema or allergic rhinitis) or food allergy in parents or siblings.
- Details of any foods that are avoided and the reasons why.
- An assessment of presenting symptoms and other symptoms that may be associated with food allergy, including questions about:
    - the age of the child or young person when symptoms first started
    - speed of onset of symptoms following food contact
    - duration of symptoms
    - severity of reaction
    - frequency of occurrence
    - setting of reaction (e.g. at school or home)
    - reproducibility of symptoms on repeated exposure
    - what food and how much exposure to it causes a reaction.

- Cultural and religious factors that affect the foods they eat.
- Who has raised the concern and suspects the food allergy.
- What the suspected allergen is.
- The child or young person's feeding history, including the age at which they were weaned and whether they were breastfed or formula fed – if the child is currently being breastfed, consider the mother's diet.
- Details of any previous treatment, including medication, for the presenting symptoms and the response to this.
- Any response to the elimination and reintroduction of foods.

The NICE Clinical Guideline 57[15] (atopic eczema in children) recommends that health-care professionals should seek to identify potential trigger factors during clinical assessment including:

- irritants
- skin infections
- contact allergens
- food allergens
- inhalant allergens.

The Royal College of Paediatrics and Child Health also provides advice on allergy-focused questions to be used when taking a clinical history. An initial screening set of questions is recommended to identify patients, in community settings, for whom a more detailed allergy history may need to be taken. If allergy is suspected, further questions are grouped into six areas:

- general history questions asking about general health, current medications, previous allergy testing, lifestyle and general home conditions
- general allergy history questions
- food-related questions
- respiratory-related questions
- ear-, nose- and throat-related questions
- skin-related questions.

If IgE-mediated allergy is suspected, based on the results of allergy-focused clinical history, NICE Clinical Guideline 116[7] (food allergy in children and young people) recommends that the child or young person should be offered a SPT and/or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens. It further recommends that these tests should be undertaken only by health-care professionals with the appropriate competencies to select, perform and interpret them, and should be undertaken only where there are facilities to deal with an anaphylactic reaction.[7] The guideline also states that the patient should be given information on when, where and how an OFC or food reintroduction procedure may be undertaken. However, these tests should not be performed in primary care.[7]

Management

The management of allergy is dependent upon type and severity and many allergies can be managed and treated in primary care settings. More severe allergies and more complex patients may require additional management and referral on to specialist services.

The NICE Clinical Guideline 116[7] (food allergy in children and young people) recommends referral to secondary or specialist care when the child or young person has:

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

The NICE Clinical Guideline 57 (atopic eczema in children) and NICE Quality Standard 44 (atopic eczema in children)[14,15] both recommend that children with a suspected food allergy should be referred for specialist investigation and management by a paediatric allergist or paediatric dermatologist.

With respect to management following a severe acute episode, NICE Clinical Guideline 134[11] (anaphylaxis assessment) recommends that prior to discharge a health-care professional with the appropriate skills and competencies should offer the following:

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

Treatment

Mild allergies can be treated using over-the-counter medications, such as antihistamines, and simple avoidance of the identified allergen(s).

The NICE Clinical Guideline 116[7] (food allergy in children and young people) recommends that, once an allergy is suspected, based on clinical history, information should be provided to the patient about:

- type of allergy suspected
- risk of severe allergic reaction
- potential impact of the suspected allergy on other health-care issues, including vaccination.

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

- what foods and drinks to avoid
- how to interpret food labels
- alternative sources of nutrition to ensure adequate nutritional intake
- the safety and limitations of an elimination diet
- the proposed duration of the elimination diet
- when, where and how an OFC or food reintroduction procedure may be undertaken.

The NICE Clinical Guideline 57[15] (atopic eczema in children) recommends that health-care professionals should use a stepped approach for managing atopic eczema in children and should tailor the treatment step to the severity of the atopic eczema. Emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments such as mild-potency topical corticosteroids (for mild eczema), moderate-potency topical corticosteroids (for moderate eczema), tacrolimus, bandages (for moderate or severe eczema), and potent topical corticosteroids, phototherapy and systemic therapy (for severe eczema only). Very potent topical corticosteroids should not be used without specialist dermatological advice.

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

- reducing allergy symptoms on subsequent allergen exposure
- improving quality of life (QoL)
- inducing long-term tolerance.

Immunotherapy is time-consuming and expensive, and there is a risk of a severe allergic reaction or anaphylaxis during administration. According to the British Society for Allergy & Clinical Immunology guidelines,[17] the main indications for immunotherapy in the UK are:

- IgE-mediated seasonal pollen-induced rhinitis, if symptoms have not responded adequately to optimal pharmacotherapy
- systemic reactions caused by hymenoptera venom allergy
- selected patients with animal dander or HDM allergy in whom rigorous allergen avoidance and reasonable pharmacotherapy fail to control symptoms.

The selection, initiation and monitoring of all patients for immunotherapy should be supervised by specialists in allergy. Immunotherapy should be administered only by physicians and nurses with specialist knowledge of allergy and specific immunotherapy. Immunotherapy is an attractive option for the treatment of food allergies, as its goal is to induce tolerance in the person. With desensitisation, the treated person manifests a decreased response to the allergen.[17]

Regarding treatment following severe acute episodes, NICE Clinical Guideline 134[11] (anaphylaxis assessment) recommends that after emergency treatment for suspected anaphylaxis patients should be offered an appropriate adrenaline injector as an interim measure before the specialist allergy service appointment. An adrenaline autoinjector is a medical device for injecting a measured dose or doses of epinephrine (adrenaline), by means of autoinjector technology. It is most often used for the treatment of anaphylaxis. Most individuals with a severe IgE-mediated food allergy are advised to carry an autoinjector in case of accidental exposure. There are many barriers to the successful use of an autoinjector, including the ability to recognise the symptoms of anaphylaxis, the availability and understanding of how to use the autoinjector, and anxiety associated with its use.

Patient issues and preferences

Allergic reactions can have a daily impact on the QoL of the individual, and can affect their ability to participate in everyday and social activities, perform work-related duties, undertake examinations and pursue their career of choice. The effect of allergies is described in two reports produced by Allergy UK. The *Stolen Lives* survey found that for 28.4% of respondents allergies had a serious effect on how they planned important life events, and for 26% their allergy severely affected their everyday life.[18] The report *The Disturbing Impact of Skin Allergy and Sensitivity in the UK* report[19] states that 78% of respondents suffered from reactions to their skin allergy all year round, and for 62% their condition had stopped them from going out socially and carrying out day-to-day activities.

Where food allergy is diagnosed, implementing special diets for children can also be difficult for families to manage, particularly where there are multiple dietary requirements in one family. A 2010[20] review on the psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families reported that non-allergic siblings often adopted the restricted diet that the allergic child followed. The same review[20] highlighted the effect of allergy on the QoL of patients and caregivers. It reported that allergy heightened patients' and caregivers' anxiety because of the need for constant vigilance, particularly in new situations. It also showed that parents tended to be overprotective of children with allergy, particularly those who have had anaphylaxis. There can also be anxiety for a parent or caregiver associated with administering an adrenaline injection.[20]

Chapter 3 Assessment of clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical effectiveness and cost-effectiveness of ImmunoCAP ISAC and Microtest for multiplex allergen testing in people with allergic disease. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[21] and the NICE *Diagnostic Assessment Programme Manual*.[22]

Systematic review methods

Search strategy

Development of search strategies followed the recommendations of the CRD guidance for undertaking reviews in health care.[21] Strategies were based on the technologies of interest.

Candidate search terms were identified from target references, browsing database thesauri (e.g. MEDLINE MeSH and EMBASE Emtree) and from existing reviews identified during the initial scoping searches. These scoping searches were used to generate test sets of target references, which informed text mining analysis of high-frequency subject indexing terms using EndNote X7 reference management software (Thomson Reuters, CA, USA). Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies were developed specifically for each database.

The following databases were searched for relevant studies from 2005 to April 2015:

- MEDLINE (via OvidSP): 1946–week 2 April 2015
- MEDLINE In-Process Citations (via OvidSP): up to 15 April 2015
- MEDLINE Daily Update (via OvidSP): up to 15 April 2015
- PubMed [National Library of Medicine (NLM)] (internet) up to 22 April 2015*
- EMBASE (via OvidSP): 1974–14 April 2015
- Cochrane Database of Systematic Reviews (CDSR) (via Wiley): 2015/April/Iss4
- Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley): Cochrane Library 2015/March/Iss3
- Database of Abstracts of Reviews of Effects (DARE) (via Wiley): Cochrane Library 2015/January/Iss1
- Health Technology Assessment database (HTA) (via Wiley): Cochrane Library 2015/January/Iss1
- Science Citation Index (SCI) (via Web of Science): 1970–21 April 2015
- Conference Proceedings Citation Index – Science (CPCI-S) (Web of Science): 1990–21 April 2015
- BIOSIS Previews (via Web of Science): 1956–21 April 2015
- Literature in the Health Sciences in Latin America and the Caribbean (LILACS) (internet; http://lilacs.bvsalud.org/en/): 1982–22 April 2015
- National Institute for Health Research (NIHR) Health Technology Assessment programme (internet; www.hta.ac.uk/): up to 23 April 2015
- US Food and Drug Administration (FDA) (internet; www.fda.gov): up to 23 April 2015.

*An additional companion PubMed search was undertaken in tandem with MEDLINE via OvidSP; this approach aims to detect the latest 'ahead of print' and 'online first' electronic content promoted by many leading journals.

A supplementary search was undertaken on the following resource to identify grey literature:

- OpenGrey (internet; www.opengrey.eu): up to 22 April 2015

Completed and ongoing trials were identified by searches of the following resources:

- National Institutes of Health (NIH) ClinicalTrials.gov (internet; www.clinicaltrials.gov/): up to 22 April 2015
- WHO International Clinical Trials Registry Platform (ICTRP) (internet; www.who.int/ictrp/en/): up to 22 April 2015
- International Standard Randomised Controlled Trial Number (ISRCTN) Registry (internet; www.isrctn.com): up to 22 April 2015.

The following key conference proceedings, were identified in consultation with clinical experts, and were screened for the last 5 years where available:

- American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting
- European Academy of Allergy and Clinical Immunology (EAACI)
- British Society for Allergy & Clinical Immunology (BSACI)
- Food Allergy and Anaphylaxis Meeting (FAAM)
- International Symposium on Molecular Allergology (ISMA)
- American Academy of Dermatology (AAD) Meeting
- British Association of Dermatologists (BAD).

No restrictions on language or publication status were applied. Searches took into account generic and other product names for the intervention. See *Appendix 1* for all search strategies. The main EMBASE strategy for each search was independently peer reviewed by a second Information Specialist, using the Canadian Agency for Drugs and Technologies in Health (CADTH) Peer Review checklist.[23] Identified references were downloaded in EndNote X7 software for further assessment and handling. References in retrieved articles were checked for additional studies.

Inclusion and exclusion criteria

Population

Adults and children with difficult to manage allergic disease who are being assessed in secondary or tertiary care settings. Owing to the paucity of available data, studies conducted in populations not specified as polysensitised or having difficult to manage allergic disease were also included. All presentations of allergic disease (respiratory, skin, gastrointestinal, anaphylaxis) were eligible for inclusion. Difficult to mange disease was defined as people who are allergic to two or more allergens and/or have allergies to unknown sources.

Intervention/index test

Multiplex allergen testing:

- ImmunoCAP ISAC 112 and previous generations of ImmunoCAP ISAC (Thermo Fisher Scientific/ Phadia AB)
- Microtest (Microtest Matrices).

Comparator

The comparator for this assessment was current standard care, which included allergy-focused clinical history, alternative tests of IgE antibody status (single IgE antibody testing), tests of clinical reactivity (such as skin prick testing or allergen challenge testing) or a combination of these approaches.

Outcomes

- Clinical outcomes (e.g. allergy symptoms, incidence of acute exacerbations, mortality, AEs of testing and treatment, health-care presentations or admissions, HRQoL, patient anxiety/preferences).
- Change to management, that is, change to treatment or treatment plan (e.g. restriction diets, immunotherapies, use of other medications such as corticosteroids, number of allergen challenge tests required).
- Additional diagnostic information – accuracy (sensitivity and specificity) for the prediction of clinical reactivity, as defined by SPTs, allergen challenge tests or response to immunotherapy, plus numbers of participants for whom multiplex allergen testing provided additional information (e.g. allergens component-specific information, cross-reactivities, information on multiple sensitisation), diagnostic yield (number of participants with a definitive diagnosis).

Study design

There were no restrictions on study design. Randomised controlled trials (RCTs), controlled clinical trials, other comparative studies (e.g. 'before-and-after' studies) and diagnostic test accuracy studies were eligible for inclusion. Observational study designs were eligible for inclusion only if they reported measures of additional diagnostic information provided by multiplex allergen testing; studies that assessed only concordance between multiplex allergen testing and single IgE antibody testing or other tests were not included.

Protocol change The protocol stated that diagnostic accuracy studies would be included only if they reported both the accuracy (sensitivity and specificity) of multiplex allergen testing for the prediction of clinical reactivity, as defined by SPTs, allergen challenge tests or response to immunotherapy, and the numbers and details of participants for whom multiplex allergen testing provided additional information. No studies of this type were identified. The inclusion criteria were expanded to allow studies that reported direct comparisons of diagnostic accuracy between single IgE testing and multiplex allergen testing, using SPTs or allergen challenge tests as the reference standard. These studies do not address the primary aim of the project, 'to assess the clinical effectiveness and cost-effectiveness of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease in secondary or tertiary care settings', because they provide no information on any additional benefit conferred by the use of multiplex testing. Studies of this type were included with the aim of providing some indication of the performance of multiplex allergen testing, compared with current single IgE antibody testing practice, for predicting clinical response. Data of this type may inform the question of whether or not multiplex testing might, in some circumstances, replace single IgE testing as well as helping to guide possible future research recommendations.

Inclusion screening and data extraction

Two reviewers (MW and SL) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in *Appendix 3*.

The principal investigators of completed trials (identified through searches of clinical trials registries) that appeared to meet our inclusion criteria but for which no publication could be identified were contacted and asked to provide publication details or unpublished data.

Data were extracted on the following: study details (including study design, country and funding); stated objective of the study; inclusion and exclusion criteria; participant characteristics (age, gender, primary presentation and previous allergy-related history); details of the multiplex allergen testing method used; details of the tests included in the standard care comparator (e.g. SPT, OFC, single IgE); details of the reference standard test (diagnostic accuracy studies only); outcome measures (included change to

treatment or treatment plan, e.g. restriction diets, immunotherapies), change to diagnosis or number of participants with a definitive diagnosis, and comparative accuracy (sensitivity and specificity) of multiplex allergen testing and single IgE for the prediction of clinical reactivity, as defined by SPTs, allergen challenge tests. Data were extracted by one reviewer, using a piloted, standard data extraction form, and checked by a second (MW and SL); any disagreements were resolved by consensus. Full data extraction tables are provided in *Appendix 2*.

Quality assessment

We planned to use the Cochrane risk-of-bias tool to assess the methodological quality of RCTs;[24] however, no RCTs or non-RCTs were identified. The methodological quality of studies providing comparative accuracy data was assessed using QUADAS-2.[25] Observational studies that used a 'before-and-after' type of study design to assess the effects of adding information from multiplex allergen testing to the standard diagnostic work-up in the same group of participants were assessed using a review-specific tool designed by the authors (MW, SL and NA). This tool has been designed to focus on elements of study design that we considered relevant to this specific study type, and is based upon the structure of the QUADAS-2 tool. The Critical Appraisal Skills Programme (CASP) cohort risk-of-bias tool was used to assess other observational studies.[26] A narrative description of the potential limitations of any other included studies is provided. The results of the quality assessment have been used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Quality assessment was undertaken by one reviewer and checked by a second reviewer (MW and SL) and any disagreements were resolved by consensus. The applicability of studies to current UK practice was also considered and a narrative description of potential applicability issues is provided. The results of the risk-of-bias assessments are summarised and presented in tables and graphs in the results of the systematic review (see *Study quality*) and are presented in full, by study, in *Appendix 4*.

Methods of analysis/synthesis

We planned to use a bivariate/hierarchical summary receiver operating characteristic random-effects model to generate summary estimates and a summary receiver operating characteristic (SROC) curve for test accuracy data,[27–29] and a DerSimonian and Laird random-effects model to generate summary estimates of treatment effects. However, because the review identified a small number of studies with between-study variations in participant characteristics (allergy history), multiplex allergen testing methods, allergens tested for, standard care comparators, and outcomes assessed, we did not consider meta-analyses to be appropriate and have provided a structured narrative synthesis. The results of studies included in this review are summarised by outcome type (clinical, change to management and diagnostic accuracy) and are further stratified by allergen type (food and aeroallergens). The results of individual studies are summarised in text and tables. The results of studies providing comparative accuracy data are also illustrated in receiver operating characteristic (ROC) space plots.

Results of the assessment of clinical effectiveness assessment

The searches of bibliographic databases and conference abstracts identified 8619 references. After initial screening of titles and abstracts, 169 were considered to be potentially relevant and ordered for full paper screening; of these, 20 were included in the review[30–49] and one[50] could not be obtained. All potentially relevant studies cited in documents supplied by the test manufacturers had already been identified by bibliographic database searches. Additional data, relating to the study by Hermansson *et al.*,[33,34] were obtained through contact with the authors. *Figure 1* shows the flow of studies through the review process, and *Appendix 3* provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage.

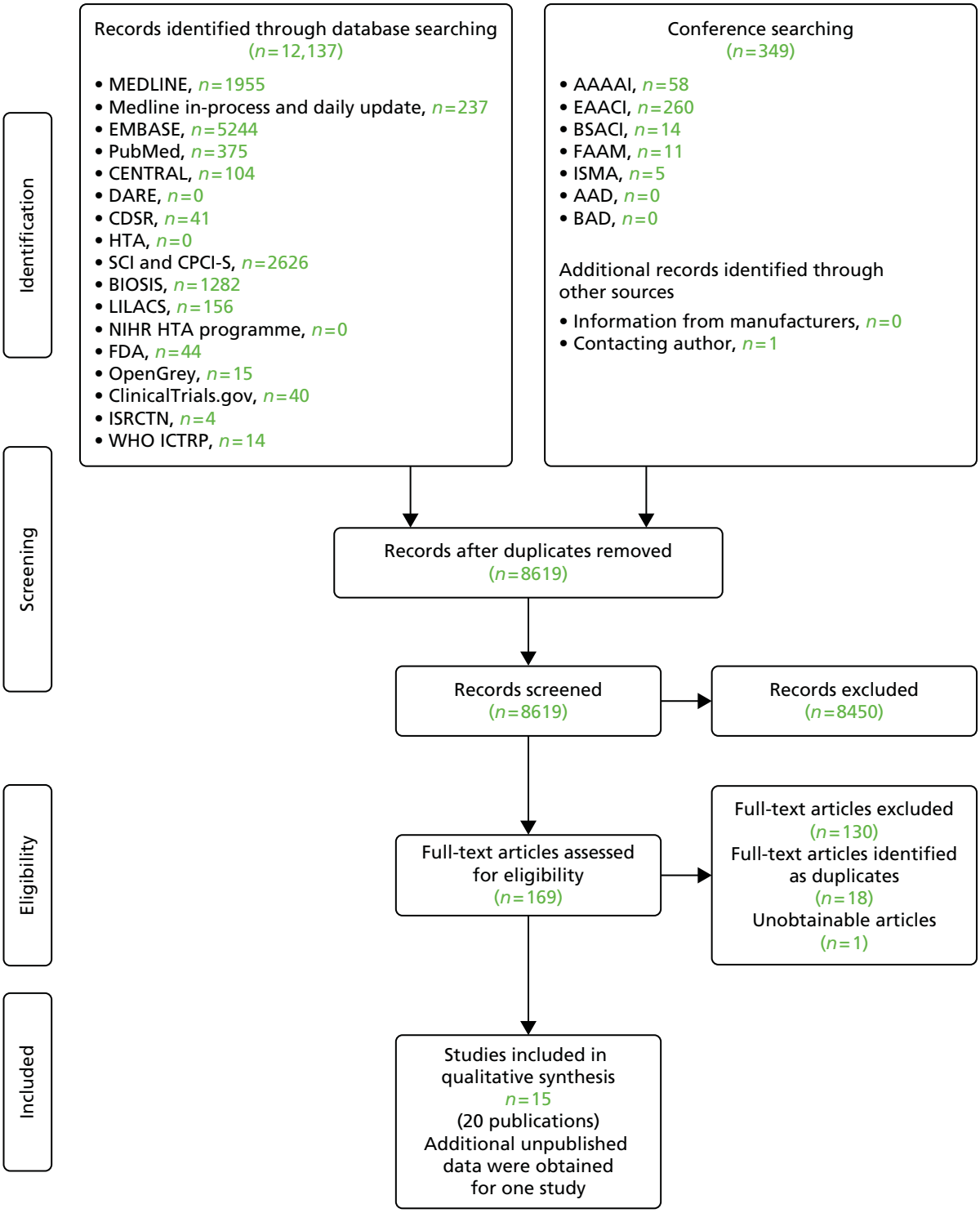

FIGURE 1 Flow of studies through the review process.

Overview of included studies

Based on the searches and inclusion screening described above (see *Search strategy* and *Inclusion and exclusion criteria*, above), 20 publications,[30–49] of 15 studies, were included in the review; the results section of this report cites studies using the primary publication and, where this is different, the publication in which the referenced data were reported.

Two of the included studies[39,40] were conducted in the UK and, where reported, the remaining studies were conducted in other European countries; one study[47] did not report location. Of the 15 included studies, four were funded by,[38,46] or received reagents and consumables[39] or testing services[45] from, the manufacturer. Five studies were publicly funded[32,42–44,49] and six studies[33,36,37,40,41,47] did not report funding sources. Full details of funding are reported in the baseline study details tables (see *Appendix 2*, *Tables A–C*).

All of the included studies evaluated versions of ImmunoCAP ISAC; one study[33] evaluated ImmunoCAP ISAC 112, five studies[37–39,42,43] evaluated ImmunoCAP ISAC 103, four studies[32,44,45,49] evaluated other versions of ImmunoCAP ISAC and five studies[36,40,41,46,47] did not specify the version used. We did not identify any studies of Microtest which met the inclusion criteria for this review.

We did not identify any studies that reported clinical outcomes (i.e. allergy symptoms, incidence of acute exacerbations, mortality, AEs of testing and treatment, health-care presentations or admissions, HRQoL, patient anxiety/preferences).

Five studies[32,33,37,38,40] assessed the effects on patient management of adding ImmunoCAP ISAC to the standard diagnostic work-up (SPT/single IgE); two studies[33,40] reported data on discontinuation or potential discontinuation of food avoidance diets, two studies[32,38] assessed changes to immunotherapy prescriptions, and one study[37] reported information on clinicians' judgement of the utility of ImmunoCAP ISAC results in informing patient management. One study[33] assesed ImmunoCAP ISAC 112, two studies[37,38] assessed ImmunoCAP ISAC 103, one study[32] assessed ImmunoCAP ISAC 96 and the remaining study[40] did not specify the version used. None of the five studies[32,33,37,38,40] reported the inclusion of patients with difficult to manage allergic disease; one study[40] reported inclusion criteria which may have been consistent with this classification (moderate to severe eczema and multiple food allergies); however, this study[40] was reported only as a conference abstract and hence provided very limited details of participants. One study[40] was conducted in the UK, two studies[32,37] were conducted in Spain, and one study was conducted in each of Finland[33] and Italy.[38]

Two studies[38,39] assessed the effects on clinical diagnosis of adding ImmunoCAP ISAC 103 to the standard diagnostic work-up: one study[39] reported data on new sensitisations identified in patients with idiopathic anaphylaxis and assessed their clinical relevance and the other study[38] reported changes to the diagnostic classification made by clinicians following access to ImmunoCAP ISAC results and was conducted in patients with allergic rhinitis, with or without concomitant food allergy. One additional study[36] assessed the relationship between change in IgE levels, measured by ImmunoCAP single IgE and an unspecified version of ImmunoCAP ISAC before and after a 3-year course of allergen-specific immunotherapy (SIT), and the clinicians' evaluation of the benefit of SIT. None of these studies reported test accuracy data. One study[39] was conducted in the UK, one study[38] was conducted in Italy and one study[36] did not report location.

Eight studies[41–47,49] compared the diagnostic accuracy of ImmunoCAP ISAC to that of alternative investigations (single IgE testing or SPT) to predict clinical reactivity as defined by SPT or OFC testing (the reference standard). Six studies[41,42,44,46,47,49] investigated people with food allergies and two studies[43,45] investigated people with allergic rhinitis/respiratory symptoms. None of the eight studies[41–47,49] reported the inclusion of patients with difficult to diagnose and manage allergic disease, or described inclusion criteria that could be considered consistent with this classification (e.g. polysensitised patients). One study[41] included patients with birch allergy, one study[42] included patients with suspected egg allergy, two studies[44,49] included patients with suspected cow's milk and/or hen's egg allergy, one study[46] included

patients with cow's milk allergy, one study[47] included patients with hazelnut allergy, one study[45] included patients with symptoms of allergic rhinitis and one study[43] included patients with pollen allergy. None of the studies was conducted in the UK, seven studies[41–46,49] were European and one study[47] was unreported. Two studies investigated ISAC 103,[42,43] one study[44] investigated ISAC 89, one study[49] investigated ISAC 59 and one study[45] investigated ISAC 50, whereas three studies[41,46,47] used unspecified ISAC.

Full details of the characteristics of study participants, study inclusion and exclusion criteria, and intervention and comparator or reference standard are reported in the data extraction tables presented in *Appendix 2* (see *Tables A–E*).

Excluded studies

One hundred and forty-eight full-text articles were retrieved: 18 were identified as duplicates and 130 were subsequently excluded. In all but two cases,[51,52] these studies reported no relevant outcomes. Further details of the 131 excluded full papers and the reasons for exclusion can be found in *Appendix 4*. One study[50] could not be obtained.

Study quality

Studies of changes to management, treatment or diagnosis

Seven studies investigated changes to treatment or management outcomes.[32–34,36–40] One very small cohort study,[36] with nine participants, assessed the relationship between change in IgE levels (measured by ImmunoCAP single IgE and an unspecified version of ImmunoCAP ISAC before and after a 3-year course of SIT) and the clinicians' evaluation of the benefit of SIT. The methodological quality of this study[36] was assessed using the CASP cohort tool. The remaining studies used a 'diagnostic before-and-after' type study design, which compared clinicians' views and decisions on management, treatment or diagnosis in a single group of patients, before and after access to the results of multiplex allergen testing. The methodological quality of these studies was assessed using a tool designed specifically for this review, which was based on the structure of QUADAS-2. Risk of bias and concerns regarding applicability are summarised in *Tables 2* and *3* and *Figure 2*; full assessments for each study are provided in *Appendix 4*.

The 'diagnostic before-and-after studies' were generally poorly reported, resulting in a high number of 'unclear' ratings, with all studies rated as 'unclear' risk of bias on at least one domain; four of the studies were published as conference abstracts only.[33,34,36,37,40] Two studies[33,38] were rated as 'high' risk of bias. One study[33] was rated as 'high' risk of bias for patient selection; participants were selected from a database of children who were receiving special diets in school catering, and reasons for exclusion

TABLE 2 Risk of bias for included diagnostic studies (change to management or treatment): review-specific QUADAS-2

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Comparator	Flow and timing	Patient	Index test	Reference standard
Heaps 2014[39]	?	+	+	+	+	+	+
Hermansson 2014[33,34]	–	?	?	?	?	+	?
Noimark 2012[40]	?	?	?	+	+	+	+
Luengo 2010[37]	?	?	?	?	?	+	+
Passalacqua 2013[38]	?	+	+	–	–	+	?
Sastre 2012[32]	?	+	+	+	–	+	?

–, high risk; +, low risk; ?, unclear risk.

TABLE 3 Risk of bias for included diagnostic studies (change to management or treatment): CASP cohort

Study	A. Are the results of the study valid?								B. What are the results?			C. Will the results help locally?		
	1. Did the study address a clearly focused issue?	2. Was the cohort recruited in an acceptable way?	3. Was the exposure accurately measured to minimise bias?	4. Was the outcome accurately measured to minimise bias?	5. (a) Have the authors identified all important confounding factors?	(b) Have they taken account of the confounding factors in the design and/or analysis?	6. (a) Was the follow-up of subjects complete enough?	(b) Was the follow-up of subjects long enough?	7. What are the results of this study?	8. How precise are the results?	9. Do you believe the results?	10. Can the results be applied to the local population?	11. Do the results of this study fit with other available evidence?	12. What are the implications of this study for practice?
Gay-Crosier 2010[36]	+	?	?	?	?	–	?	+	+	?	?	?	?	?

–, high risk; +, low risk; ?, unclear risk.

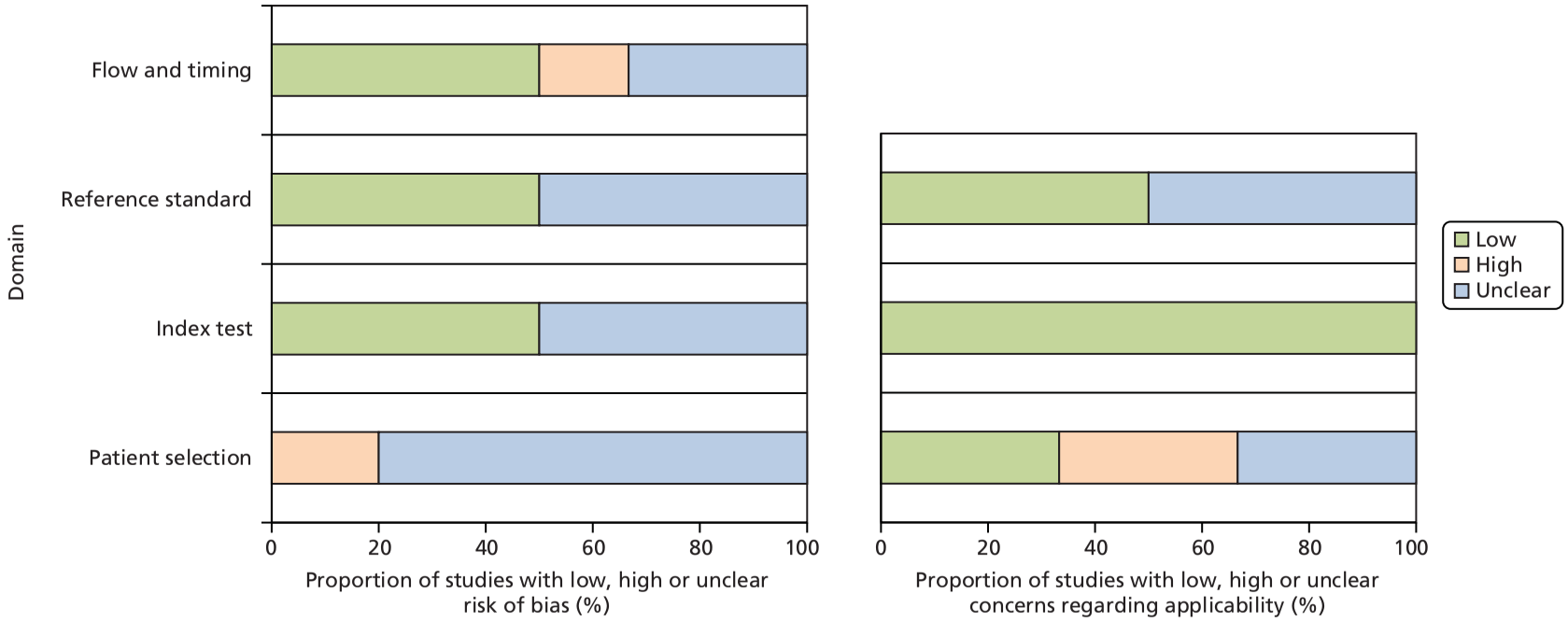

FIGURE 2 Risk of bias across included 'diagnostic before-and-after' studies (change to management or treatment).

included 'no longer allergic' (according to self-report or nurse interview) and unwillingness to participate because of, for example, fear of needles, lack of trust in tests and multiple previous testing. The second study[38] was rated as 'high' risk of bias for flow and timing because the standard care comparator differed between participants; all participants received SPT, and single IgE testing was used 'as required.' Although this is likely to be representative of standard practice, it remains a potential source of bias when estimating test performance.

Although this review included patients with any allergy, the primary objective was to assess the clinical effectiveness of multiplex allergen testing in people with complex or difficult to manage allergies, in UK health-care settings. Studies that did not specify that they included participants with difficult to manage allergic disease, or describe inclusion criteria which could be considered consistent with this classification (e.g. polysensitised patients), were therefore rated as having 'high' concerns regarding applicability. Studies that were conducted in non-UK settings and which assessed allergens considered unlikely to be relevant to UK populations (e.g. aeroallergens associated with Mediterranean countries) were also rated as having 'high' concerns regarding applicability. Two studies[39,40] were rated as having 'low' concerns regarding participant applicability, and in two studies[33,37] insufficient reporting details prevented a judgement and therefore they were rated 'unclear'. The remaining two studies[32,38] were rated as having 'high' concerns regarding participant applicability: for both this was because the patients were not from the UK and in one study[38] patients did not have difficult to manage disease.

The small observational study[36] that was assessed using the CASP cohort tool for risk of bias was reported only as conference abstract; therefore, risk of bias was largely unclear owing to lack of study details.

Studies of diagnostic accuracy

Eight studies[41–47,49] compared the diagnostic accuracy of ImmunoCAP ISAC to that of alternative investigations (single IgE testing or SPT) to predict clinical reactivity as defined by SPT or OFC testing (the reference standard). The methodological quality of these studies was assessed using the QUADAS-2 tool (summarised in *Table 4* and *Figure 3*). The full QUADAS-2 assessments for each study are provided in *Appendix 4*.

TABLE 4 QUADAS-2 assessments for included diagnostic accuracy studies

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Albarini 2013[47]	?	?	+	?	–	?	+
Alessandri 2012[42]	?	–	?	–	–	+	+
Cabrera–Freitag 2011[43]	–	–	+	?	–	+	+
De Swert 2012[41]	–	–	+	–	–	+	+
D'Urbano 2010[44]	–	–	?	+	–	+	+
Ott 2008[49]	?	–	?	?	–	+	+
Sokolova 2009[46]	–	?	+	?	–	+	+
Wöhrl 2006[45]	–	–	+	?	–	+	+

–, high risk; +, low risk; ?, unclear risk.

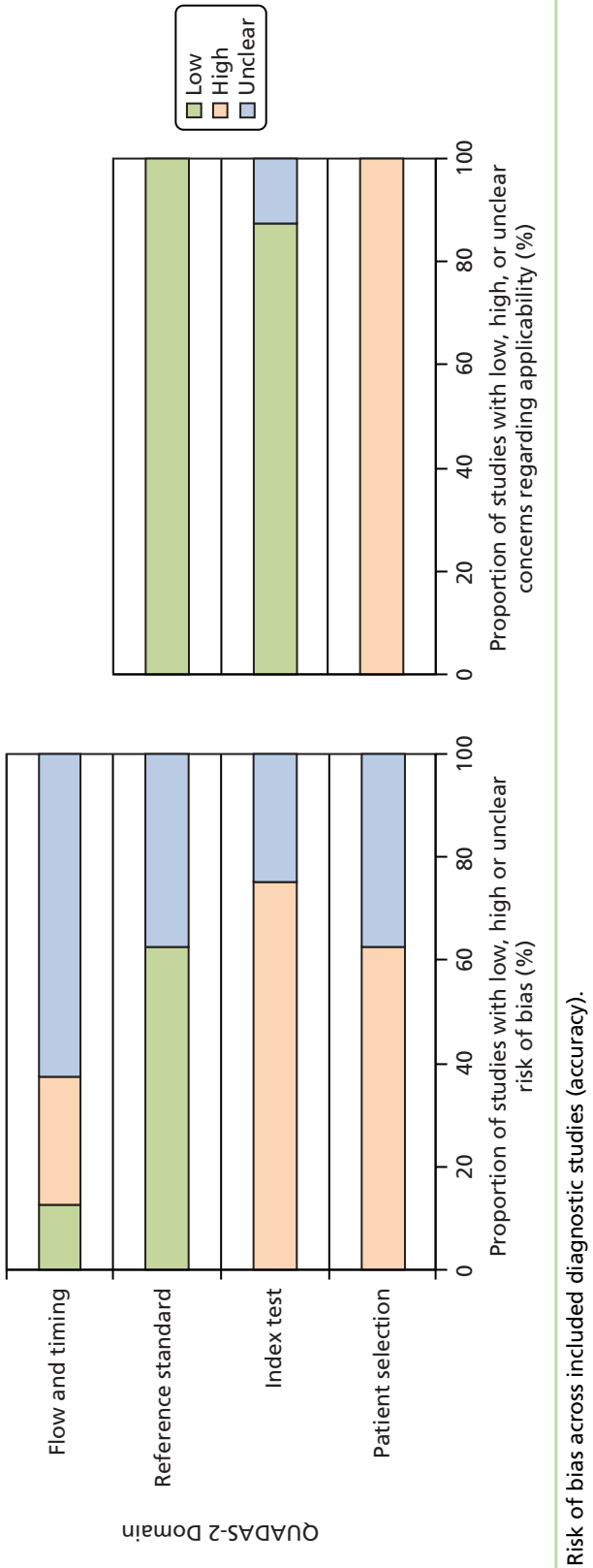

FIGURE 3 Risk of bias across included diagnostic studies (accuracy).

The comparative accuracy studies were generally poorly reported; seven[42–47,49] of the eight studies were rated as 'unclear' risk of bias on at least one QUADAS-2 domain. One study[47] was reported only as a conference abstract.

Seven studies[41–46,49] were rated as 'high' risk of bias on at least one domain. The main potential sources of bias were in relation to participant selection and application of the index test. Five studies[41,43–46] were rated as 'high' risk of bias for participant selection because they used a diagnostic case–control design, a design likely to produce inflated estimates of test performance, or applied inappropriate exclusion criteria (patients with eczema,[44] high levels of single IgE[45] or complex allergy[43]). Five studies[41,43–46] were rated as 'high' risk of bias for the index test. In all cases this was because diagnostic thresholds were not prespecified, but were optimised using ROC analyses in the same population that was used to assess test performance, an approach that is likely to result in inflated estimates of test performance. Two of these studies[41,42] were also rated as 'high' risk of bias for flow and timing, because not all the participants were included in the analysis[41] or because not all participants received the same reference standard.[42]

As was the case for studies of change to management, treatment or diagnosis, studies that did not specify that they included participants with difficult to manage allergic disease or describe inclusion criteria that could be considered consistent with this classification (e.g. polysensitised patients) were therefore rated as having 'high' concerns regarding applicability, and studies that were conducted in non-UK settings and which assessed allergens considered unlikely to be relevant to UK populations (e.g. aeroallergens associated with Mediterranean countries) were also rated as having 'high' concerns regarding applicability. All eight comparative accuracy studies[41–47,49] were rated as having 'high' concerns regarding participant applicability because they did not include people with difficult to manage allergic disease, and three of these studies[41,43,45] also focused on allergens that were considered unlikely to be fully applicable to the UK.

Effects on management, treatment and diagnostic classification of adding multiplex allergen testing to the diagnostic work-up of people with difficult to manage allergic disease

Study details

Six studies[32,33,37–40] assessed the effects of adding multiplex allergen testing to the standard diagnostic work-up (SPT/single IgE) on the management, treatment or diagnosis of patients. One study assessed ImmunoCAP ISAC 112,[33] three studies assessed ImmunoCAP ISAC 103,[37–39] one study assessed ImmunoCAP ISAC 96[32] and the remaining study used an unspecified version of ImmunoCAP ISAC.[40] All six studies[32,33,37–40] used a 'diagnostic before-and-after' type study design to assess the effects of adding ImmunoCAP ISAC results to the information available to clinicians on their judgements regarding the management, treatment or diagnosis of a given group of patients.

Change to management or treatment

Two studies investigated the use of ImmunoCAP ISAC to guide decisions on the discontinuation of restrictive diets in children with food allergies.[33,40] Both studies were reported as conference abstracts only and hence provided only limited study details and results. Hermansson *et al.*[33] used a database to identify 199 school children in Härkätie, Finland, receiving special diets in school catering; (confidential information has been removed) (e-mail from Johannes Savolainen, University of Turku, Finland, to Shona Lang, 23 June 2015, personal communication). (Confidential information has been removed) (Johannes Savolainen, personal communication). The Hermansson study[33] did not report any information on clinical outcomes following changes to dietary management. Noimark and Harnik[40] investigated 12 children selected from patients attending an East London allergy clinic (no details of the selection criteria were reported). Participants were investigated using SPT and/or single IgE, and an unspecified version of ImmunoCAP ISAC. The authors reported that ISAC enabled potential food reintroductions (peanut $n = 4$,

soy $n = 2$, wheat $n = 4$), additional to that indicated by single IgE alone; the numbers of potential reintroductions based on standard diagnostic work-up (SPT and/or single IgE) were not reported. No details were reported of which single IgE/SPTs were conducted or which ISAC components were assessed. Noimark and Harnik[40] did not report the number of food reintroductions that occurred following testing or clinical outcomes of any changes to dietary management.

Two studies[37,38] assessed the views of clinicians on whether or not ImmunoCAP ISAC testing provided information useful in the management of patients. Luengo *et al.*[37] performed ImmunoCAP ISAC 103 testing in 55 well-characterised, polysensitised patients (as assessed by SPTs and single IgE tests) with various allergies; no details were reported of which ISAC components were assessed or how these were interpreted. Participating clinicians judged that ImmunoCAP ISAC 103 provided new information useful in the management of the patient in 50 (91%) cases.[37] The added value was in the ability of ImmunoCAP ISAC to differentiate between protein homologues and hence to aid in the discrimination of allergens that were cross-immunoreactive rather than those that were responsible for sensitisation. In 34 (62%) cases the clinicians considered that it would have been useful to perform ImmunoCAP ISAC 103 testing before SPT, as several protein homologues can be investigated at once using ImmunoCAP ISAC.[37] Passalacqua *et al.*[38] investigated 318 consecutive polysensitised (at least two positive SPTs) patients with respiratory allergy in six allergy units in Italy. Participants were initially investigated using clinical history, SPT and single IgE testing (including mites, grass, olive, *Parietaria*, birch, cypress, ragweed, mugwort, cat and dog dander, *Alternaria* and *Aspergillus*) and were assessed using ImmunoCAP ISAC 103 (no details reported of components assessed or interpretation, but cross-immunoreactive allergens were considered); treating clinicians were required to review their diagnosis/treatment based on the ImmunoCAP ISAC 103 results and provide a judgement of the value of any additional information provided.[38] New information was classified as 'remarkable' if it could not be obtained using standard diagnostic work-up and could impact upon accuracy of diagnosis or SIT prescription; new information related to patient management was classified as 'remarkable' in 299 (95%) cases and 'to some extent' (not defined) in 232 (73%) cases.[38]

Two studies[32,38] investigated the effect on SIT prescriptions of adding ImmunoCAP ISAC testing to the standard diagnostic work-up of people with respiratory allergy. Passalacqua *et al.*[38] (described above) reported that a SIT prescription was made for 85 new patients, following testing with ImmunoCAP ISAC 103, who would not have received SIT based on standard diagnostic work-up (SPT/single IgE) alone. In addition, the existing SIT prescription was changed in a further three patients, following ImmunoCAP ISAC 103 testing.[38] Sastre *et al.*[32] investigated 141 people with respiratory allergy (with or without concomitant food allergy) in one allergy outpatient clinic in Spain. SIT indications were initially assessed based on clinical history and SPT (Olea e, Platanus a, Cupressus a, grass mix, Cynodon d, Phragmites c, Artemisia v, Salsola k and Plantago l), blind to the results of ImmunoCAP 96 testing (Ole e1, Cup s1, Cry j1, Pla a1, Pla a2, Phl p1, Phl p5, Phl p4, Phl p6, rPhl p11, Phl p12, Cyn d1, Sal k1, Aln g1, Bet v1, Cor a1.0101, Amb a1, Art v1, Art v3 and Par j2).[32] Clinicians then reassessed SIT indications based on all diagnostic information, including ImmunoCAP ISAC 96 results.[32] Disagreements on the SIT prescription based on standard diagnostic work-up and that based on all information, including ImmunoCAP ISAC, occurred for 79 (54%) study participants; details are reported in *Table 5*.[32] Neither study reported details of which SIT prescriptions were actually used, or any subsequent clinical outcomes.

Change to diagnostic classification

Two studies investigated the effect on diagnostic classification of adding ImmunoCAP ISAC 103 testing to the standard diagnostic work-up of people with allergic disease.[38,39] Heaps *et al.*[39] investigated 110 patients, from five UK specialist allergy centres, who had a diagnosis of idiopathic anaphylaxis [based on clinical assessment, SPT, single IgE testing and mast cell tryptase (MCT)]. Study participants were reassessed using ImmunoCAP ISAC 103 and clinicians were asked to score the additional information provided. Information

TABLE 5 Change to management or treatment

Study details	Known/suspected allergy (*n*)	Multiplex allergen test	Standard care	Outcome measure	Component	No. with outcome based on standard care	No. with outcome based on standard care + multiplex allergen test	No. with change in outcome	Additional information
Hermansson 2014[33] (Johannes Savolainen, personal communication)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Luengo 2010[37]	Multisensitised allergic patients (55)	ImmunoCAP ISAC 103	Clinical history SPT and sIgE	Clinicians' judgement on value of information added by ISAC	New information useful in the management of the patient	NA	50	NA	
					New/more/faster information meaning that it would have been useful to perform ISAC before SPT	NA	34	NA	
Noimark 2012[40]	Children with moderate to severe eczema and multiple food allergies (12)	ImmunoCAP ISAC (unspecified version)	SPT and/or specific sIgE	Potential food introduction	Peanut introduction	NR	4	NR	The authors concluded that more foods need to be represented on the chip, to allow the introduction of foods which might be avoided in children with multiple food allergies
					Soy introduction	NR	2	NR	
					Wheat introduction	NR	4	NR	

continued

TABLE 5 Change to management or treatment (*continued*)

Study details	Known/suspected allergy (*n*)	Multiplex allergen test	Standard care	Outcome measure	Component	No. with outcome based on standard care	No. with outcome based on standard care + multiplex allergen test	No. with change in outcome	Additional information
Passalacqua 2013[38]	Polysensitised (at least two positive SPTs) patients with respiratory allergy (318) Healthy controls (91)	ImmunoCAP ISAC 103	Clinical history and SPT, followed by specific sIgE assay(s) as required	New prescription of SIT	NR	32	117	85	31 new prescriptions of a single extract and 54 of two or more extracts
				Change to prescription of SIT	NR	NA	NA	3	Prescriptions were changed in three patients after ISAC
				Clinicians' judgement on relevance of information added by ISAC	New information related to management	NA	'To some extent': 232 'Remarkable': 299	NA	Clinicians judged that a more confident therapeutic approach was achieved in approximately one-third of cases
					More confident in management	NA	'To some extent': 232 'Remarkable': 286	NA	
Sastre 2012[32]	Patients with allergic rhinoconjunctivitis and/or asthma who were sensitised to pollen, with or without concomitant food allergy (141)	ImmunoCAP ISAC 96	Clinical history, taking into consideration the time of year of respiratory symptoms and European Academy of Allergy and Clinical Immunology guidelines, + SPT	Prescription of SIT (based on agreement of three blinded authors)	Grass	17	10	44[a]	Agreement in SIT indication before and after ImmunoCAP ISAC results occurred in 46% of participants. The authors concluded that this value makes the case for the usefulness of ISAC, at least in areas of complex sensitisation to pollen, to facilitate accurate prescription
					Olive	1	1	9[a]	
					Grass + olive	4	1	40[a]	
					Grass + cypress	0	1	9[a]	
					Grass + plane	0	1	8[a]	
					Olive + cypress	0	2	0[a]	
					Other extracts	3	4	12[a]	
					Total	25	20	79[a]	

NA, not applicable; NR, not reported.

a Number of patients with disagreement between SIT based on standard care and SIT based on standard care + ImmunoCAP ISAC. Note the numbers are not mutually exclusive (for each patient, there may have been disagreement in relation to more than one component of SIT).

provided by ImmunoCAP ISAC 103 was given the highest score (new heat- and digestion-stable sensitisations found, which were thought to have a strong association with anaphylaxis) for 22 (20%) of participants; however, large numbers of sensitisations that were not thought to be associated with anaphylaxis were also identified (see *Table 6* for full details).[39] In addition, for a further 35 (32%) of participants the information provided by ImmunoCAP ISAC was deemed to have identified only additional sensitisations which were not thought to be associated with anaphylaxis.[39] Passalacqua *et al.*[38] (described above; see *Change to management or treatment*) reported clinicians' ratings of the value of additional diagnostic information provided by ImmunoCAP ISAC 103 (see *Table 6*). In addition, this study[38] reported detailed information on changes to diagnostic category using five classifications (see *Table 6*); the addition of ImmunoCAP ISAC 103 testing resulted in increases in the numbers of people classified as 'poly sensitised with suspected cross-reactivity' and the number of people diagnosed with both inhalant and food allergies, as well as facilitating a diagnosis for eight previously unclassifiable patients.[38] Full details are provided in *Table 6*.

Other

We identified one additional study[36] that assessed the relationship between change in IgE levels measured by ImmunoCAP single IgE and change in IgE levels measured by an unspecified version of ImmunoCAP ISAC before and after a 3-year course of SIT, and the clinicians' evaluation of the benefit of SIT. This study[36] included only nine participants who received a total of 31 courses of SIT (no details of diagnosis were reported). The median specific IgE levels, measured by ISAC, decreased from 5.6 ISU/ml at the beginning of SIT to 0.01 ISU/ml at the end of SIT, and this change correlated with clinical benefit of SIT (evaluated by clinicians) (Spearman's $r = 0.46$; $p = 0.02$).[36] Conversely, allergen-specific single IgE measurements did not show a decrease from the beginning to the end of SIT.[36]

Summary

The results of studies in this section provide some indication that the addition of ImmunoCAP ISAC to standard diagnostic work-up can change clinicians' views on the diagnosis, management and treatment of patients. There was some indication that the use of ImmunoCAP ISAC testing may guide decisions on the discontinuation of restrictive diets, the content of SIT prescriptions, and whether or not patients should receive SIT. However, importantly, none of the studies that we identified reported any information on clinical outcomes subsequent to changes in treatment or management based on ImmunoCAP ISAC. Three studies report the usefulness of ImmunoCAP ISAC for discriminating allergens that are structurally similar and are recognised by the same IgE antibody (cross-immunoreactive); this discrimination appears to be particularly useful for identifying the cause of food allergies. The UK-based study on the use of ImmunoCAP ISAC to investigate idiopathic anaphylaxis indicated that the addition of ImmunoCAP ISAC to standard diagnostic work-up may identify a potentially causative agent in previously undiagnosed patients. However, it should be noted that the addition of ImmunoCAP ISAC also resulted in the identification of large numbers of sensitisations that were not considered to be associated with the anaphylaxis, that is, large numbers of clinically false-positive test results or sensitisations associated with other allergic conditions such as rhinitis.

TABLE 6 Change to diagnosis results

Study details	Known/suspected allergy (*n*)	Multiplex allergen test	Standard care	Outcome measure	Component	No. with outcome based on standard care	No. with outcome based on standard care + multiplex allergen test	No. with change in outcome	Additional information
Heaps 2014[39]	Idiopathic anaphylaxis (110)	ImmunoCAP ISAC 103	Clinical history, SPT, specific sIgE, MCT	Clinicians' judgement on relevance of information added by ISAC	ISAC score I: no new sensitisation found	NA	53	NA	39 patients had blank reactions, 14 patients had positive ISAC to known sensitisations
					ISAC score II: new allergen sensitisations found, but these were not thought to be associated with the anaphylaxis	NA	35	NA	322 new sensitisations, including: pollens (24 patients); HDM (22 patients); animal danders (15 patients)
					ISAC score III: new sensitisations (heat and digestion stable) found, which were thought to have a strong association with the anaphylaxis	NA	22 (11 substantiated on recall by additional clinical information, SPT, self-challenge, controlled clinical challenge, or accidental exposure)	NA	203 new sensitisations, of which 35 were thought to be highly likely to be responsible for the anaphylaxis, including components of wheat, shrimp, peanut, soy bean, latex, fish, peach, hazelnut, kiwi, egg, cow's milk and beef meat The authors concluded that, in these patients, the new information could lead to targeted risk reduction and less uncertainty 8 patients had more than one potential anaphylaxis trigger identified

Study details	Known/suspected allergy (*n*)	Multiplex allergen test	Standard care	Outcome measure	Component	No. with outcome based on standard care	No. with outcome based on standard care + multiplex allergen test	No. with change in outcome	Additional information
Passalacqua 2013[38]	Polysensitised (at least two positive SPTs) patients with respiratory allergy (318) Healthy controls (91)	ImmunoCAP ISAC 103	Clinical history and SPT, followed by specific sIgE assay(s) as required	Diagnostic category	A: Polysensitised with only one clinically relevant sensitisation	56	33	A→B: 32 A→C: 4 A→D: 7 A→E: 0	There were no patients for whom a diagnosis could not be reached following ISAC
					B: True polysensitised with more than one clinically relevant sensitisation	176	117	B→A: 15 B→C: 54 B→D: 35 B→E: 0	
					C: Polysensitised with suspected cross-reactivity	44	99	C→A: 0 C→B: 6 C→D: 6 C→E: 0	
					D: Sensitised to inhalants and foods	34	69	D→A: 2 D→B: 5 D→C: 9 D→E: 0	
					E: Non-classifiable	8	0	E→A: 3 E→B: 2 E→C: 0 E→D: 3	
				Clinicians' judgement on relevance of information added by ISAC	New information related to diagnosis	NA	'To some extent': 220 'Remarkable': 87	NA	Clinicians judged that a more confident diagnostic approach was achieved in approximately one-third of cases
					More confident in diagnosis	NA	'To some extent': 227 'Remarkable': 295	NA	

NA, not applicable.

Diagnostic accuracy of ImmunoCAP Immuno Solid-phase Allergen Chip, compared with other testing options, for the prediction of allergic response

Study details

Six studies[41,42,44,46,47,49] were identified which compared the accuracy of ImmunoCAP ISAC to existing diagnostic tests (SPT or single IgE tests) in people with food allergies; two studies[43,45] were identified of people with allergies to aeroallergens. None of the studies looked at ISAC 112, two investigated ISAC 103,[42,43] one investigated ISAC 89,[44] two investigated ISAC 50/51[45,49] and three investigated unknown ISAC versions.[41,46,47] The results of the comparative diagnostic accuracy studies are summarised in *Table 7*.

Diagnosis of food allergy

De Swert *et al.*[41] investigated soy flour allergy. The diagnostic accuracy of an unknown ISAC version to measure the soy flour component rGly m4 was compared with the single IgE test for the same component and to a SPT for soy flour. Cut-off values were reported separately for each test and OFC testing was used as the reference standard. ISAC had the highest sensitivity, 86% (95% CI 42% to 100%), but the lowest specificity, 80% (95% CI 28% to 100%). The single IgE test and SPT had similar sensitivity (75%) and specificity (100%).

Alessandri *et al.*[42] investigated allergy to boiled or raw egg. The diagnostic accuracy of ISAC 103, when used to measure three individual egg components (Gal d1 or Gal d2 or Gal d3), was compared with the accuracy of single IgE tests (egg yolk or egg white) and compared with the accuracy of SPTs (egg white extract or raw egg white or boiled egg white or egg yolk extract or raw egg yolk or boiled egg yolk). Cut-off values were reported separately for each test and OFC testing was used as the reference standard. SPT had the highest sensitivity for prediction of allergic response to raw egg white, 88% (95% CI 71.8% to 96.6%), whereas Gal d3 measured using ISAC 103 had the highest specificity, 100% (95% CI 90% to 100%). Results for raw egg were similar to those for boiled egg. In general, single IgE performed similarly to SPT (both measured whole extracts), whereas ISAC 103 gave much more variable results for the three different components measured. No measure of the overall diagnostic performance of ISAC 103 (all components combined) was reported.

Two studies[44,49] investigated allergy to cow's milk and hen's egg. D'Urbano *et al.*[44] compared the accuracy of ISAC 89, used to measure two individual components (Gal d1 or Bos d8), to the accuracy of single IgE tests (egg white or cow's milk). Cut-off values were reported separately for each test and OFC testing was used as the reference standard. Specificity was consistent (96%) for both ISAC 89 components and for cow's milk and egg white single IgE. Sensitivity values were higher for ISAC 89 components (78% for Bos d8 and 73% for Gal d1) than for the corresponding whole-allergen single IgE tests (41% for cow's milk and 27% for egg white). When whole-allergen single IgE tests and ISAC 89 were used in series (i.e. ISAC 89 results were considered only in single IgE-negative participants), the combined sensitivity was greater than that for single IgE alone (84% compared with 41% for cow's milk allergy, and 73% compared with 27% for hen's egg allergy); specificity was 92% in both cases. Ott *et al.*[49] compared the accuracy of ISAC 51, used to measure eight individual components (α-casein, β-casein, κ-casein, Bos d4, Bos d5, Gal d1, Gal d2, Gal d4), with the accuracy of single IgE tests (hen's egg or cow's milk extract) and to the accuracy of SPTs (native hen's egg or native cow's milk). Cut-off values were reported separately for each test and OFC testing was used as the reference standard. The results were very variable between tests. SPT had the highest sensitivity for cow's milk allergy, 93.6% (95% CI 78.5% to 99%). The ISAC 51 components all had low sensitivity for cow's milk allergy (ranging from 23.9% to 50% for the five components assessed). Conversely, all five ISAC 51 components had high specificity for cow's milk allergy (ranging from 88.4% to 97.7%), whereas SPT had low specificity, 48.2% (95% CI 28.7% to 68%). Single IgE testing had the highest sensitivity for hen's egg allergy, 71.1% (95% CI 55.7% to 83.6%). All three ISAC 51 components had low sensitivity (ranging from 17.8% to 57.8%) and high specificity for hen's egg allergy; the individual specificities of the ISAC 51 components were 100% for Gal d4, 86.7% for Gal d1 and 80% for Gal d2. Single IgE testing and skin prick testing had comparable specificity (86.7% and 100%, respectively). No measure of the overall diagnostic performance of ISAC 51 (all relevant components combined) was reported for either cow's milk or hen's egg allergy.

TABLE 7 Accuracy of ImmunoCAP ISAC, compared with other allergen testing techniques

Study ID	No. of participants, suspected allergy	Reference standard	Index test or comparator	Component/allergen (cut-off point)	TP	FN	FP	TN	Sensitivity% (95% CI)	Specificity% (95% CI)	Additional information
Food											
Albarini 2013[47]	35, hazelnut allergy	DBPCFC	ISAC-NR	Cor.a.1.1010 (NR)	9	7	5	14	56.3 (29.9 to 80.2)[a]	73.7 (48.8 to 90.9)[a]	The authors concluded that the association among symptoms and sIgE profile should be carefully investigated considering the natural history and evident food allergy
				Cor.a.1.0401 (NR)	7	9	3	16	43.8 (19.8 to 70.1)[a]	84.2 (60.4 to 96.6)[a]	
				Cor.a.8 (NR)	2	14	2	17	12.5 (1.6 to 38.3)[a]	89.5 (66.9 to 98.7)[a]	
				Cor.a.9 (NR)	1	15	0	19	6.3 (0.2 to 30.2)[a]	100 (82.4 to 100)[a]	
			sIgE	Hazelnut (0.35 kUI/l)	16	0	15	4	100 (79.4 to 100)[a]	21.1 (6.1 to 45.6)[a]	
			SPT	NR (> 3 mm diameter)	16	0	9	10	100 (79.4 to 100)[a]	52.6 (28.9 to 75.6)[a]	
Alessandri 2011[42]	68, egg	Double-blind food challenge boiled eggs	ISAC 103	Gal d1 (0)	NR[b]	NR[b]	NR[b]	NR[b]	61 (42.1 to 77.1)	97 (85.1 to 99.9)	The authors reported that evaluation of 103 allergenic molecules by means of the ISAC microarray approach allowed detection of significant clinical sensitisations to other important allergenic sources, confirming that hen's egg sensitisation is often associated with other sensitisations to food and inhalants
				Gal d2 (0.21)	NR[b]	NR[b]	NR[b]	NR[b]	40 (22.9 to 57.9)	94 (80.8 to 99.3)	
				Gal d3 (0.06)	NR[b]	NR[b]	NR[b]	NR[b]	18 (7 to 35.5)	100 (90 to 100)	
			sIgE	Egg white (1.23)	NR[b]	NR[b]	NR[b]	NR[b]	79 (61.1 to 91)	71 (53.7 to 85.4)	
				Egg yolk (0.11)	NR[b]	NR[b]	NR[b]	NR[b]	64 (45.1 to 79.6)	88 (72.5 to 96.7)	
			SPT	Egg white extract (8)	NR[b]	NR[b]	NR[b]	NR[b]	84 (67.2 to 94.7)	77 (59.9 to 89.6)	
				Raw egg white (48)	NR[b]	NR[b]	NR[b]	NR[b]	88 (71.8 to 96.6)	80 (63.1 to 91.6)	
				Boiled egg white (11.6)	NR[b]	NR[b]	NR[b]	NR[b]	85 (68.1 to 94.9)	94 (80.8 to 99.3)	
				Egg yolk extract (0)	NR[b]	NR[b]	NR[b]	NR[b]	70 (51.3 to 84.4)	83 (66.4 to 93.4)	
				Raw egg yolk (8.4)	NR[b]	NR[b]	NR[b]	NR[b]	79 (61.1 to 91)	80 (63.1 to 91.6)	
				Boiled egg yolk (4.3)	NR[b]	NR[b]	NR[b]	NR[b]	45 (28.1 to 63.6)	94 (80.8 to 99.3)	

continued

TABLE 7 Accuracy of ImmunoCAP ISAC, compared with other allergen testing techniques (*continued*)

Study ID	No. of participants, suspected allergy	Reference standard	Index test or comparator	Component/allergen (cut-off point)	TP	FN	FP	TN	Sensitivity% (95% CI)	Specificity% (95% CI)	Additional information
		Double-blind food challenge raw eggs	ISAC 103	Gal d1 (0)	NR[b]	NR[b]	NR[b]	NR[b]	84 (60.4 to 96.6)	90 (80.4 to 97.7)	
				Gal d2 (0)	NR[b]	NR[b]	NR[b]	NR[b]	53 (28.9 to 75.6)	84 (70.3 to 92.7)	
				Gal d3 (0.41)	NR[b]	NR[b]	NR[b]	NR[b]	21 (6.1 to 45.6)	98 (89.1 to 99.7)	
			sIgE	Egg white (2.25)	NR[b]	NR[b]	NR[b]	NR[b]	84 (60.4 to 96.6)	75 (61.1 to 86.7)	
				Egg yolk (0.11)	NR[b]	NR[b]	NR[b]	NR[b]	84 (60.4 to 96.6)	81 (67.4 to 91.1)	
			SPT	Egg white extract (11)	NR[b]	NR[b]	NR[b]	NR[b]	89 (66.9 to 98.7)	73 (58.9 to 85.1)	
				Raw Egg white (71.2)	NR[b]	NR[b]	NR[b]	NR[b]	79 (54.4 to 93.9)	90 (77.8 to 96.6)	
				Boiled egg white (23.3)	NR[b]	NR[b]	NR[b]	NR[b]	95 (74 to 99.9)	86 (72.8 to 94.1)	
				Egg yolk extract (10.7)	NR[b]	NR[b]	NR[b]	NR[b]	58 (33.5 to 79.7)	86 (72.8 to 94.1)	
				Raw egg yolk (8.4)	NR[b]	NR[b]	NR[b]	NR[b]	68 (43.4 to 87.4)	59 (44.2 to 73)	
				Boiled egg yolk (4)	NR[b]	NR[b]	NR[b]	NR[b]	53 (28.9 to 75.6)	86 (72.8 to 94.1)	
De Swert 2012[41]	15 patients, (with birch pollen allergy), soy	Open challenge with Alpro® (Alpro, Ghent, Belgium) soya natural drink	ISAC – NR	rGly m4 (1 ISU)	6	1	1	4	86 (42 to 100)[a]	80 (28 to 100)	Levels reported for nGly m5 and nGly m6, for both sIgE and ISAC but no cut-off values to allow determination of sensitivity and specificity
			sIgE	rGly m4 (17.6 kU/l)	6	2	0	7	75 (35 to 100)[a]	100 (59 to 100)	
			SPT	Soy flour (7 mm)	6	2	0	6	75 (35 to 100)[a]	100 (54 to 100)	

Study ID	No. of participants, suspected allergy	Reference standard	Index test or comparator	Component/allergen (cut-off point)	TP	FN	FP	TN	Sensitivity% (95% CI)	Specificity% (95% CI)	Additional information
D'Urbano 2010[44]	104, cow's milk 58 or hen's egg 46	Open food challenge	ISAC 89	Bos d8 (> 0.60 ISU)	25	1	7	25	78 (60 to 91)	96 (80 to 99)	
				Gal d1 (> 0.86 ISU)	16	1	6	23	73 (50 to 89)	96 (79 to 99)	
			sIgE	Cow's milk (≥ 16.6 kU/l)	13	1	19	25	41 (24 to 60)	96 (80 to 99)	
				Egg white (> 25.3 kU/l)	6	1	16	23	27 (11 to 50)	96 (79 to 99)	
			Serial testing, where ISAC results are considered only in sIgE-negative participants	Cow's milk (≥ 16.6 kU/l on sIgE or < 16.6 kU/l on sIgE and (> 0.60 ISU on ISAC)	27	2	5	24	84 (67 to 95)	92 (75 to 99)	
				Hen's egg (≥ 25.3 kU/l on sIgE or < 25.3 kU/l on sIgE and (> 0.86 ISU on ISAC)	16	2	6	22	73 (50 to 89)	92 (73 to 99)	
Ott 2008[49]	130, cow's milk 85, hen's egg 60	Double-blind food challenge, or open food challenge in young infants	ISAC 51	αα casein (0.1)	11[a]	31[a]	1[a]	42[a]	26.2 (13.9 to 42)	97.7 (87.7 to 99.6)	The authors concluded that allergen microarrays provide a new tool to diagnose symptomatic cow's milk and hen's egg allergy. They show performance characteristics comparable to the current diagnostic tests and may be indicated in small children in whom only small blood volumes are obtainable However, they are not capable of replacing double-blind, placebo-controlled food challenges in most cases
				ββ casein (0.1)	11[a]	31[a]	3[a]	40[a]	26.2 (13.9 to 42)	93 (89.9 to 98.5)	
				κκ casein (0.2)	16[a]	26[a]	6[a]	38[a]	38.1 (23.6 to 54.4)	88.4 (74.9 to 96.1)	
				Bos d4 (0.1)	21[a]	21[a]	3[a]	40[a]	50 (34.2 to 65.8)	93 (80.9 to 98.5)	
				Bos d5 (0.1)	10[a]	32[a]	2[a]	41[a]	23.9 (12.1 to 39.5)	95.3 (84.2 to 99.3)	
				Gal d1 (> 0)	26[a]	21[a]	2[a]	13[a]	57.8 (42.2 to 72.3)	86.7 (59.5 to 98)	
				Gal d2 (> 0)	26[a]	21[a]	3[a]	12[a]	57.8 (42.2 to 72.3)	80 (51.9 to 95.4)	
				Gal d4 (> 0)	8[a]	37[a]	0[a]	15[a]	17.8 (8 to 32.1)	100 (100)	
			sIgE	Cow's milk extract (8.1)	22[a]	20[a]	8[a]	35[a]	51.2 (35.5 to 66.7)	81.4 (66.6 to 91.6)	
				Hen's egg extract (2.9)	32[a]	13[a]	2[a]	13[a]	71.1 (55.7 to 83.6)	86.7 (59.5 to 98)	
			SPT	Native cow's milk (3)	39[a]	3[a]	22[a]	21[a]	93.6 (78.5 to 99)	48.2 (28.7 to 68)	
				Native hen's egg (9)	27[a]	18[a]	0[a]	15[a]	60.7 (54.6 to 78.5)	100 (71.3 to 100)	

continued

TABLE 7 Accuracy of ImmunoCAP ISAC, compared with other allergen testing techniques (*continued*)

Study ID	No. of participants, suspected allergy	Reference standard	Index test or comparator	Component/allergen (cut-off point)	TP	FN	FP	TN	Sensitivity% (95% CI)	Specificity% (95% CI)	Additional information
Sokolova 2009[46]	37 (CMPA), 4 controls (no history of allergy and drank milk daily)	Oral challenge test	ISAC – NR	At least one cow's milk allergen component positive: α-lactalbumin (Bos d4), bovine serum albumin (Bos d6), IgG heavy chain (Bos d7), casein (Bos d8) and its fractions (α-S1, β and κ), lactoferrin (Bos d lactoferrin) and β-lactoglobulin (Bos d5.0101 (NR)	17	0	2	22	100[a] (80.5 to 100)	91.7[a] (73 to 99)	The authors concluded that the characterisation of patient sensitisation profiles before and after acquisition of tolerance to cow's milk protein may contribute to the identification of possible indicators of prognosis of this food allergy
			sIgE	At least one cow's milk allergen component positive: whole milk, α-lactoalbumin, β-lactoglobulin and casein (NR)	17	0	15	9	100[a] (80.5 to 100)	37.5[a] (18.8 to 59.4)	

Study ID	No. of participants, suspected allergy	Reference standard	Index test or comparator	Component/allergen (cut-off point)	TP	FN	FP	TN	Sensitivity% (95% CI)	Specificity% (95% CI)	Additional information
Aeroallergens											
Cabrera-Freitag 2011[43]	173 patients, (43 grass pollen plus 26 controls and 12 cypress pollen plus 92 controls)	Clinical history and SPT	ISAC – 103	At least one grass pollen component positive: rPhl p1, rPhl p2, nPhl p4, rPhl p5, rPhl p6, rPhl p7, rPhl p11, rPhl p12 (0.3)	42[a]	1[a]	2[a]	24[a]	97.7 (87.7 to 99.9)	92.3 (74.9 to 99.0)	
				At least one grass pollen component positive: rPhl p1, rPhl p2, nPhl p4, rPhl p5, rPhl p6, rPhl p7, rPhl p11, rPhl p12 (0.4)	41[a]	2[a]	1[a]	25[a]	95.3 (84.2 to 99.4)	96.1 (80.4 to 99.9)	
				Cypress pollen, nCup a1 (0.3)	11[a]	1[a]	8[a]	84[a]	91.7 (61.5 to 99.8)	91.3 (85.5 to 97.1)	
				Cypress pollen nCup a1 (0.82)	11[a]	1[a]	4[a]	88[a]	91.7 (61.5 to 99.8)	95.6 (91.5 to 99.8)	
			sIgE	*Phleum pratense* (0.35)	41[a]	2[a]	1[a]	25[a]	95.3 (84.2 to 99.4)	96.1 (80.4 to 99.9)	
				P. pratense (0.33)	41[a]	2[a]	1[a]	25[a]	95.3 (84.2 to 99.3)	96.1 (80.3 to 99.4)	
				Cupressus arizonica (0.35)	11[a]	1[a]	18[a]	74[a]	91.7 (61.5 to 99.8)	80.4 (72.3 to 88.5)	
				C. arizonica (0.66)	11[a]	1[a]	10[a]	82[a]	91.7 (61.5 to 98.6)	89.1 (80.9 to 94.7)	

continued

TABLE 7 Accuracy of ImmunoCAP ISAC, compared with other allergen testing techniques (*continued*)

Study ID	No. of participants, suspected allergy	Reference standard	Index test or comparator	Component/allergen (cut-off point)	TP	FN	FP	TN	Sensitivity% (95% CI)	Specificity% (95% CI)	Additional information
Wöhrl 2006[45]	120 patients with symptoms of allergic rhinitis	Clinical history and SPT	ISAC 50	At least one HDM allergen component positive: Der p1 and Der p2 (NR)	18[a]	8[a]	11[a]	85[a]	69.2 (48.2 to 86.6)	90.4 (82.6 to 95.5)	
				Cat: Fel d1 (NR)	18[a]	5[a]	9[a]	88[a]	78.3 (56.3 to 92.5)	90.7 (83.1 to 95.7)	
				At least one birch pollen component positive: rBet v1a, rBet v1b, and rBet v2 (NR)	27[a]	4[a]	9[a]	80[a]	87.1 (70.1 to 96.3)	89.9 (81.7 to 95.3	
				At least one grass pollen component positive: rPhl p1, 2, 5, 6, 7 (NR)	42[a]	5[a]	7[a]	66[a]	89.4 (76.9 to 96.4)	90.4 (81.2 to 96.0	
				Mugwort pollen: rArt v1 (> 0 kUA/l)	8[a]	9[a]	2[a]	101[a]	47.1 (23.0 to 72.1)	98.1 (93.1 to 99.7)	
			sIgE	HDM: whole allergen extract (NR)	23[a]	3[a]	9[a]	85[a]	88.5 (69.8 to 97.4	90.4 (82.6 to 95.5)	
				Cat: whole allergen extract (NR)	20[a]	3[a]	6[a]	88[a]	87.0 (66.4 to 97.1)	90.7 (83.1 to 95.7)	
				Birch pollen: whole allergen extract (NR)	24[a]	7[a]	10[a]	79[a]	77.4 (58.9 to 90.4)	88.8 (80.3 to 94.5)	
				Grass pollen: whole allergen extract (NR)	41[a]	6[a]	7[a]	66[a]	87.2 (74.2 to 95.1)	90.4 (81.2 to 96.0)	
				Mugwort pollen: whole allergen extract (NR)	15[a]	2[a]	11[a]	92[a]	88.2 (63.5 to 98.2)	89.3 (81.7 to 94.5)	

CMPA, cow's milk protein allergy; DBPCFC, double-blind placebo-controlled food challenge; FN, false negative; FP, false positive; kU/l, kilo International Unit per litre; NR, not reported; sIgE, single IgE test; TN, true negative; TP, true positive.

a Data calculated by authors.

b Values could not be calculated because 19 patients were classified as allergic and 14 patients as partially tolerant, but these numbers plus the reported sensitivity and specificity did not give whole number values.

Sokolova *et al.*[46] investigated milk allergy. The diagnostic accuracy of an unknown ISAC version, used to measure nine individual components (Bos d 4, Bos d 6, Bos d 7, Bos d 8, casein α-S1, casein β and casein κ, Bos d lactoferrin, Bos d 5.0101), was compared with the accuracy of single IgE tests for four allergens (whole milk, α-lactoalbumin, ββ-lactoglobulin and casein). For both methods, a positive result was defined as positive for at least one component or whole allergen; the cut-off values used to define positivity for individual components and allergens were not reported. OFC testing was used as the reference standard. Both combined ISAC testing and combined single IgE testing had 100% sensitivity; however, ISAC testing had much higher specificity, 91.7% (95% CI 73% to 99%), than the single IgE testing, 37.5% (95% CI 18.8% to 59.4%).

Albarini *et al.*[47] investigated hazelnut allergy. The diagnostic accuracy of an unknown ISAC version, used to measure four individual components (Cor.a.1.1010, Cor.a.1.0401, Cor.a.8, Cor.a.9), was compared to the accuracy of single IgE tests (hazelnut) and to SPT. Cut-off values were not reported for the ISAC test. OFC testing was used as the reference standard. Both the SPT and the single IgE test had 100% sensitivity, whereas the ISAC components generally had low sensitivity (ranging from 6.3% to 56.3%). However, the ISAC components had higher specificity (ranging from 73.7% to 100%) than either single IgE (21.1%) or skin prick testing (52.6%).

Diagnosis of aeroallergy

Wöhrl 2006[45] investigated five different aeroallergens (HDM, cat dander, birch pollen, grass pollen and mugwort pollen). The diagnostic accuracy of ISAC 50, used to measure the presence of one or more aeroallergens (up to five), was compared with the accuracy of single IgE tests of whole allergens. Where multiple ISAC components were assessed, a positive result was defined as positive for at least one component. The cut-off points for each test were not reported. Skin prick testing was used as the reference standard. The specificity of ISAC 50 was high for all aeroallergens investigated, regardless of whether a single component or multiple components were assessed (range 89.9–98.1%), and, with the exception of mugwort pollen, was comparable to the specificity estimate for the corresponding whole allergen single IgE test for all aeroallergens investigated (see *Table 7*). The sensitivity of ISAC 50 was lower than that of single IgE tests for HDM, cat and mugwort pollen. The sensitivities and specificities of the individual components ISAC 50 components were not reported.

Cabrera-Freitag *et al.*[43] investigated two different pollens (grass pollen or *Phleum pratense* and cypress pollen or *C. arizonica*). Two cut-off points (manufacturers' recommended and ROC optimised) were reported per test and SPT was used as the reference standard. The diagnostic accuracy of ISAC 103, when used to measure the eight components for grass pollen (rPhl p1, rPhl p2, nPhl p4, rPhl p5, rPhl p6, rPhl p7, rPhl p11, rPhl p12), was compared with the accuracy of a single IgE test to measure *P. pratense*; a positive result was defined as positive for at least one component. The sensitivity and specificity for ISAC 103 and single IgE were similar, irrespective of the cut-off point used. Sensitivity and specificity estimates for individual grass pollen ISAC 103 components were not reported. In addition, the accuracy of ISAC 103 was used to measure the presence of a one component for cypress pollen (nCup a1) in comparison with the accuracy of single IgE tests to measure *C. arizonica*. The sensitivity estimates for the two tests were equal at both cut-off points (91.7%); however, specificity was higher for ISAC 103 at both cut-off points (91.3% and 95.6%) than for the single IgE test (range 80.4–89.1%).

Summary

The diagnostic performance of ImmunoCAP ISAC in comparison with other tests (single IgE and SPT) varied considerably between studies, according to the allergens investigated and the way in which ISAC testing was applied. In general, individual ISAC components tended to have high specificity, but low sensitivity, relative to whole-allergen single IgE tests or SPT for the prediction of allergic response. The relatively low sensitivities of individual ISAC components are likely to be indicative of the proportions of patients in whom each component is associated with the observed allergic response. Conversely, a high specificity is indicative of a strong association between ISAC positivity for the individual component and an allergic response to whole allergen. However, when ISAC was used to measure the same component as single IgE testing or to measure multiple components (homologous proteins), with a positive test defined as any component positive, it appeared that

equivalent sensitivities could be achieved without corresponding loss of specificity. The ability of ImmunoCAP ISAC to discriminate between allergens that are structurally similar and are recognised by the same IgE antibody (cross-immunoreactive) may represent clinically useful additional information (see *Effects on management, treatment and diagnostic classification of adding multiplex allergen testing to the diagnostic work-up of people with difficult to manage allergic disease*, above). Therefore, if the focused use of groups of ISAC components can achieve equivalent sensitivity and specificity to that of single IgE testing, ISAC testing may be preferred.

The results of the only study to investigate serial testing suggested that use of ImmunoCAP ISAC after single IgE testing only in participants who were negative on single IgE could increase sensitivity relative to single IgE alone without any loss in specificity. None of the comparative diagnostic accuracy studies included in this review was conducted in people with difficult to manage allergic disease, and all studies investigated the diagnostic performance of a limited range of ISAC components of a specified allergen. These studies are therefore unable to provide any information on the specificity of the whole ISAC panel when used to investigate people with difficult to manage allergic disease, that is, the extent to which the multiplex allergen testing may produce 'false-positive' results by detecting sensitisations that are not clinically relevant. This indicates the importance of using confirmatory tests after the array and that the current array cannot wholly replace OFC or SPT as a diagnostic procedure.

Chapter 4 Assessment of cost-effectiveness

This chapter explores the cost-effectiveness of multiplex allergen testing compared with current clinical assessment in patients referred for specialist allergy investigation in secondary or tertiary care settings. More specifically, the following research question will be addressed:

- What is the cost-effectiveness of adding multiplex allergen testing to the investigation of people with difficult to manage IgE-mediated allergic disease in secondary or tertiary care settings?

Review of economic analyses of multiplex allergen testing

Search strategy

Searches were undertaken to locate relevant economic evaluations on adults and children undergoing specialist allergy investigation in secondary or tertiary care settings.

The following databases were searched for relevant studies from 2005 to May 2015:

- NHS Economic Evaluation Database (NHS EED) (via Wiley): 2005–Issue 2 of 2015/May/Iss2
- IDEAS via Research Papers in Economics (REPEC) (internet; http://repec.org/): 2005–26 May 2015
- EconLIT (via EBSCO*host*): 2005–21 May 2015
- EMBASE (via OvidSP): 1974–21 May 2015
- MEDLINE (via OvidSP): 1946–May Week 3 2015
- MEDLINE In-Process and Daily Update (via OvidSP): up to 20 May 2015.

Inclusion criteria

Studies reporting outcomes of a full cost-effectiveness analysis, with (at least) one of the comparators including multiplex allergen testing, were eligible for inclusion.

Quality assessment

Included studies are appraised using a quality checklist based on that of Drummond *et al.*[53]

Results

The literature search identified 311 records from bibliographic database searches and supplementary searching (e.g. reference/citation checking, additional database searches including the database search for the assessment of clinical effectiveness). After removing duplicates, and title and abstract screening, 15 records were considered to be potentially relevant; after full-text screening four studies (nine publications, all abstracts) were considered eligible for inclusion (*Figure 4*). All four included studies are authored by Hermansson (as either first or second author), an employee of Thermo Fisher Scientific. Three studies, reported in six publications,[33,34,54–57] considered multiplex allergen testing for children with suspected food allergy (specifically peanut allergy in two studies) and one study, reported in three publications,[58–60] considered multiplex allergen testing for patients sensitised to pollen. These studies are described in more detail below and summarised in *Table 8*. The results of the quality assessment are shown in *Table 9*.

Hermansson 2014

Hermansson *et al.*[33,34] considered the cost-effectiveness of ImmunoCAP ISAC in addition to a standard diagnostic work-up compared with standard diagnostic work-up without ImmunoCAP ISAC for Finnish school children with a restricted diet as a result of suspected food allergy (community setting). The analysis was informed by 24 children from a larger database (including a total of 2317 school children). The results indicated an unnecessary restricted diet for 63% of the children, resulting in a cost per avoided unnecessary diet of €480 for ImmunoCAP ISAC.

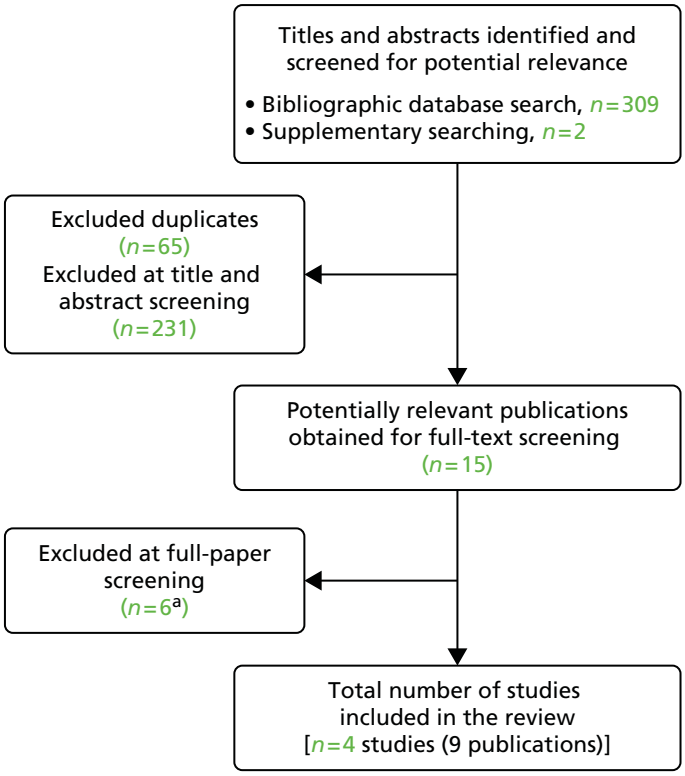

FIGURE 4 Flow chart (review of economic analyses). a, Reasons for exclusion: did not report outcomes of a full cost-effectiveness analysis ($n = 6$).

TABLE 8 Summary of included economic evaluations (all abstracts)

	Hermansson 2014[33,34]	Hermansson 2013,[54] 2012[55,56]	Glaumann 2013[57]	Mascialino 2013,[58,59] Hermansson 2012[60]
Population	Finnish suspected food-allergic school children	Children with suspected peanut allergy	Children with suspected peanut allergy	Spanish patients with allergic rhinoconjunctivitis and/or asthma sensitised to pollen from a complex pollen area
Setting	Primary care	Primary care	Primary care	NR
Time horizon	NR	5 years	5 years	9 years
Objective	To evaluate the health-economic benefit of ImmunoCAP ISAC	To demonstrate that MA for peanut allergy at the general practitioner level could increase QALYs and have a considerable economic impact	To compare different diagnostic methods: MA, SPT, OFC and DBPCFC for children with a suspected peanut allergy and to evaluate the patients' QoL and the economic impact for the health-care system in Sweden	To analyse the cost-effectiveness of MA for SIT indication and QoL
Source of effectiveness information	Database from Primary Care Unit ($n = 24$ children agreed to participate)	Literature	Literature	Database of 141 patients with allergic rhinoconjunctivitis and/or asthma sensitised to pollen from a complex pollen area[32]
Comparators	Traditional diagnostic algorithm with and without ImmunoCAP ISAC added	Different diagnostic approaches including DBPCFC, SPT and/or MA	Different diagnostic approaches including DBPCFC, OC, SPT and/or MA	SPT and MA vs. SPT

TABLE 8 Summary of included economic evaluations (all abstracts) (*continued*)

	Hermansson 2014[33,34]	Hermansson 2013,[54] 2012[55,56]	Glaumann 2013[57]	Mascialino 2013,[58,59] Hermansson 2012[60]
Costs items	NR	General practitioner visit, specialist visitor, tests, allergic reaction, allergy treatment (including EpiPen and antihistamine), indirect costs (for sensitivity analysis)	Doctor visits, tests, allergic reaction, allergy treatment (including EpiPen and antihistamine), indirect costs (for sensitivity analysis)	General practitioner visit, nurse visit, specialist visitor, emergency visit, tests, SIT, symptomatic treatment, indirect costs
Main measure of benefit	Unnecessary diets	QALYs	QALYs	QALYs
Assumptions	NR	NR	NR	Patients would get 6 years of 'sustained effect' (i.e. remain healthy) after 3 years of SIT
Perspective	NR	Health care	Health care	NR
Discount rate	NR	NR	NR	NR
Uncertainty around cost-effectiveness ratio expressed	No	No	No	No
Sensitivity analysis	No	No	No	No
Monetary outcomes	€	SEK (Sweden), USD (USA), RMB (China)	SEK (Sweden)	€
Outcomes per comparator	QALYs: NR Other outcomes: adding ImmunoCAP ISAC could identify 63% of the patients as having an unnecessary diet (this was 70% on the posters) Costs: NR	MA vs. DBPCFC vs. SPT: QALYs: 3.97 vs. 2.54 vs. 3.86 Costs: • Sweden: 70,051 SEK vs. 77,840 SEK vs. 130,306 SEK • USA: 27,023 USD vs. 27,892 USD vs. 45,010 USD • China: 8963 RMB vs. 25,982 RMB vs. 41,437 RMB The results presented on the posters differed but the order of the cost and effects of the comparators remained the same, except for China on one poster, where DBPCFC became most expensive while MA remained least expensive. Moreover, on another poster MA became most expensive for Korea and second most expensive for Japan (DBPCFC was least expensive)	MA vs. DBPCFC vs. OC vs. SPT: QALYs: 4.34 vs. 3.22 vs. 2.23 vs. 3.66 Costs: 11,267 SEK vs. 24,278 SEK vs. 33,031 SEK vs. 44,851 SEK The results presented on the poster differed but the order of the cost and effects of the comparators remained the same	MA reduces SIT by at least 20% SPT and MA vs. SPT: QALY: 7.03 vs. 6.88 Costs: €2538 vs. €2608 The costs for SPT and MA presented on the poster were slightly higher (€2583) Moreover, the results presented on the presentation slides differed but the order of the cost and effects of the comparators remained the same

continued

TABLE 8 Summary of included economic evaluations (all abstracts) (*continued*)

	Hermansson 2014[33,34]	Hermansson 2013,[54] 2012[55,56]	Glaumann 2013[57]	Mascialino 2013,[58,59] Hermansson 2012[60]
Summary of incremental analysis	Adding ImmunoCAP ISAC resulted in a cost per avoided unnecessary diet of €480 (€15 was reported on the poster)	MA is both more effective and less expensive than alternative diagnostic strategies	MA is both more effective and less expensive than alternative diagnostic strategies	SPT and MA combined is both more effective and less expensive than SPT only

DBPCFC, double-blind placebo-controlled food challenge; MA, molecular allergology; NA, not applicable; NR, not reported; OC, open oral food challenge; RMB, Chinese renminbi; SEK, Swedish krona; SIT, specific immunotherapy; USD, US dollar.

TABLE 9 Study quality checklist for included studies

	Hermansson 2014[33,34]	Hermansson 2013,[54] 2012[55,56]	Glaumann 2013[57]	Mascialino 2013,[58,59] Hermansson 2012[60]
Study design				
The research question is stated	✗	✗	✗	✗
The economic importance of the research question is stated	✗	✗	✗	✗
The viewpoint(s) of the analysis are clearly stated and justified	✗	✗	✗	✗
The rationale for choosing alternative programmes or interventions compared is stated	✗	✗	✗	✗
The alternatives being compared are clearly described	✗	✗	✗	✗
The form of economic evaluation used is stated	✗	✓	✓	✓
The choice of form of economic evaluation is justified in relation to the questions addressed	✗	✗	✗	✗
Data collection				
The source(s) of effectiveness estimates used are stated	✓	✗	✗	✓
Details of the design and results of effectiveness study are given (if based on a single study)	✗	✗	✗	✗
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA[a]	✗	✗	NA[a]
The primary outcome measure(s) for the economic evaluation are clearly stated	✗	✗	✗	✗
Methods to value benefits are stated	NA	✗	✗	✗
Details of the subjects from whom valuations were obtained were given	NA	✗	✗	✗
Productivity changes (if included) are reported separately	✗	✗	✗	✗

TABLE 9 Study quality checklist for included studies (*continued*)

	Hermansson 2014[33,34]	Hermansson 2013,[54] 2012[55,56]	Glaumann 2013[57]	Mascialino 2013,[58,59] Hermansson 2012[60]
The relevance of productivity changes to the study question is discussed	✗	✗	✗	✗
Quantities of resource use are reported separately from their unit costs	✗	✗	✗	✗
Methods for the estimation of quantities and unit costs are described	✗	✗	✗	✗
Currency and price data are recorded	✗	✗	✗	✗
Details of currency of price adjustments for inflation or currency conversion are given	✗	✗	✗	✗
Details of any model used are given	NA[a]	✗	✗	✗
The choice of model used and the key parameters on which it is based are justified	NA[a]	✗	✗	✗
Analysis and interpretation of results				
Time horizon of costs and benefits is stated	NA[a]	✓	✓	✓
The discount rate(s) is stated	✗	✗	✗	✗
The choice of discount rate(s) is justified	✗	✗	✗	✗
An explanation is given if costs and benefits are not discounted	✗	✗	✗	✗
Details of statistical tests and CIs are given for stochastic data	NA	NA	NA	NA
The approach to sensitivity analysis is given	NA	NA	NA	NA
The choice of variables for sensitivity analysis is justified	NA	NA	NA	NA
The ranges over which the variables are varied are justified	NA	NA	NA	NA
Relevant alternatives are compared	✓	✓	✓	✓
Incremental analysis is reported	✓	✗	✗	✗
Major outcomes are presented in a disaggregated as well as aggregated form	✗	✗	✗	✗
The answer to the study question is given	✗	✗	✗	✗
Conclusions follow from the data reported	✗[b]	✓	✓	✓
Conclusions are accompanied by the appropriate caveats	✗	✗	✗	✗

QALY, quality-adjusted life-year; NA, not applicable; ✗, no; ✓, yes.
a This assessment is likely to be directly based on trial data, hence this item is probably not applicable.
b It is unclear why this ICER is considered cost-effective.
Note that the quality assessment was based on the published abstracts only.

Hermansson 2013 and Hermansson 2012

Another study by Hermansson *et al.*[54–56] examined the cost-effectiveness of ImmunoCAP ISAC compared with double-blind placebo-controlled food challenge (DBPCFC) and skin prick testing for children with suspected peanut allergy. For this purpose, a Markov model was constructed with a 5-year time horizon. Health states included non-allergic and allergic, and mild and severe allergic reactions were modelled as events. The costs were considered for Sweden, the USA and China. The results indicated that ImmunoCAP ISAC is least expensive, whereas SPT is most expensive, in all three countries. Moreover, ImmunoCAP ISAC was also found to be most effective, leading to 3.97 quality-adjusted life-years (QALYs), whereas the DBPCFC strategy is least effective (2.54 QALYs). Consequently, ImmunoCAP ISAC dominated both the SPT and DBPCFC strategies.

Glaumann 2013

Glaumann *et al.*[57] examined the cost-effectiveness of ImmunoCAP ISAC compared with DBPCFC, open OFC and SPT for children with suspected peanut allergy in Sweden. A Markov model with a 5-year time horizon was constructed for this purpose. Health states included non-allergic and allergic, and mild and severe allergic reactions were modelled as events. The results indicated that ImmunoCAP ISAC is least expensive, whereas SPT is most expensive. Furthermore, ImmunoCAP ISAC was also found to be most effective, leading to 4.34 QALYs, whereas the OFC strategy was considered least effective (2.23 QALYs). Consequently, ImmunoCAP ISAC dominated all three alternative strategies.

Mascialino 2013 and Hermansson 2012

Mascialino *et al.*[58,59] and Hermansson *et al.*[60] examined the cost-effectiveness of ImmunoCAP ISAC with SPT compared with SPT only for Spanish patients sensitised to pollen in a complex pollen area. The analysis was based on a Markov model with a 9-year time horizon and the assumption that patients on specific immunotherapy (SIT) continue this treatment for 3 years and remain healthy for the subsequent 6 years or discontinue SIT and move to symptom management treatment until year 9. The analysis was informed by a data set of 141 patients with allergic rhinoconjunctivitis and/or asthma sensitised to pollen.[32] The results indicated that the addition of ImmunoCAP ISAC to SPT reduces SIT prescriptions and hence results in cost savings compared with SPT only (€2538 vs. €2608). ImmunoCAP ISAC with SPT was also found to be more effective (7.03 QALYs) than SPT only (6.88 QALYs); hence ImmunoCAP ISAC with SPT dominated SPT only.

Quality assessment and summary of studies in the cost-effectiveness review

All four studies[33,34,54–60] reported benefits associated with adding ImmunoCAP ISAC to the diagnostic work-up (increased effectiveness), and three out of four studies also showed cost savings when using ImmunoCAP ISAC. However, as all included studies were reported only as conference abstracts, the methods and assumptions used were largely unclear; this severely hampered the assessment of the validity of the results. It was often unclear precisely which diagnostic strategies were examined. The lack of information about these studies is illustrated in *Table 9* (study quality checklist for included papers). Besides this transparency issue, the credibility of the sources used in these studies may be questionable. Fundamental inputs of the model were based on expert opinion, inaccessible references, or no references were provided (information was still lacking after full retrieving of copies of the posters and a presentation supplied by the authors). For example, the numbers of true positives, false positives, false negatives and true negatives for ImmunoCAP ISAC appeared to be based on expert opinion in most cases.[33,34,54–57,59,60] In addition, two assessments from this group[54–57] focused on the same population, both using a Markov model with a 5-year time horizon, but the reported QALYs and outcomes differed substantially (see *Table 8*). In conclusion, the available economic assessments indicate that the addition of ImmunoCAP ISAC will increase effectiveness and can be cost-saving. However, given the lack of detail on how these results were produced and the use of expert opinion for key inputs, these findings should be interpreted with extreme caution.

Overview of potentially relevant excluded studies

In addition to the included studies described above, one potentially relevant study[61] that considered the incremental costs of multiplex allergen testing was excluded, as it did not report effectiveness outcomes and, as a result, was not considered to be a full cost-effectiveness analysis. For completeness, the results of

this study[61] (also reported only as a conference abstract) are summarised below (despite efforts in contacting the authors, the full copy of the poster could not be retrieved).

The study by Rodriguez-Ferran *et al.*[61] considered the costs of SPT, Phadiatop and ImmunoCAP Rapid for screening respiratory allergy in children in primary care. Their results showed that SPT is least expensive (€10–15), followed by ImmunoCAP® RAPID (Thermo Fisher Scientific/Phadia AB, Uppsala, Sweden; €30) and Phadiatop® (Phadia AB, Uppsala, Sweden; €36–67). The authors stated that they believe SPT is cost-effective.

Review of health-related quality of life studies

Search strategy

Searches were undertaken to locate relevant utility studies on adults and children with allergic conditions.

The following databases were searched for relevant studies from database inception date to July 2015:

- MEDLINE (via OvidSP): 1946–June Week 3 2015
- MEDLINE In-Process Citations and Daily Update (via OvidSP): up to 29 June 2015
- EMBASE (via OvidSP): 1974 to 29 June 2015
- Patient-Reported Outcome and Quality Of Life Instruments Database (PROQOLID) (internet; www.proqolid.org/): up to 1 July 2015
- NHS EED (via Wiley): 2005–Issue 2, April 2015
- Cost-Effectiveness Analysis (CEA) Registry (internet; www.ceareregistry.org): up to 1 July 2015.

Inclusion criteria

Studies were required to include utility values obtained using a preference-based instrument. Also, studies were limited to a population with an allergic condition associated with food or pollen. This limitation was applied in order to be pragmatic and focus on allergies for which there was at least some evidence, albeit limited, from the clinical effectiveness review. Non-English-language studies were excluded.

Results

Searches identified 1300 (1074 after removing duplicates) potentially relevant publications, of which 1028 were excluded at the abstract screening stage. Full texts were obtained for the 46 publications that were potentially relevant. Thirty-one publications were excluded at the full-text screening stage because no utility values were reported ($n = 29$) or the study was not written in English ($n = 2$). Four of the excluded publications were reviews. The studies included in these reviews were all present in the search results. Three additional publications were identified through reference checking of the included studies. The four studies[33,34,54–59] identified in the review of economic analyses of multiplex allergen testing were also identified in this review, but excluded because no original utility data were provided. Seventeen publications were included,[62–77] describing 14 studies (*Figure 5*).

Fourteen studies reporting health-state utilities for allergic conditions were found. Ten studies, reported in 13 publications, used the EuroQol instrument, and reported either the European Quality of Life-5 Dimensions (EQ-5D) utility score[62–67] or the visual analogue scale (VAS) score.[68–73] One study reported utilities obtained by the HUI Mark III instrument.[74] Three studies used a direct utility elicitation technique.[75–77] The 10 studies reported on 28 populations: 14 studies with rhinitis/rhinosinusitis/rhinoconjunctivitis/asthma,[62–66,68–73,78] 11 studies with eczema,[67,73,75–77] two studies with food allergy[73,74] and one study with mixed allergies except food allergies.[74] Utility values ranged from 0.5000 for patients with allergic rhinitis receiving allergy vaccination[72] to 0.970 for persons with mild eczema.[76] Patients who sought help from a specialised allergy clinic (to receive allergy vaccination) and patients currently exposed to allergens seemed to have lower utility scores than the other populations. Only two studies reported on the relationship between the severity of allergic symptoms and utility value[75,76] (*Table 10*).

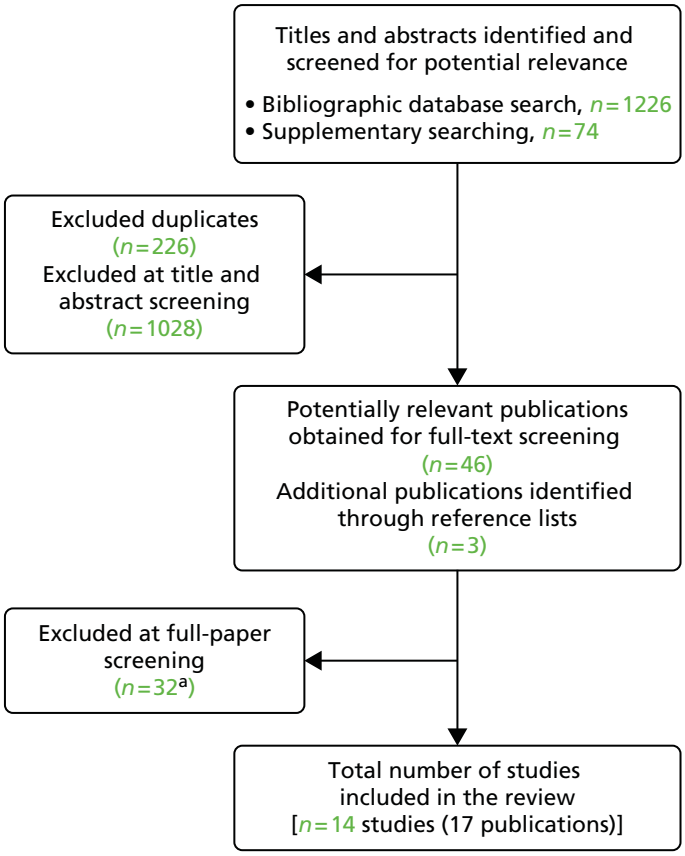

FIGURE 5 Flow chart (review of HRQoL studies). a, Reasons for exclusion: no utility values ($n = 30$), non-English ($n = 2$).

TABLE 10 Health-state utilities and values for allergic conditions

Source	Population	*N*	Country	Instrument	Health-state utility or value	
					Mean	SD or 95% CI
Remenschneider 2015[62]	Chronic rhinosinusitis	242	USA	EQ-5D	0.8100	0.1300
Pitt 2004[68]	Seasonal allergic conjunctivitis	310	UK	EUROQOL-VAS	0.8169[a]	0.1489
Poole 2014,[63] Canonica 2007,[64] Bachert 2007,[65] Currie 2014[63]	Seasonal allergic rhinoconjunctivitis	634	Europe, including UK	EQ-5D	0.9380	0.9320 to 0.9430
Smith 2005[69]	Seasonal allergic rhinoconjunctivitis	200	Spain	EUROQOL-VAS	0.8009	0.1524
Wasserfallen 1999[70]	Allergic rhinitis	21	USA	EUROQOL-VAS	0.6250[b]	0.1300
Petersen 2013[66]	Allergic rhinoconjunctivitis or asthma	248	Denmark	EQ-5D	0.7000[b]	0.2000
	Grass pollen induced	169			0.7000[b]	0.1800
	HDM induced	25			0.6000[b]	0.3000
	Grass and HDM induced	54			0.7200[b]	0.1800

TABLE 10 Health-state utilities and values for allergic conditions (*continued*)

Source	Population	*N*	Country	Instrument	Health-state utility or value	
					Mean	SD or 95% CI
Egert-Schmidt 2014 [71]	Rhinitis, conjunctivitis, asthma	753	Germany	EUROQOL-VAS	0.7000[c]	NR
Petersen 2011[72]	Allergic rhinitis patients receiving allergy vaccination	366	Denmark	EUROQOL-VAS	0.5000	0.2000
Covaciu 2013[73]	Any allergic disease	3137	Sweden	EUROQOL-VAS	0.9260	0.0860
	Asthma	3220			0.8990	0.0100
	Rhinitis	3214			0.9230	0.0860
	Food hypersensitivity	3218	Sweden	EUROQOL-VAS	0.9220	0.0870
	Eczema	3156	Sweden	EUROQOL-VAS	0.9220	0.0910
Mittmann 1999[74]	Food allergy	1075	Canada	HUI Mark III	0.8500	0.1700
	Other allergies	3102			0.8800	0.1500
Moberg 2009[67]	Hand eczema	25247	Sweden	EQ-5D	0.7820	0.7720 to 0.7920
Lundberg 1999[77]	Atopic eczema	132	Sweden	VAS	0.7300	NR
				TTO	0.9300	NR
				SG	0.9800	NR
Stephens 2005[75]	Mild atopic eczema in children	150	UK	SG	0.8625	NR
	Moderate atopic eczema in children				0.6900	NR
	Severe atopic eczema in children				0.5900	NR
Friedman 2004[76]	Mild atopic eczema	3539	USA	VAS converted to utilities using 2.4 in the power function	0.9970	NR
	Mild to moderate atopic eczema				0.9876	NR
	Moderate atopic eczema				0.9571	NR
	Moderate to severe atopic eczema				0.8971	NR
	Severe atopic eczema				0.8052	NR

NR, not reported; SD, standard deviation; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale.
a During pollen season.
b On days with symptoms.
c Median.

Six studies,[63,67–69,73,78] describing 10 populations, compared health-state utility scores for persons with and without allergic conditions. The largest difference was observed for persons with asthma (–0.0530, EQ-5D) and eczema [–0.0660, EuroQol Visual Analogue Scale (Euroqol-VAS)]. For the other populations (food and airway allergies) the differences ranged between –0.0240 and –0.0330 (*Table 11*).

TABLE 11 Comparisons of health-state utility scores for persons with and without allergic conditions

					Health-state utility or value with allergy		Health-state utility or value without allergy		Difference	
Source	Population	*N*	Country	Instrument	Mean	SD or 95% CI	Mean	SD or 95% CI	Mean	SD
Pickard 2013[78]	Hay fever	79	USA	EQ-5D	NR	NR	NR	NR	–0.0240	0.0520
Pitt 2004[68]	Seasonal allergic conjunctivitis	310	UK	EUROQOL-VAS	0.8169	0.1489	0.8492	0.1254	–0.0323[a,b]	NR
Poole 2014[63]	Seasonal allergic rhinoconjunctivitis	634	Europe, including UK	EQ-5D	0.9380	0.9320 to 0.9430	0.9140	0.9070 to 0.9210	0.0240[b]	NR
Smith 2005[69]	Seasonal allergic rhinoconjunctivitis	200	Spain	EUROQOL-VAS	0.8009	0.1524	0.8334	0.1186	–0.0325[b]	NR
Moberg 2009[67]	Hand eczema	25247	Sweden	EQ-5D	0.7820	0.7720 to 0.7920	0.8480	0.8450 to 0.8510	–0.0660[b]	NR
Covaciu 2013[73]	Allergic diseases	3137	Sweden	EUROQOL-VAS	0.9260	0.0860	0.9590	0.0650	–0.0330[b]	NR
	Asthma	3220			0.8990	0.0100	0.9520	0.0710	–0.0530[b]	NR
	Rhinitis	3214			0.9230	0.0860	0.9520	0.0710	–0.0290[b]	NR
	Eczema	3156			0.9220	0.0910	0.9540	0.0690	–0.0320[b]	NR
	Food hypersensitivity	3218			0.9220	0.0870	0.9530	0.0710	–0.0310[b]	NR

NR, not reported; SD, standard deviation; VAS, visual analogue scale.
a During pollen season.
b Calculated by the authors of this report.

Of the excluded studies, three are worth mentioning because they were conducted in UK health-care settings:

- Armstrong *et al.*[79] investigated the cost-effectiveness of a specialist allergy service and adrenaline injectors for those who had suffered anaphylaxis. In this study[79] the impact of anaphylactic shock on QoL was, in absence of utility evidence, assumed by the authors to be equal to zero utility for a duration of 9 days at maximum.
- Meadows *et al.*[80] investigated immunotherapy in adults and children with seasonal allergic rhinitis. They used mapping to obtain EQ-5D change scores from changes in scores on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).[81] The RQLQ scale ranges from 0 (best) to 6 (worst). It was assumed that the top end of the scale maps to the EQ-5D state representing no problems in any of the five dimensions. The bottom end of the RQLQ scale was mapped to the EQ-5D state representing maximum problems with usual activities, pain/discomfort and anxiety/depression, but no problems with mobility or self-care, which were assumed to be unaffected by seasonal allergic rhinitis. This state has a QoL score of –0.07 on the standard UK tariff. As a result, going from worst to best was a 6-point reduction in RQLQ and a 1.07-point increase in the EQ-5D score. Each unit decrease (improvement) in RQLQ was assumed to map to a 0.178-point increase in QoL score (assuming that a unit decrease has the same value at all points on the scale). The authors state that it could be argued that mapping the RQLQ to the whole range of three of the five dimensions of the EQ-5D scale could have led to an overestimation of utility gains, as the bottom score of –0.07 on the EQ-5D (representing a state worse than death) would not be equivalent to the worst score on the RQLQ.
- Garside *et al.*[82] investigated the effectiveness of treatments for atopic eczema. In the absence of utility values in the literature they used a UK Utility Panel ($n = 15$ laypeople) to estimate utilities for three severity stages of atopic eczema using the standard gamble. They used the Dermatology Life Quality Index[83] to develop scenarios and obtained valuations of these using SG. The median results were 0.985 for mild eczema, 0.875 for moderate eczema and 0.675 for severe eczema.

Methodology

The aim of this assessment was to compare the cost-effectiveness of adding multiplex allergen testing to current clinical practice with current clinical practice alone for people with difficult to manage IgE-mediated allergic disease in secondary or tertiary care settings. In this setting, multiplex allergen testing might be used to inform clinical decisions (e.g. to perform a food challenge and/or to initiate SIT) through aiding allergy diagnosis, predicting the probability of allergic reactions and/or predicting response to SIT. However, given the paucity of data on the clinical effectiveness of multiplex allergen testing (see *Chapter 3*), no long-term cost-effectiveness model is developed. This is in accordance with the published protocol for this assessment (PROSPERO registration no. CRD42015019739). More specifically, the lack of data on the clinical consequences of adding multiplex allergen testing to current clinical practice renders the development of a long-term economic model unusable to inform health policy decision-making.

Instead of developing a long-term cost-effectiveness model, the following sections aim to inform research decisions and support future model-based economic evaluations and include the following components:

- relevant cost-effectiveness analyses are identified and reviewed (see *Review of economic analyses of multiplex allergen testing*, above)
- available health-state utility studies are identified and reviewed (see *Review of health-related quality of life studies*, above)
- the current clinical diagnostic pathway as well as the potential place for multiplex allergen testing are examined (see *Current clinical diagnostic pathways*, below)
- a concept model structure is developed (see *Model structure*, below)
- a survey is performed to retrieve the proportions of patients receiving each test (see *Model parameters*, below)

- test costs were calculated (see *Model parameters*, below), and
- cost analyses were performed to examine the short-term costs of diagnostic pathways *with* ImmunoCAP ISAC vs. *with* Microtest vs. *without* either (standard diagnostic pathway) (see *Cost analyses*, below).

Current clinical diagnostic pathways

Current clinical diagnostic pathways for patients referred for specialist allergy investigation in secondary or tertiary care settings may include SPT, single IgE testing and an OFC test where appropriate, combined with clinical history. SPT is often the first investigation performed in allergy diagnostics.[84,85] Based on consultations with clinical experts, it is assumed that single IgE testing will be performed in cases where the results of the SPT are not consistent with the clinical history of a patient (e-mail from Roisin Fitzsimons, Guys and St Thomas' NHS Foundation Trust, 15 July 2015, personal communication). Inconsistency can occur if the SPT for the most likely allergen (based on clinical history) is negative or if a SPT is positive for an allergen that does not seem to explain the symptoms completely. Additionally, an OFC test is usually performed to confirm or rule out allergy to a specific food-related allergen or allergens.[85–87] If SPT is not considered acceptable/practical (e.g. in children with atopic eczema), single IgE testing might be the first-line investigation, using confirmatory OFC or SPT as necessary. Moreover, it might be possible to proceed to OFC based on SPT (and patient history) alone. *Figure 6* provides an overview of the possible diagnostic pathways with and without SPT. It should be noted that it is unclear whether or not this theoretical diagnostic pathway (based on clinical expertise and literature) is representative of current UK clinical practice in all secondary or tertiary care settings.

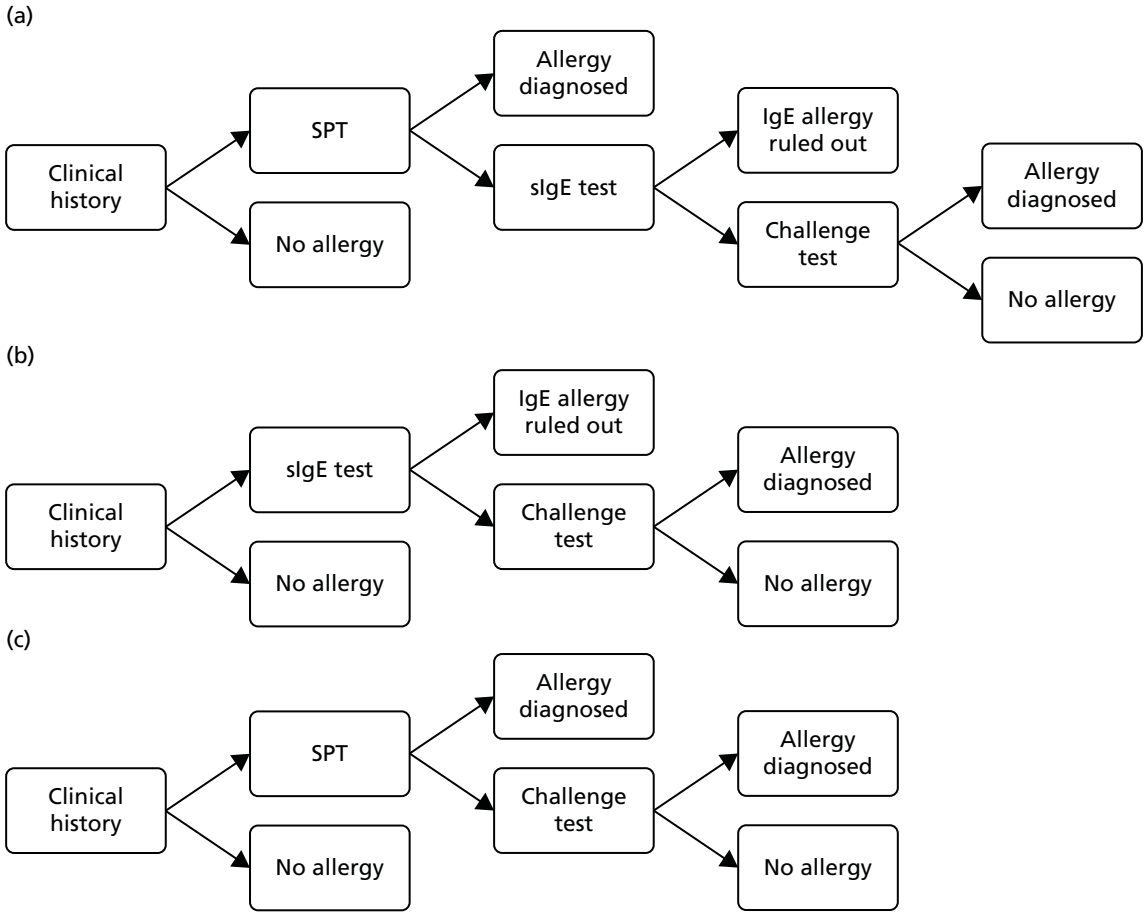

FIGURE 6 Current diagnostic pathways. In these pathways it is assumed that *no* further testing will be performed if IgE-mediated allergic response can be ruled out as an explanation for the observed symptoms. In all other cases it is assumed that further testing will be performed.

When considering patients with difficult to manage allergic disease who have been referred for assessment in secondary or tertiary care settings, multiplex allergen testing is likely to occur as a first-line investigation (assuming that all of the allergens of interest are on the array). Its role would be to identify which allergens a patient is sensitive to. Any allergens identified would have to be confirmed by SPT or OFC. The potential advantage of the array is that it can simultaneously test for homologous proteins or cross-sensitive proteins and therefore can aid the clinician in tailoring which confirmatory tests are required. For example, if the test is negative for particular proteins this might rule out the need for OFC. It is likely that multiplex allergen testing would replace single IgE testing, although some single IgE testing might still be required, for example if the array does not test for all suspected allergens. *Figure 7* provides an overview of potential diagnostic pathways including multiplex allergen testing. In some pathways (see *Figure 7a* and *b*) it is

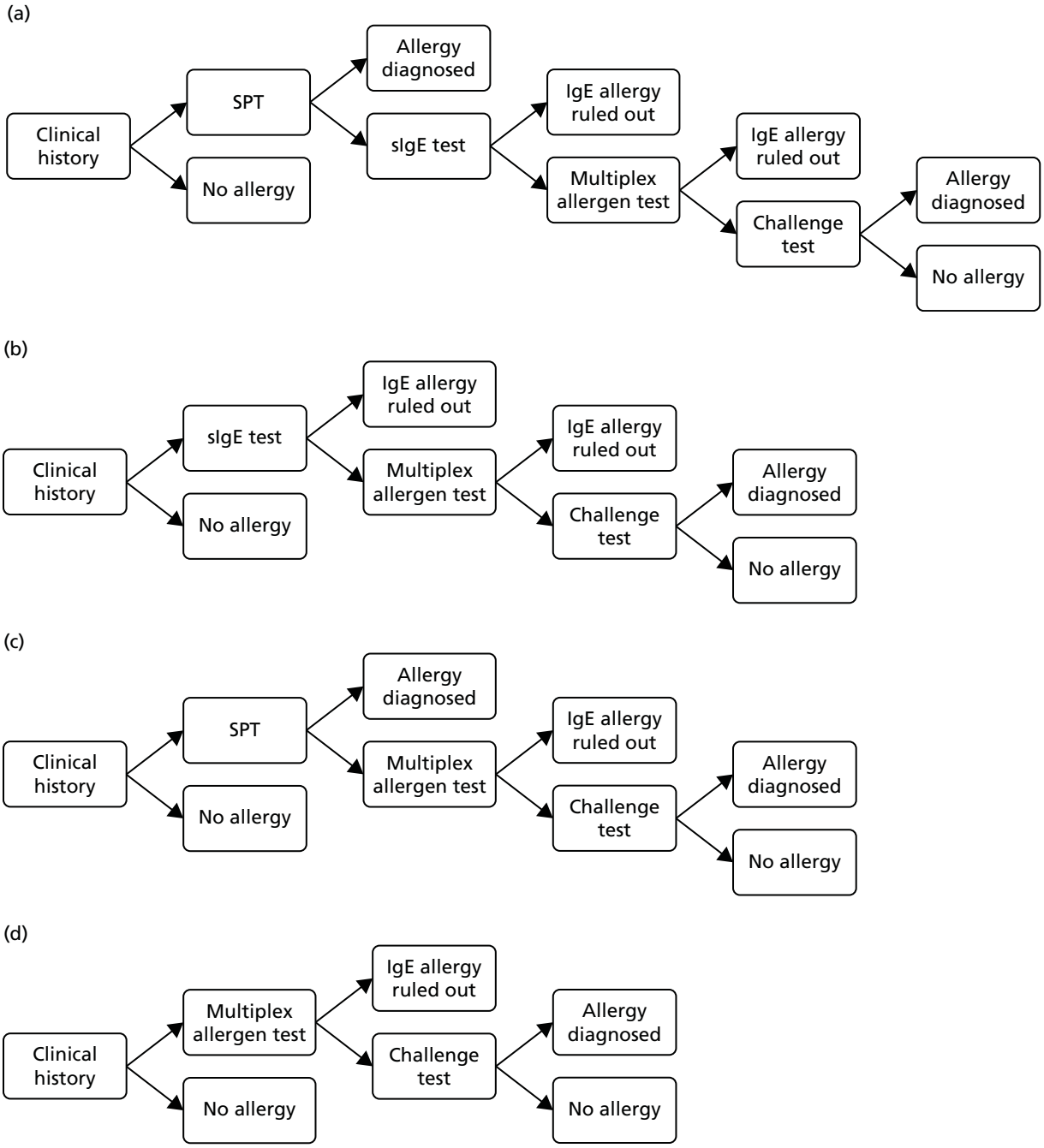

FIGURE 7 Potential diagnostic pathways including multiplex allergen testing. In these pathways it is assumed that *no* further testing will be performed if IgE-mediated allergic response can be ruled out as an explanation for the observed symptoms. In all other cases it is assumed that further testing will be performed.

assumed, based on clinical opinion (e-mail from Paul Turner, Imperial College London and St Mary's Hospital, London, 15 July 2015, personal communication), that single IgE testing will always be performed before multiplex allergen testing (if single IgE testing is applicable). However, this might not always be the case, as multiplex allergen testing may also be performed instead of single IgE testing (see *Figure 7a* and *d*). The most important point is that multiplex allergen testing would be likely to reduce the number of single IgE tests, by ruling out particular allergens, thereby reducing the need for OFC.

Model structure

This section describes a model structure that could potentially be used to assess the cost-effectiveness of multiplex allergen testing compared with current clinical practice for people with difficult to manage allergic disease in secondary or tertiary care settings. Three comparators would be evaluated in the economic model:

- ImmunoCAP ISAC testing
- Microtest testing
- current (standard) diagnostic pathway.

The health-economic model would potentially consist of a decision tree and a state-transition (i.e. Markov) model. The decision tree can be used to model the short-term outcomes, based on test results and the accompanying treatment decision. These outcomes consist of 'at risk of allergic reaction (treated)', 'not at risk of allergic reaction (treated)', 'at risk of allergic reaction (untreated)' and 'not at risk of allergic reaction (untreated)'. Moreover, potential AEs of testing can be considered in the decision tree. The decision tree is shown in *Figure 8*.

The long-term consequences in terms of costs and QALYs can be estimated using a state-transition cohort model (*Figure 9*) with a lifetime time horizon. The initial health state in the state-transition model is determined by the short-term outcome from the decision tree. The following health states are included in the state-transition model:

- at risk of allergic reaction
- not at risk of allergic reaction/remission
- allergic reaction (experienced during cycle)
- death (either background mortality or death due to an allergic reaction).

Different types and severities of allergic reactions can be included in the model separately. Given the diversity of allergy reactions, which depend on the type of allergy, separate models would ideally be developed for separate populations, for example those suspected of having clinical reactivity to an inhaled versus an ingested allergen.

Model parameters

Decision tree

To inform the decision tree for the diagnostic pathway the following parameters are required:

- proportion of patients who receive a particular test (i.e. SPT, single IgE test, multiplex allergen test and/or OFC test) as well as the number of SPTs and/or single IgE tests per patient
- accuracy of the diagnostic pathways (i.e. proportion of true positives, false positives, false negatives and true negatives as a result of the combined diagnostic performance of SPT, single IgE and/or multiplex testing)
- the treatment decision.

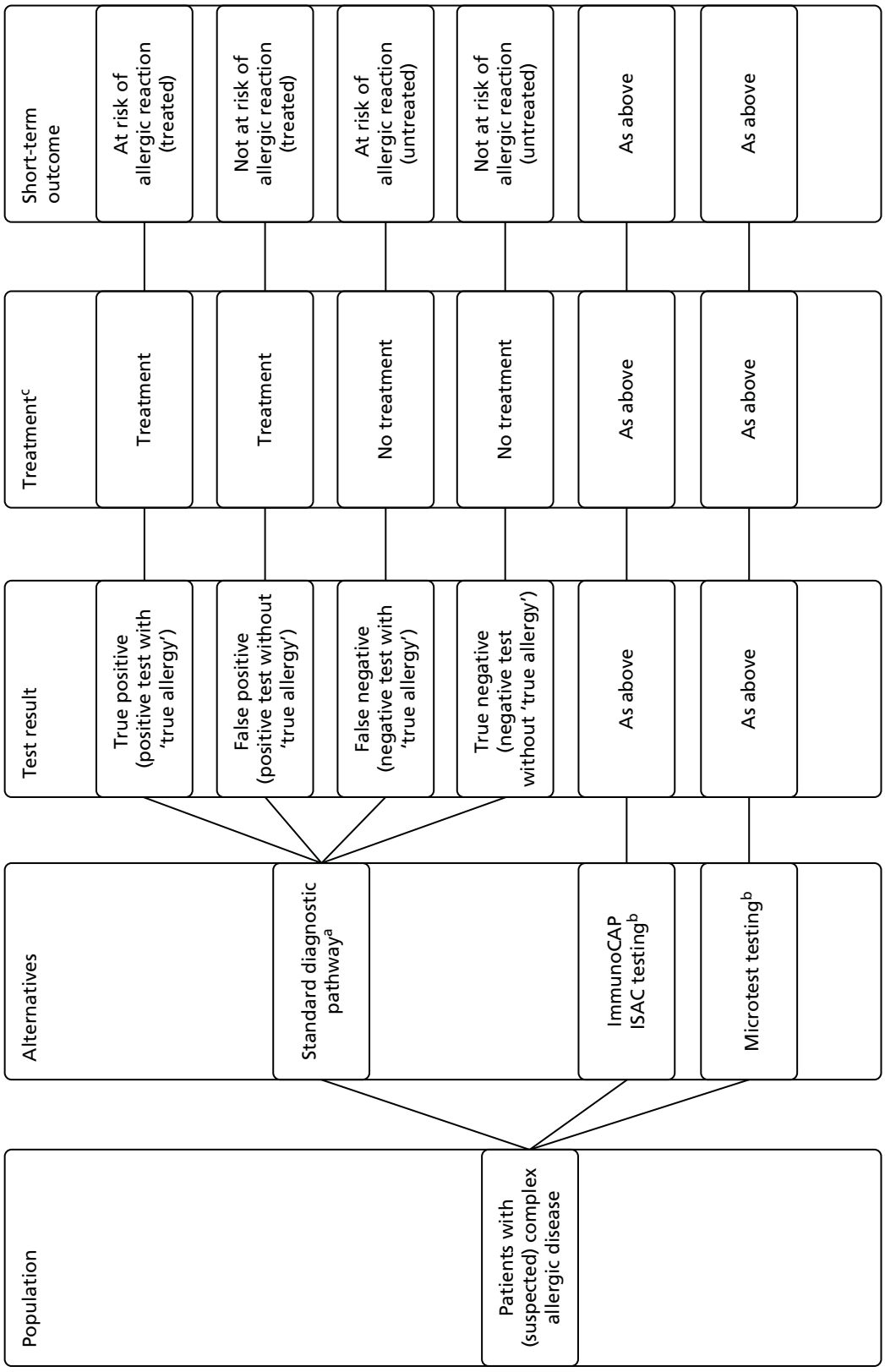

FIGURE 8 Potential decision tree for the diagnostic pathway. a, Standard diagnostic pathway may consist of SPTs, single IgE testing and/or food challenge (see *Figure 6*); b, multiplex allergen testing might be performed in addition to the standard diagnostic pathway or instead of (part of) the standard diagnostic pathway (see *Figure 7*); c, treatment may consist of immunotherapy and/or symptom management (i.e. antihistamines and/or avoidance of the allergen) and is likely to lower the likelihood and/or severity of an allergic reaction.[86]

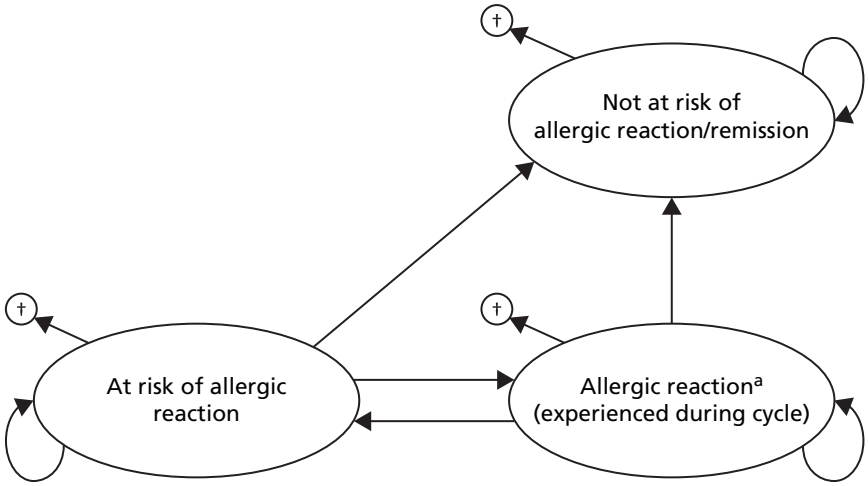

FIGURE 9 Potential state-transition model structure. a, Different types and severities of allergic reactions can be separately included in the model. †Death.

The proportions of patients receiving a particular test and the number of tests per patient are unclear for both the standard diagnostic pathway and the diagnostic pathway including multiplex allergen testing. To alleviate this issue, a survey was sent to clinicians to inform these parameters (see *Appendix 6* for the survey). However, no valid responses were received for multiplex allergen testing; the only respondent who indicated having any experience with ImmunoCAP ISAC responded that the number of OFC tests used was too few to comment on. Hence it was not possible to use the survey results in the cost analyses. Moreover, as described in the systematic review (see *Effects on management, treatment and diagnostic classification of adding multiplex allergen testing to the diagnostic work-up of people with difficult to manage allergic disease*, above), full information on the accuracy of the diagnostic pathways is not available. Finally, information on how treatment decisions relate to the diagnostic pathways is not available. Although two studies examined changes in SIT prescriptions[32,38] following the addition of multiplex allergen testing results to standard diagnostic work-up, the results of these studies were not consistent: one study[38] described an increase in SIT prescriptions following multiplex allergen testing, whereas the other study[32] described a decrease in SIT prescriptions following multiplex allergen testing (see *Table 5* for more details).

State-transition model

To inform the long-term state-transition model, the following parameters would be required (all conditional on the test result):

- probability of allergic reactions (might be multiple allergic reactions and population specific)
- probability of remission, and
- probability of dying.

No long-term consequences for multiplex allergen testing were identified in the systematic review (see *Chapter 3, Overview of included studies*).

Health-state utilities

The evidence on utility values for allergic conditions in the UK population was limited. For food allergies, no utility values were found. For seasonal allergic rhinoconjunctivitis, EuroQol VAS scores from Pitt *et al.*[68] or EQ-5D scores from a European study[63–65] could be taken. Stephens *et al.*[75] used standard gamble to obtain utility values for atopic eczema in UK children. Only in the study by Stephens *et al.*[75] were utilities reported per degree of severity of the allergic conditions (see *Tables 10* and *11*). Utility values for complications of allergies, such as anaphylactic shock, could not be found in the literature, apart from the assumption made by Armstrong *et al.*[79] that the impact of anaphylactic shock on QoL was equal to zero utility for a duration of 9 days at maximum.

Resource use and costs

To estimate the costs of the individual tests, a detailed cost calculation (see *Appendix 7*) was performed considering test costs, capital costs (if applicable), service and maintenance costs and personnel costs for performing and interpreting the tests. The results of the detailed test cost calculation are presented in *Table 12*. For ImmunoCAP ISAC and Microtest testing, the minimum and maximum prices were calculated and subsequently averaged. For ImmunoCAP ISAC testing, the main differences between the minimum and maximum prices can be attributed to the difference in time (between 5 and 60 minutes) that was needed to interpret the test results. This also holds true for Microtest testing, although the range was smaller (between 5 and 10 minutes). Additionally, for Microtest testing it is assumed that the test sample would be sent to the Microtest DX laboratory, where the test would be performed (companies preferred and most conservative scenario), whereas for ImmunoCAP ISAC testing it is assumed that the test would be performed at the service provider laboratory. Hence, for ImmunoCAP ISAC testing capital costs are included while for Microtest testing it is assumed that these costs would be included in the test costs (see *Appendix 7*). Capital costs are annuitised using a cost discount rate of 3.5%.

Additional costs that would be considered in a long-term cost (-effectiveness) analysis may include the costs of SIT, health-state costs for being at risk of allergic reaction, and health-state costs for having experienced an allergic reaction. These costs are likely to be very specific for the population to be considered. Moreover, different types of SIT might be provided within a specific population (see, for example, the study by Sastre *et al.*[32]). Hence the specific type(s) of SIT prescribed and the SIT duration would be required to calculate these costs (see, for example, the study by Meadows *et al.*[80] for a calculation of the immunotherapy costs for rhinitis).

Cost analyses

In this section we report on a cost comparison of three diagnostic strategies: with ImmunoCAP ISAC versus with Microtest versus the standard diagnostic pathway without multiplex allergen testing.

Given that the proportion of patients receiving single IgE and OFC tests in addition to ImmunoCAP ISAC or Microtest is unclear, the cost analyses are performed using two-way threshold analysis for these parameters.[90] Specifically, in pairwise comparisons of two test strategies, the minimal reduction (i.e. threshold) in proportions of single IgE and OFC tests is identified that was needed for the most expensive test strategy to become cheaper than the alternative test strategy, assuming that everything else remains equal. Here, 100% for both tests was defined as all patients receiving eight single IgE tests on average and all patients receiving on average one OFC test (see *Appendix 7*). Therefore, for example, if it was assumed that the use of multiplex allergen testing would result in no single IgE testing then this would imply a 100% reduction in single IgE testing compared with the standard diagnostic pathway. Given that multiplex allergen testing is more costly than single IgE testing, threshold analysis could then show what percentage reduction in OFC tests would be required to give the multiplex allergen pathway the same cost as the standard diagnostic pathway. On the other hand, if it was instead assumed that there

TABLE 12 Results of the test cost calculation (see *Appendix 7* for more details)

	£ per patient tested	Sources
SPT	62.28	NICE 2011,[86] Curtis[88]
IgE test	136.37	NICE 2011,[86] Curtis[88]
OFC test	570.00	NICE 2011,[86] Department of Health (NHS reference costs 2013–14[89])
ImmunoCAP ISAC	219.51	Information submitted to NICE by Thermo Fisher Scientific, Curtis[88]
Microtest	156.85	Information submitted to NICE by Microtest DX, Curtis[88]

was no reduction in single IgE testing by use of multiplex allergen, then this would result in a different threshold for the percentage reduction in OFC tests required to give the multiplex allergen pathway the same cost as the standard diagnostic pathway.

As previously stated, in these analyses, it is assumed everything except the number of single IgE tests and the number of OFC tests remains equal; this includes the assumption that the proportion of patients receiving any SPT is equal for all test strategies. Although this assumption is debatable, it might be justified given that SPT is a simple, safe and quick test (providing results within 15–20 minutes) that is often the first-line investigation in allergy diagnostics. Moreover, one clinician (e-mail from Paul Turner, personal communication), with experience with ImmunoCAP ISAC testing, indicated that all patients would receive SPT when using ImmunoCAP ISAC.

Scenario analyses

Several scenario analyses were performed:

1. In the calculation of the base-case costs for ImmunoCAP ISAC it is assumed that the LuxScan 10k reader would be used only for ImmunoCAP ISAC testing (on average 386 tests per year). However, the LuxScan 10k reader might be used for other purposes. Therefore, in the first scenario analysis, it is assumed that the LuxScan 10k reader would be fully occupied for 253 days per year. This reduces the ImmunoCAP ISAC testing costs to £201.91 per patient tested.
2. The second scenario analysis considered a scenario wherein the Microtest test would be performed at the service provider laboratory instead of at the Microtest DX laboratory (as assumed in the base-case analysis). This scenario reduces the costs of Microtest testing to £149.37 per patient tested (see *Appendix 8*).
3. The third scenario analysis considered the impact of the number of allergens tested using single IgE testing (base-case value = eight allergens tested per person).[86] The number of allergens was set to 1 and 20, respectively.
4. The final scenario analysis considered a reduced OFC costs of £256.00, excluding the costs of implementing the food elimination diet.

Threshold analyses

For the situation where ImmunoCAP ISAC or Microtest are used as replacement test(s) for single IgE testing (rather than as an add-on), a threshold analysis was performed to examine the minimum number of allergens to be tested with single IgE tests in order for single IgE testing to be equally as expensive as, or more expensive than multiplex allergen testing, assuming that everything else remains equal. This analysis was also performed for SPT.

Results of cost analyses

The cost analyses consider the short-term test costs using two-way threshold analyses for the proportion of single IgE tests and the proportion of OFC tests. The base-case analysis indicated that in order for ImmunoCAP ISAC and Microtest to be cost-saving compared with the standard diagnostic pathway, the absolute proportion of OFC tests should be reduced by at least 15 and 4 percentage points, respectively (e.g. from 50% to 35% or from 50% to 46%, respectively), if there was a 100% reduction in single IgE tests (i.e. from 100% to 0%). On the other hand, if there is no reduction in the proportion of single IgE tests (assuming an average of eight per person), the reduction in OFC tests should be at least 39% and 28% for ImmunoCAP ISAC and Microtest, respectively. Moreover, for ImmunoCAP ISAC compared with Microtest, the proportion of OFC tests for ImmunoCAP ISAC should be reduced by at least 11% if there is no reduction in the proportion of single IgE tests. When assuming no reduction in the proportion of OFC tests, the proportion of patients receiving an average of eight single IgE tests for ImmunoCAP ISAC should be reduced by at least 44% (*Figure 10*).

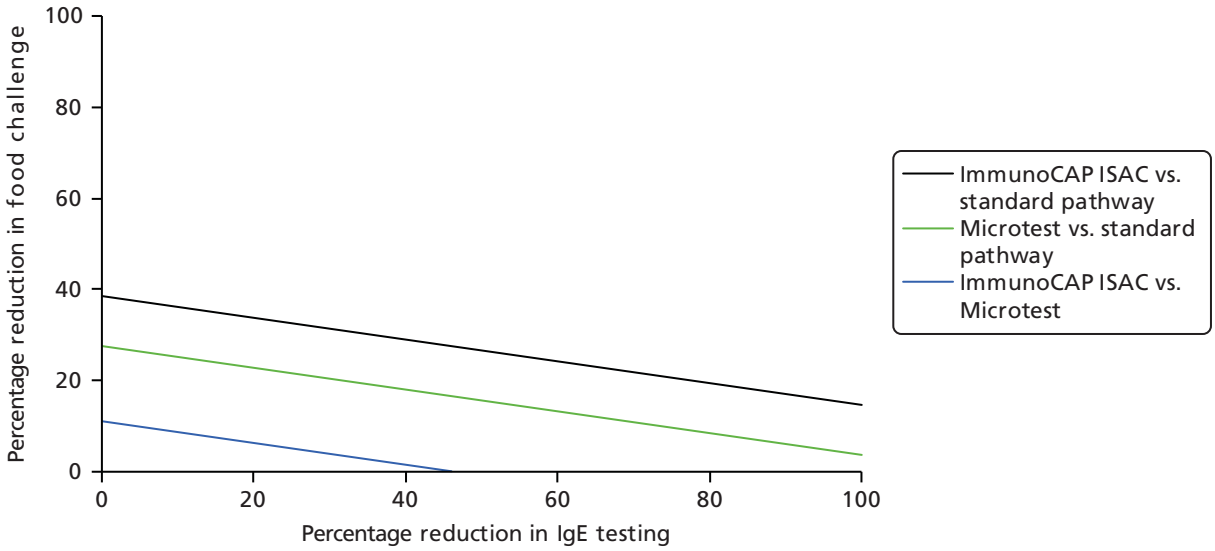

FIGURE 10 Results of two-way threshold analyses (base case). Combinations of percentage reductions in food challenge and single IgE testing above a line lead to lower costs, and below a line lead to higher costs.

Scenario analyses

1. The ImmunoCAP ISAC costs are reduced by £18 when assuming that the LuxScan 10k reader would be fully occupied. This resulted in a decrease in the proportions for ImmunoCAP ISAC needed to reduce in order to be cost-saving compared with the standard diagnostic pathway and Microtest (*Figure 11*).
2. The Microtest costs are reduced by £7 when assuming that the Microtest test would be performed at the service provider laboratory instead of at the Microtest DX laboratory. This resulted in a decrease in the proportions for Microtest tests needed to reduce in order to be cost-saving compared with the standard diagnostic pathway (*Figure 12*).

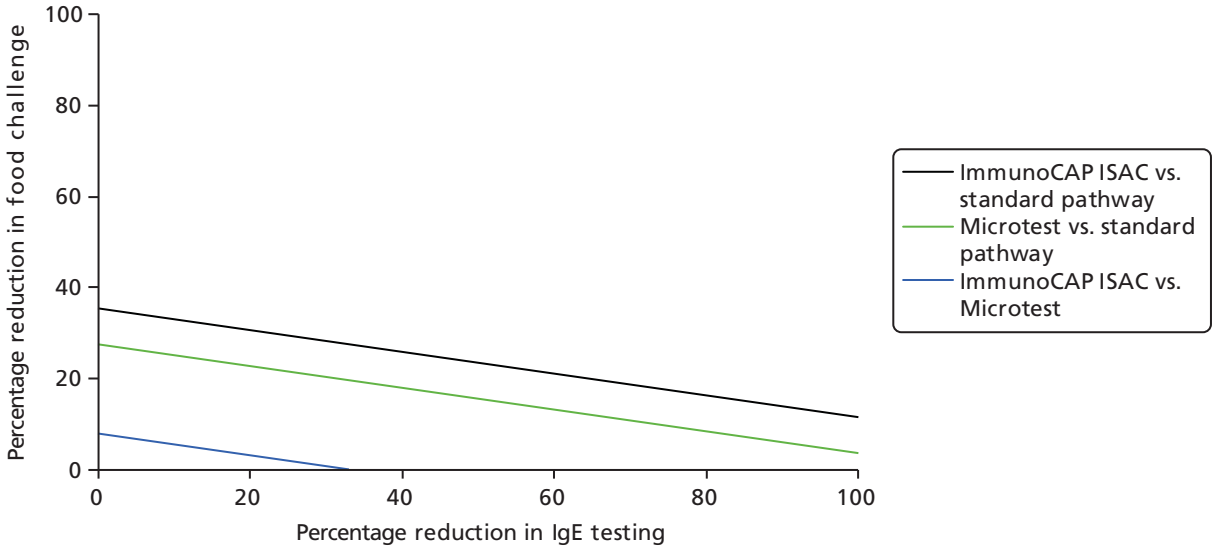

FIGURE 11 Results of two-way threshold analyses (assuming that the LuxScan 10k reader would be fully occupied). Combinations of percentage reductions in food challenge and IgE testing above a line lead to lower costs, and below a line lead to higher costs.

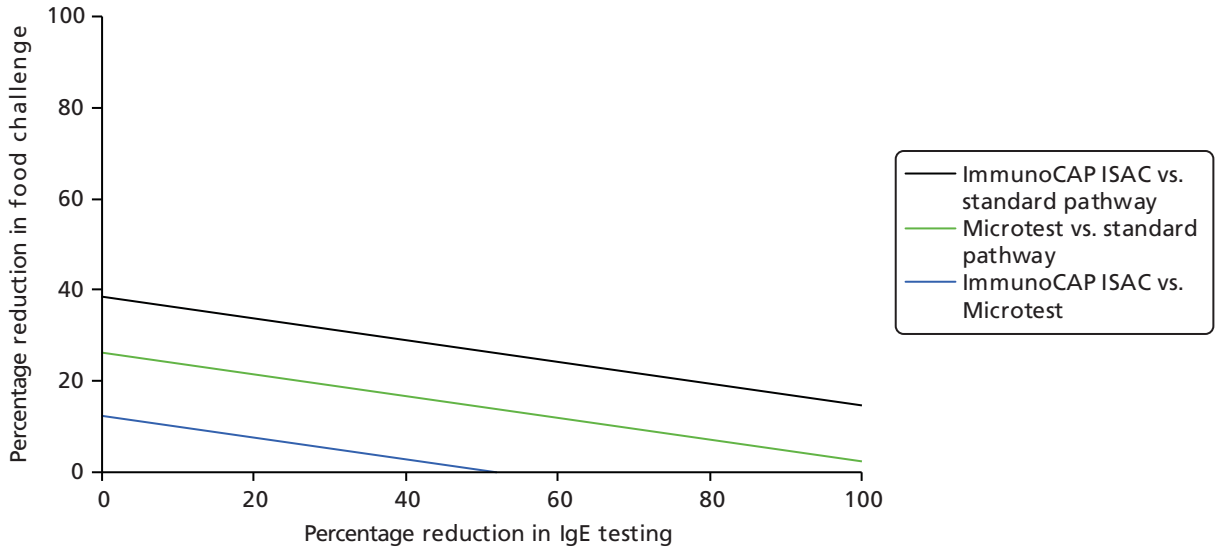

FIGURE 12 Results of two-way threshold analyses (assuming that the Microtest test would be performed at the service provider lab). Combinations of percentage reductions in food challenge and IgE testing above a line lead to lower costs, and below a line lead to higher costs.

3. Assuming that the number of allergens tested using single IgE testing is 'one' decreases the impact of reducing the proportion of patients with single IgE tests, while assuming 20 allergens tested increases the impact of reducing the proportion of patients with single IgE tests (*Figures 13* and *14*).
4. Finally, decreasing the OFC costs to £256.00 substantially increases the reduction in OFC needed in order for multiplex allergen testing to be cost-saving (*Figure 15*).

Threshold analyses

In these analyses, it is assumed that there is no reduction in OFC testing with multiplex testing.
The minimum numbers of allergens tested using single IgE tests were 13 and 10 in order for the standard pathway to be as expensive as or more expensive than the ImmunoCAP ISAC and Microtest pathways, respectively. This means that, if multiplex testing replaced single IgE testing, then it would have to replace at least 13 or 10 tests to be cost-saving. For SPT these numbers were 39 and 27, respectively.

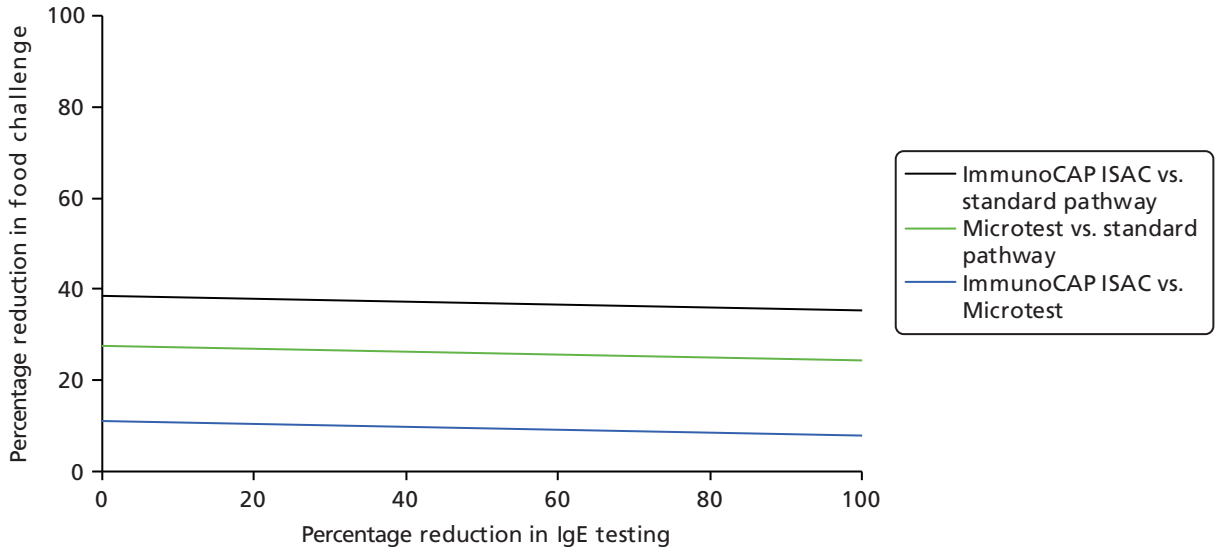

FIGURE 13 Results of two-way threshold analyses (assuming one allergy tested during single IgE test). Combinations of percentage reductions in food challenge and IgE testing above a line lead to lower costs, and below a line lead to higher costs.

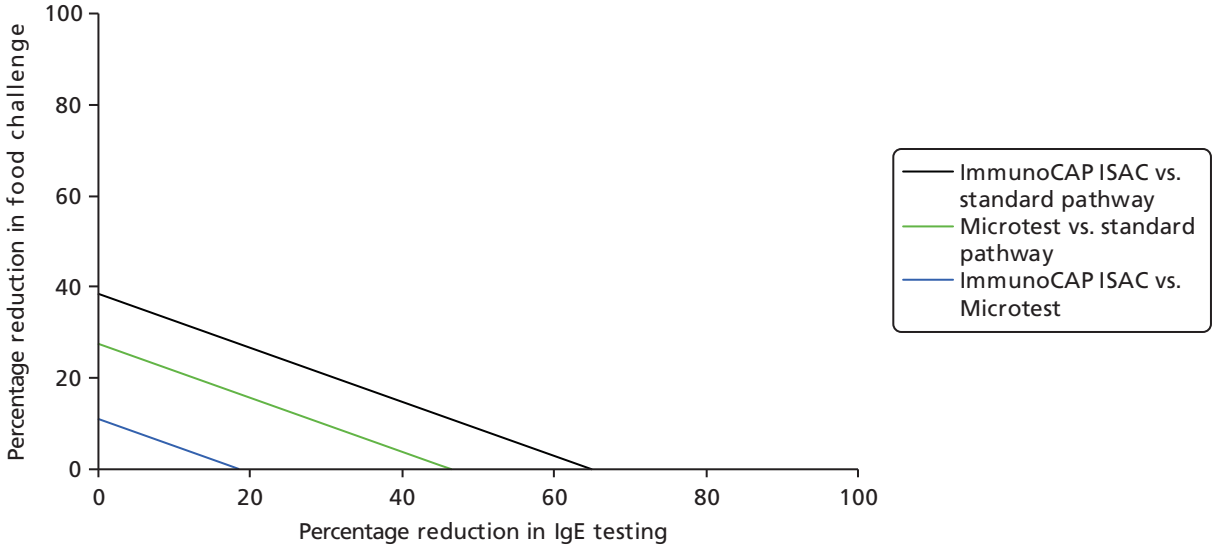

FIGURE 14 Results of two-way threshold analyses (assuming 20 allergens tested during single IgE test). Combinations of percentage reductions in food challenge and IgE testing above a line lead to lower costs, and below a line lead to higher costs.

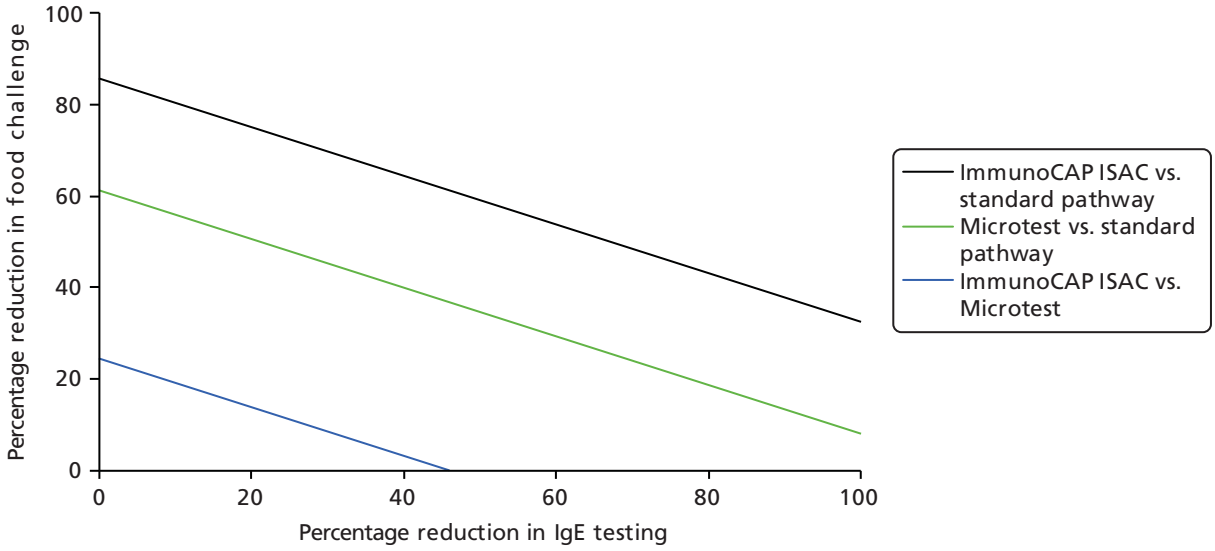

FIGURE 15 Results of two-way threshold analyses (assuming OFC costs of £256.00). Combinations of percentage reductions in food challenge and IgE testing above a line lead to lower costs, and below a line lead to higher costs.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness

The results of the very limited number of available studies provide some indication that the addition of multiplex allergen testing (ImmunoCAP ISAC) to standard diagnostic work-up can change clinicians' views on the diagnosis, management and treatment of patients; no data were available for Microtest. There was some indication that the use of ImmunoCAP ISAC testing may guide decisions on the discontinuation of restrictive diets, the content of SIT prescriptions, and whether or not patients should receive SIT. However, importantly, none of the studies that we identified reported any information on clinical outcomes subsequent to changes in treatment or management based on ImmunoCAP ISAC. There was some evidence that ImmunoCAP ISAC may be useful for discriminating allergens that are structurally similar and are recognised by the same IgE antibody (cross-immunoreactive), and this may be useful for identifying the cause of food allergies. A UK-based study on the use of ImmunoCAP ISAC to investigate idiopathic anaphylaxis indicated that the addition of ImmunoCAP ISAC to standard diagnostic work-up may identify a potentially causative agent in previously undiagnosed patients.[39] However, it should be noted that the addition of ImmunoCAP ISAC also resulted in the identification of large numbers of sensitisations that were not considered to be associated with the anaphylaxis (i.e. large numbers of clinically false-positive test results).

The diagnostic performance of ImmunoCAP ISAC in comparison with other tests (single IgE and SPT) varied considerably between studies, according to the allergens investigated and the way in which ISAC testing was applied. In general, individual ISAC components tended to have high specificity, but low sensitivity, relative to whole-allergen single IgE tests or SPTs for the prediction of allergic response. The relatively low sensitivities of individual ISAC components are likely to be indicative of the proportions of patients in whom each component is associated with the observed allergic response. Conversely, a high specificity is indicative of a strong association between ISAC positivity for the individual component and an allergic response to whole allergen. When ISAC was used to measure the same component as single IgE testing or to measure multiple components (homologous proteins) with a positive test defined as any component positive, it appeared that equivalent sensitivities could be achieved without corresponding loss of specificity. As noted above, the ability of ImmunoCAP ISAC to discriminate between allergens that are structurally similar and are recognised by the same IgE antibody (cross-immunoreactive) may represent clinically useful additional information. Therefore, if the focused use of groups of ISAC components can achieve equivalent sensitivity and specificity to that of single IgE testing, ISAC testing may be preferred.

The clinical effects of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease have yet to be adequately investigated; in particular, the clinical consequences of changes to diagnosis or treatment, and the frequency and relevance of clinically false-positive sensitisations has been under investigated.

Cost-effectiveness

The initial aim of this assessment was to compare the cost-effectiveness of multiplex allergen testing with current clinical practice for people with difficult to manage allergic disease in secondary or tertiary care settings. However, the lack of data on the clinical consequences of multiplex allergen testing rendered the development of a long-term economic model uninformative for health policy decision-making. Therefore, instead of developing a long-term cost-effectiveness model, this assessment aimed to inform research decisions and support future model-based economic evaluations. For this purpose, relevant cost-effectiveness analyses and available health-state utility studies were identified and reviewed. Also, the current clinical diagnostic pathway, as well as the potential place for multiplex allergen testing, were

examined, and a concept model structure was developed. Finally, a survey was performed to retrieve the number of patients receiving each test, test costs were calculated and cost analyses were performed to examine the short-term costs of the test strategies.

All four identified cost-effectiveness studies[33,34,54–60] (all abstracts) showed an increased effectiveness when using ImmunoCAP ISAC and three[54–60] out of four studies also showed cost savings when using ImmunoCAP ISAC. However, the methods and assumptions used in these assessments are largely unclear, severely hampering the assessment of the validity of the results. In addition, the credibility of these assessments was questioned as fundamental inputs of their models were based on expert opinion or inaccessible references, or no references were provided. Therefore, these findings should be interpreted with extreme caution.

The evidence on utility values for allergic conditions in the UK population was limited. For food allergies no utility values were found, whereas UK utility values were available for seasonal allergic rhinoconjunctivitis and atopic eczema in children.

Test costs for ImmunoCAP ISAC and Microtest were estimated to be £219.51 and £156.85, respectively. For SPT, single IgE and the food challenge test these were £62.29, £136.37 and £570.00, respectively. Detailed cost analyses were performed to estimate the short-term cost of diagnostic pathways with and without multiplex allergen testing. As the place of multiplex allergen testing in the diagnostic pathway and the proportions of patients receiving a particular test are unclear, and the survey did not provide the required results, different scenario and threshold analyses were performed. The results of these analyses depend on precisely the effect of multiplex testing on the need for single IgE, SPT and OFC testing. For example, if multiplex testing replaced single IgE testing (assuming eight tests per person) then a 15% or 4% reduction in OFC would be required for ImmunoCAP ISAC and Microtest, respectively, to be cost-saving. However, if there was no reduction in OFC testing, then the number of single IgE tests or SPTs per patient that needed replacing would have to be at least 39% or 28% for ImmunoCAP ISAC and Microtest, respectively, to be cost-saving.

Strengths and limitations of assessment

Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Despite this, we were unable to identify any studies that reported clinical outcomes and available data were generally very sparse.

The possibility of publication bias cannot be ruled out. Owing to the small number of included studies and between-study clinical heterogeneity, we were unable to perform any meta-analyses or to undertake a formal assessment of publication bias. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts.

Clear inclusion criteria were specified in the registered protocol for this review (PROSPERO registration no. CRD42015019739). One change was made to the published protocol, expanding the inclusion criteria to allow inclusion of studies that reported direct comparisons of diagnostic accuracy between single IgE testing and multiplex allergen testing, using SPTs or allergen challenge tests as the reference standard, but did not report details of any participants for whom multiplex allergen testing provided additional information (details provided in *Chapter 3*; see *Inclusion and exclusion criteria*). These studies were included with the aim of providing some indication of the performance of multiplex allergen testing, compared with current single IgE antibody testing practice, for predicting clinical response; studies that reported only the accuracy of multiplex allergen testing, without a comparison to current testing practice, were therefore not included. In addition, we have provided specific reasons for exclusion for all of the studies that were considered potentially relevant at initial citation screening and were subsequently excluded on assessment of the full publication (see *Appendix 3*). The eligibility of studies for inclusion is therefore transparent.

The review process followed recommended methods to minimise the potential for error and/or bias;[21] studies were independently screened for inclusion by two reviewers, and data extraction and quality assessment were done by one reviewer and checked by a second (MW and SL). Any disagreements were resolved by consensus.

Studies included in this review were assessed for risk of bias, where possible using published validated tools [the QUADAS-2 tool[25] and CASP cohort risk-of-bias tool (www.casp-uk.net/)]. The review included a number of observational studies, which used a 'before-and-after' type study design to assess the effects of adding information from multiplex allergen testing to the standard diagnostic work-up in the same group of participants. We are not aware of any published risk-of-bias tool that is appropriate for the assessment of this type of study. A review-specific tool was therefore designed by the authors (MW, SL and NA) to allow the methodological quality of these studies to be systematically assessed and described. This tool focuses on elements of study design that we considered relevant to this specific study type, and is based upon the structure of the QUADAS-2 tool. The results of the risk-of-bias assessment are reported, in full, for all included studies in *Appendix 4* and are summarised in *Chapter 3* (see *Study quality*). Studies were generally of unclear quality due to limitations in reporting, with full publications lacking for many studies (reported as conference abstracts only). None of the studies included in this review can be considered to have low risk of bias; all studies were rated as 'high' or 'unclear' risk of bias on at least one domain of the relevant tool. The main 'high' risk-of-bias areas identified were participant selection (inappropriate exclusions) and application of testing procedures (variation in testing procedures between study participants and within-study optimisation of the diagnostic threshold).

An important potential advantage of ImmunoCAP ISAC and other multicomponent arrays is their ability to differentiate between allergens that have similar structures; these homologous allergens maybe recognised by the same antibody (cross-reactivity) or homologous allergens may cause the same allergic response (cross-sensitisation). For example, a blood sample that shows immunoreactivity to Bet v1 may indicate that a patient is sensitised to birch pollen or they may be sensitised to one of many protein homologues (proteins of similar molecular structure to Bet v1), or they may be sensitised to both. Bet v1 is a PR10 protein that has several homologues or protein family members. On the ISAC 112 chip there are nine Bet v1 homologues: rCor a1.0401 (hazelnut), rGly m4 (soybean), rAra h8 (peanut), rAct d8 (kiwi), rApi g1 (celery), rMal d1 (apple), rPru p1 (peach), rAln g1 (alder) and rCor a1.0101 (hazel). Therefore, ISAC 112 has the potential to discriminate between immunoreactivity to Bet v1 and nine homologues, a process that would take much longer by single allergen (single IgE) testing. According to the ImmunoCAP ISAC 112 technical brochure[91] there are seven other protein families represented on the chip; therefore, its potential to provide information regarding cross-immunoreactivity of homologous proteins is apparent. However, data showing the effects of providing additional information of this type were very limited. It is important to note that ISAC multiplex testing on its own can differentiate between the immunoreactivity of a given allergen and a homologue only if that homologue is present on the array chip. Several reports raised the fact that not all useful components were present on the array.[37,39,40] These reports were carried out on earlier versions of ISAC and some of the suggested components now appear on ISAC 112. Further research maybe needed to target specific conditions and interpretation of data should always bear in mind what components are not on the array as well as what components are on the array.

Predominantly, the accuracy studies included in this review compared the performance of whole allergens (single IgE) to the ability of allergen components (ImmunoCAP ISAC) to detect specific IgE. Although both are aiming to identify the presence of specific antibodies in a patient serum sample, this is more likely to occur if using the whole allergen than part of the allergen. Classically, the interaction between an antibody and an antigen (allergen) occurs through very specific binding sites on both molecules. Therefore, the selected allergen component(s) may or may not contain this binding site. Furthermore, multiple antibodies may have been produced to one allergen each using different binding sites. The use of whole allergens is likely to give very different results to using a component and this may explain some of the discrepancies seen between the accuracy studies.

Overall, only one of the diagnostic studies compared like with like. Only one study compared the ability of the same component (rGLy m4) to detect specific antibodies using single IgE testing and ImmunoCAP ISAC. Interestingly, the two methods reported different sensitivities and specificities, indicating that they perform differently. This was not unexpected as the performance of the single IgE test will be maximised to give the best result for the single allergen of interest, whereas ImmunoCAP ISAC is developed to give the best results for a range of allergens. Therefore, the effect of non-specific binding within these two systems on diagnostic accuracy is unknown.

Studies often included patients with a clinical history of an immediate reaction to an allergen, indicating that these patients were likely to have had an IgE-mediated event, and excluded patients with delayed reactions possibly caused by mechanisms other than IgE. This must be borne in mind when evaluating the clinical performance of tests based on single IgE measurement, in that the research populations may be unrepresentative of those for whom the test would be used in practice. Nevertheless, it is expected that these tests will be used only on patients who are strongly suspected of an IgE-mediated reaction.

Finally, the studies included in this systematic review may have limited applicability to the specified population of interest (people with complex or difficult to manage allergies who are being assessed in UK secondary or tertiary health-care settings). Studies that did not specify that they included participants with difficult to manage allergic disease, or described inclusion criteria that could be considered consistent with this classification (e.g. polysensitised patients), were classified as having 'high' concerns regarding applicability. Studies that were conducted in non-UK settings and which assessed allergens considered unlikely to be relevant to UK populations (e.g. aeroallergens associated with Mediterranean countries) were also classified as having 'high' concerns regarding applicability. Only two[39,40] of the studies included in the review were rated as having 'low' concerns with respect to both of these issues. None of the comparative accuracy studies was conducted in populations likely to be representative of people with difficult to manage allergic disease and two[43,45] of these studies explicitly excluded people with complex allergies.

The studies identified by our systematic review did not provide sufficient evidence to adequately assess the clinical effectiveness of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease, in secondary or tertiary UK health-care settings. However, we believe that our comprehensive assessment of the limited available evidence has highlighted key areas in which data are lacking and provides a useful framework to guide the development of research recommendations.

Cost-effectiveness

This is the first time that a model structure including diagnostic pathways has been attempted to examine the place of multiplex testing in the UK. Our cost analysis is also the first to assess the short-term costs of multiplex allergen testing in the UK. For this purpose a detailed cost analysis was performed, and multiple scenario and threshold analyses were conducted. Extensive literature searches were conducted to provide an overview of available cost-effectiveness analyses and available health-state utilities. Additional searching in terms of reference checking and extensive hand searching was performed to maximise retrieval of relevant studies (including conference abstracts). Clear inclusion criteria were specified for selecting relevant studies. Relevant papers were summarised and the quality of cost-effectiveness analyses was assessed. Authors were contacted to provide more details if needed.

The main limitations of this assessment are the lack of information of the place of multiplex testing in the care pathway and any effectiveness evidence. There is therefore an inability to incorporate long-term costs and consequences (i.e. life-years and QALYs), particularly long-term outcomes conditional on the short-term test outcomes. As illustrated by previous assessments for the UK,[80,82] it is possible to estimate long-term outcomes for treatments of allergic conditions (not conditional on a test result). Nevertheless, these assessments had severe limitations including that they required extensive assumptions (including mapping of utility values).[80]

Uncertainties

Clinical effectiveness

The potential role of multiplex allergen testing in the care pathway of patients with complex allergic disease remains unclear. As described in the objectives for this assessment, multiplex allergen testing could be added to existing standard diagnostic work-up or could be used to replace some or all of the single IgE tests that would otherwise be used in some patients.

In order to adequately assess the effectiveness of multiplex allergen testing as an add-on test, studies would be required that compare the management of patients based on standard diagnostic work-up to management based on standard diagnostic work-up with the addition of multiplex allergen testing and which provide information on subsequent clinical outcomes. Although it might be suggested that RCTs represent the 'gold standard' for this comparison, other study designs may provide relevant information. In particular, earlier stage, exploratory studies can be important in determining whether RCTs or other large-scale comparative studies are justified and in informing the design of such studies. The seven 'diagnostic before-and-after' studies included in this assessment show participating clinicians changing various aspects of their judgement about a given group of patients when they have access to the results of ImmunoCAP ISAC testing. The findings of these studies indicate that multiplex allergen testing may provide information, additional to that obtained from standard diagnostic work-up, which can affect clinicians' decision-making. However, the studies did not clearly report the extent to which the changes in clinicians' judgement resulted in implementation of changes to the care of patients. Further, if additional information provided by multiplex allergen testing results in changes to the care of patients, it is important to collect information on subsequent clinical outcomes and to compare these outcomes with those seen in patients whose care has been based on standard diagnostic work-up. Such comparisons are necessary to assess whether care decisions based on information that included the results of multiplex allergen testing ultimately result in benefit or detriment to patients, or have no significant effect.

One study indicated that ImmunoCAP ISAC should be used before single IgE testing. This relates to the ability of the microarray to analyse 56 allergens and provide data to help identify allergens that are cross-sensitive or those that are cross-immunoreactive. This has been applied to complex food allergy, for which ImmunoCAP ISAC can help determine to which food allergens a patient is sensitised; in particular, it is able to determine which homologous allergens give rise to the sensitivity observed in a single IgE test. When several food allergens are suspected ImmunoCAP ISAC testing can allow the clinician to quickly determine and reduce the number of confirmatory oral challenges required. In the absence of information on clinical outcomes, it may therefore be useful to obtain information on how the addition of multiple allergen testing to the standard diagnostic work-up of people with difficult to manage allergic disease affects the overall testing burden (e.g. the number of single IgE tests and/or confirmatory challenge tests used) or other resource-use outcomes (e.g. the number of subsequent consultations with health-care professionals). We did not identify any studies that reported resource-use outcomes.

This assessment also includes eight studies that report information on the accuracy of various components and combinations of components on the ImmunoCAP ISAC chip compared with the accuracy of other testing options (single IgE or SPT) to predict allergic response (as defined by SPT or OFC). Studies of this type can determine whether multiplex allergen testing provides similar diagnostic information to that provided by single IgE or other testing options, when used in the same group of patients; comparable performance may be considered indicative of the potential of multiplex allergen testing to replace other tests without significant adverse diagnostic consequences (missed diagnoses or false positives). However, none of the comparative accuracy studies identified was conducted in populations with difficult to manage allergic disease. Studies therefore evaluated the diagnostic performance of single components or small groups of components on the ImmunoCAP ISAC chip that were relevant to the investigation of specific allergies (e.g. Gal d1, Gal d2 and Gal d3 for hen's egg allergy). The focused use of the ImmunoCAP ISAC chip is likely to result in low numbers of false positives and high specificity estimates (i.e. sensitisations detected are likely to be associated with observed allergic response). These studies have limited

applicability to the investigation of people with difficult to manage allergic disease, for whom there is greater diagnostic uncertainty and for whom it might be expected that all or a greater proportion of the components of the microchip might be used. If multiplex allergen testing is applied in this way, it might be expected that greater numbers of false positives would be generated (i.e. more sensitisations that are not associated with observed allergic response would be identified). Some evidence of this can be seen from the results of Heaps 2014,[39] described in *Chapter 3* (see *Effects on management, treatment and diagnostic classification of adding multiplex allergen testing to the diagnostic work-up of people with difficult to manage allergic disease*), which, as well as identifying sensitisations thought to be associated with anaphylaxis in some patients, identified large numbers of sensitisations that were not considered to be clinically relevant. In addition, two studies[92,93] that did not meet the inclusion criteria of this systematic review reported data comparing rates of sensitisation to various allergen groups relevant to plant-food allergy in allergic and tolerant individuals. Both studies were conducted in Spain. The first study included 123 children with food allergy, of whom 55 were classified as peanut allergic and 68 as peanut tolerant (SPT and single IgE) and used ImmunoCAP ISAC 103 to assess sensitisation to a range of allergenic components.[92] There were no significant differences between peanut-allergic and peanut-tolerant children in the rates of sensitisation to pathogenesis-related protein family PR-10 allergens (Ara h8, Act d8, Cor a1, Gly m4, Mal d1, Pru p1), profilins (Bet v2, Ole e2, Hev b8, Mer a1, Phl p12), some lipid transfer proteins (LTPs) (Par j2, Pru p3), cross-reactive carbohydrate determinant Ana c2, or pollens (Ole e1, Phl p1).[92] The second study included 130 children with plant-food allergy and LTP sensitisation and found that sensitisation to a particular plant-food LTP, as determined by ImmunoCAP ISAC 112, was not always associated with clinical symptoms of allergy to that plant food: 69% (40/58) and 63% (17/27) of peach- and walnut-tolerant children were sensitised to Pru p3 and Jug r3, respectively; 60% (21/35) of children without seed/nut allergy were sensitised to storage proteins.[93] The potential of multiplex allergen testing to detect clinically false-positive sensitisations has not yet been adequately investigated and the long-term relevance of such sensitisations is unknown. However, the limited available data indicate a need for care in the application and interpretation of multiplex allergen testing.

Finally, we did not identify any studies of multiplex allergen testing using Microtest that met the inclusion criteria for this assessment. The manufacturer provided unpublished data on the concordance between test methods (Microtest, ImmunoCAP single IgE, ImmunoCAP ISAC and SPT). These data are summarised in *Appendix 5*, for information only.

Cost-effectiveness

The credibility of available cost-effectiveness studies in the literature can be questioned given the use of expert opinion for fundamental model inputs. Moreover, (UK) health-state utility values for allergic conditions are scarce (e.g. utilities for food allergy and for test AEs are lacking). However, the main source of uncertainty regarding the cost-effectiveness of multiplex allergen testing compared with current clinical practice for people with difficult to manage allergic disease was the lack of data on long-term clinical consequences conditional on test results of a diagnostic pathway including multiplex allergen testing.

The place of multiplex allergen testing in the diagnostic pathway and the proportions of patients receiving a particular test was unclear (for both the current diagnostic pathway and the diagnostic pathway including multiplex allergen testing). Therefore, speculative two-way threshold analyses were performed in this assessment to consider the diagnostic pathway costs only. These analyses required assumptions regarding all key parameters relating to the pathway, including the proportions/numbers per patient of single IgE and OFC tests and SPT. For example, it does seem likely that multiplex testing, by ruling out some allergens, might avoid confirmatory testing with OFC or SPT. However, SPT is a simple, safe and quick test (providing results within 15–20 minutes) and it is often the first-line investigation in allergy. In addition, one clinician (e-mail from Paul Turner, personal communication), with experience with ImmunoCAP ISAC testing, indicated that all patients would receive SPT when using ImmunoCAP ISAC. Hence, it might be that multiplex allergen testing would not reduce the number of SPT. Finally, whether single IgE might be used as an add-on to multiplex allergen testing or would be replaced by multiplex testing remains uncertain, particularly given the limited experience with multiplex allergen testing in the UK.

Chapter 6 Conclusions

Implications for service provision

No recommendations for service provision can be made based on the analyses included in this report. The clinical effectiveness and cost-effectiveness of using multiplex allergen testing in the investigation of people with difficult to manage allergic disease have yet to be adequately investigated. In particular, the clinical consequences of changes to diagnosis or treatment and the frequency and relevance of clinically false-positive sensitisations have been under investigated. From the limited evidence available it appears that the most likely role of multiplex allergen testing would be to replace some or all single IgE testing. The ability of multiplex testing to simultaneously identify multiple antibodies in the serum samples, combined with its ability to identify which homologous allergens are cross-immunoreactive, means that these tests have the potential to provide a lot of information in a single step. Although confirmatory testing (SPT or OFC) is still likely to be required, multiplex testing could be used to tailor confirmatory testing to the individual patient and thus reduce the overall testing burden; no studies were identified that assessed overall testing burden. It should be noted that all of the evidence identified related to one test (ImmunoCAP ISAC) and conclusions on the potential utility of multiplex allergen testing may not be generalisible to other products.

Suggested research priorities

There remains considerable uncertainty about the possible role of multiplex allergen testing in the investigation of people with difficult to manage allergic disease in the UK. The formulation of a consensus-based protocol for the use of multiplex allergen testing may represent a useful starting point for future research. A prospective study would then be needed to investigate the clinical effectiveness of the proposed protocol. The preferred design would be a RCT comparing diagnostic pathways with and without multiplex allergen testing. Alternatively, an observational study to compare outcomes in centres using multiplex allergen testing to those using diagnostic pathways without multiplex allergen testing may also be a useful approach. Such an approach would, however, require careful consideration of between-centre differences in patient care pathways (other than the use of multiplex allergen testing). Outcomes measured could include:

- Short-term outcomes:
    - diagnostic performance, including discrimination between allergens responsible for allergic reactions and those that are cross-immunoreactive, and false-positive rate (i.e. the number of sensitisations identified that are not associated with allergic response) when the full panels of multiplex allergen testing devices are used in people with difficult to manage allergic disease
    - treatments or management decisions (including type and duration and the use and extent of restriction diets)
    - overall testing burden (i.e. the total number of tests, including multiplex allergen testing, single IgE testing, SPTs and OFC tests, required to reach a diagnosis and formulate a treatment/management plan)
    - any AEs associated with testing.

- Long-term outcomes:
  - incidence and severity of allergic reactions
  - mortality
  - service use (e.g. repeat presentations with allergy symptoms requiring further investigation and/or treatment).

If different possible methods of multiplex allergen testing are being considered, then direct head-to-head comparisons would be needed.

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This is a systematic review and therefore all extracted data are included in the report. Further information can be obtained from the corresponding author.

Contributions of authors

Marie Westwood and **Shona Lang** planned and performed the systematic review and interpretation of evidence.

Bram Ramaekers planned and performed the cost-effectiveness analyses and interpreted results.

Nigel Armstrong contributed to planning and interpretation of cost-effectiveness analyses, acquisition of input data and conducted model peer review.

Caro Noake and **Shelley de Kock** devised and performed the literature searches and provided information support to the project.

Manuela Joore, Johan Severens and **Jos Kleijnen** provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively.

All parties were involved in drafting and/or commenting on the report.

Data sharing statement

This is a systematic review; therefore, there are no additional data to share. Further information can be obtained from the corresponding author.

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200. Tripathi A, Workman LJ, Commins S, Barnes B, Hamilton RG, Platts-Mills TAE, *et al.* Challenges with measurement of IgE antibodies to minor components in food allergy: eosinophilic esophagitis, peanut allergy, and delayed anaphylaxis to mammalian meat. Proceedings of the American Academy of Allergy, Asthma and Immunology, 2014 Annual Meeting (AAAAI 2014), 28 February–4 March 2014, San Diego, CA, USA. *J Allergy Clin Immunol* 2014;**133**(Suppl. 1):AB260. http://dx.doi.org/10.1016/j.jaci.2013.12.922

201. Tripathi A, Workman LJ, Commins SP, Hamilton R, Erwin EA, Platts-Mills TA. Challenges with measurement of IgE antibodies in eosinophilic esophagitis, peanut allergy, and mammalian meat allergy. Proceedings of the American College of Allergy, Asthma and Immunology, 2014 Annual Meeting, 6–10 November 2014, Atlanta, GA, USA. *Ann Allergy Asthma Immunol* 2014;**113**(Suppl. 1):A16.

202. Uriarte SA, Sastre J. Molecular diagnosis in dog allergy. Proceedings of the European Academy of Allergy and Clinical Immunology and World Allergy Organization, World Allergy and Asthma Congress 2013, 22 June 2013, Milan, Italy. *Allergy* 2013;**68**:312.

203. Vitte J, Agabriel C, Liabeuf V, Cleach I, Grob JJ, Sarles JJ, *et al.* Sequential allergen microarray testing during the follow-up of allergic patients. Proceedings of the European Academy of Allergy and Clinical Immunology (EAACI), 5th International Symposium on Molecular Allergology (ISMA 2013), 6–7 December 2013, Vienna, Austria. *Clin Transl Allergy* 2014;**4**(Suppl. 2):P48. http://dx.doi.org/10.1186/2045-7022-4-S2-P48

204. Weimann A, Suer W, Vetter K, Schnell S, Busekow A, Probst C, *et al.* Component-resolved multiparameter assays for the diagnosis of birch pollen and grass pollen allergy. Proceedings of the European Academy of Allergy and Clinical Immunology, 30th Congress, 11–15 June 2011, Istanbul, Turkey. *Allergy* 2011;**66**:721.

205. Confidential information has been removed.

206. Mohamad Yadzir ZH, Misnan R, Abdullah N, Bakhtiar F, Leecyous B, Murad S. Component-resolved diagnosis (CRD): is it worth it? Frequency and differentiation in rhinitis patients with mite reactivity. *Iran J Allergy Asthma Immunol* 2014;**13**:240–6.

207. Young S, North J, Karanam S, Makwana N, Noorani S. The utility of ISAC (immuno solid-phase allergen chip) in identifying clinically relevant IgE reactivity in patients with atopic dermatitis. Proceedings of the British Society for Allergy and Clinical Immunology, 2012 Annual Meeting, 2–4 July 2012, Nottingham, UK. *Clin Exp Allergy* 2012;**42**:1838.

Appendix 1 Literature search strategies

Clinical effectiveness searches

EMBASE (via OvidSP): 1974–14 April 2015

Searched: 16 April 2015

1. allergy rapid test/ (334)
2. (ImmunoCAP or Immuno-CAP or Thermo Scientific).af. (2136)
3. ISAC.ti,ab,ot. (497)
4. (Immuno$ adj3 solid$ adj3 phase$ adj3 allerg$ adj3 chip$).af. (49)
5. (compon$ adj3 resolv$ adj3 diagnos$).af. (545)
6. (multi adj3 compon$ adj3 assay$).af. (14)
7. 23$ allerg$.ti,ab,ot,hw. (52)
8. 26$ allerg$.ti,ab,ot,hw. (52)
9. 103$ allerg$.ti,ab,ot,hw. (35)
10. 112$ allerg$.ti,ab,ot,hw. (21)
11. (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX").af. (807)
12. or/1-11 (3743)
13. exp microarray analysis/ or (microarray$ or micro array$ or nanoarray$).ti,ab,ot,hw. (138,557)
14. (multiplex adj3 (test$ or assay$)).ti,ab,ot,hw. (5972)
15. or/13-14 (144,221)
16. exp hypersensitivity/ or (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (572,729)
17. 15 and 16 (2744)
18. 12 or 17 (6131)
19. **limit 18 to yr="2005-Current" (5244)**

MEDLINE (via OvidSP): 1946–week 2 April 2015

Searched: 16 April 2015

1. (ImmunoCAP or Immuno-CAP or Thermo Scientific).af. (465)
2. ISAC.ti,ab,ot. (116)
3. (Immuno$ adj3 solid$ adj3 phase$ adj3 allerg$ adj3 chip$).af. (9)
4. (compon$ adj3 resolv$ adj3 diagnos$).af. (223)
5. (multi adj3 compon$ adj3 assay$).af. (11)
6. 23$ allerg$.ti,ab,ot,hw. (33)
7. 26$ allerg$.ti,ab,ot,hw. (34)
8. 103$ allerg$.ti,ab,ot,hw. (9)
9. 112$ allerg$.ti,ab,ot,hw. (5)
10. (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX").af. (520)
11. or/1-10 (1327)
12. exp Microarray Analysis/ or (microarray$ or micro array$ or nanoarray$).ti,ab,ot,hw. (103,970)
13. (multiplex adj3 (test$ or assay$)).ti,ab,ot,hw. (3489)

14. or/12-13 (107,253)
15. exp Hypersensitivity/ or (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (373,147)
16. 14 and 15 (1420)
17. 11 or 16 (2648)
18. **limit 17 to yr="2005-Current" (1955)**

MEDLINE In-Process Citations (via OvidSP): up to 15 April 2015; MEDLINE Daily Update (via OvidSP): up to 15 April 2015

Searched: 16 April 2015

1. (ImmunoCAP or Immuno-CAP or Thermo Scientific).af. (97)
2. ISAC.ti,ab,ot. (37)
3. (Immuno$ adj3 solid$ adj3 phase$ adj3 allerg$ adj3 chip$).af. (4)
4. (compon$ adj3 resolv$ adj3 diagnos$).af. (31)
5. (multi adj3 compon$ adj3 assay$).af. (0)
6. 23$ allerg$.ti,ab,ot,hw. (2)
7. 26$ allerg$.ti,ab,ot,hw. (2)
8. 103$ allerg$.ti,ab,ot,hw. (2)
9. 112$ allerg$.ti,ab,ot,hw. (1)
10. (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX").af. (22)
11. or/1-10 (173)
12. exp Microarray Analysis/ or (microarray$ or micro array$ or nanoarray$).ti,ab,ot,hw. (7177)
13. (multiplex adj3 (test$ or assay$)).ti,ab,ot,hw. (423)
14. or/12-13 (7590)
15. exp Hypersensitivity/ or (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (11,416)
16. 14 and 15 (80)
17. **11 or 16 (237)**

NLM PubMed (internet): up to 22 April 2015

Searched: 22 April 2015

#6 Search (#4 and #5) (375)

#5 Search ((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])) (1,919,020)

#4 Search (#1 or #2 or #3) (2631)

#3 Search ((Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX")) (528)

#2 Search ISAC (373)

#1 Search (ImmunoCAP or Immuno-CAP or Thermo Scientific) (1776)

CDSR (via Wiley): 2015/April/Iss4; DARE (via Wiley): 2015/January/Iss1; CENTRAL (via Wiley): 2015/March/Iss3; HTA database (via Wiley): 2015/January/Iss1

Searched: 16 April 2015

#1 (ImmunoCAP or Immuno-CAP or Thermo Scientific) (48)

#2 ISAC (20)

#3 (Immuno* near/3 solid* adj3 phase* near/3 allerg* near/3 chip*) (0)

#4 (compon* near/3 resolv* near/3 diagnos*) (5)

#5 (multi near/3 compon* near/3 assay*) (0)

#6 23* near/1 allerg* (46)

#7 26* near/1 allerg* (7)

#8 103* near/1 allerg* (2)

#9 112* near/1 allerg* (1)

#10 (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX") (56)

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 (175)

#12 MeSH descriptor: [Microarray Analysis] explode all trees (275)

#13 (microarray* or micro array* or nanoarray*) (575)

#14 (multiplex near/3 (test* or assay*)) (65)

#15 #12 or #13 or #14 (747)

#16 MeSH descriptor: [Hypersensitivity] explode all trees (15,709)

#17 (allerg* or anaphyla* or hypersensiti* or hyper-sensiti* or poly-sensiti* or polysensiti* or paucisensiti*) (25,363)

#18 #16 or #17 (32,535)

#19 #15 and #18 (39)

#20 #11 or #19 (210)

#21 #20 Publication Year from 2005 to 2015 (147)

- CDSR search retrieved 41 records
- DARE search retrieved 0 records*
- Central search retrieved 104 records
- HTA search retrieved 0 records.

*Please note: Records ceased to be added to the DARE resource on 31 March 2015; this search was for archival material only.

Science Citation Index Expanded (Web of Knowledge) 1970–21 April 2015; CPCI-S (via Web of Knowledge) 1990–21 April 2015

Searched: 23 April 2015
Indexes=SCI-EXPANDED, CPCI-S Timespan=2005–2015

#13 (2626) #12 OR #7

#12 (1312) #11 AND #10

#11 (108,808) TS=(allerg* or anaphyla* or hypersensiti* or hyper-sensiti* or poly-sensiti* or polysensiti* or paucisensiti*)

#10 (105,467) #9 OR #8

#9 (5844) TS=(multiplex NEAR/3 (test* or assay*))

#8 (100,025) TS=(microarray* or micro array* or nanoarray*)

#7 (1450) #6 OR #5 OR #4 OR #3 OR #2 OR #1

#6 (149) TS=(Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX")

#5 (11) TS=(multi NEAR/3 compon* NEAR/3 assay*)

#4 (368) TS=(compon* NEAR/3 resolv* NEAR/3 diagnos*)

#3 (16) TS=(Immuno* NEAR/3 solid* NEAR/3 phase* NEAR/3 allerg* NEAR/3 chip*)

#2 (454) TS=(ISAC)

#1 (581) TS=(ImmunoCAP or Immuno-CAP or "Thermo Scientific")

BIOSIS Previews (via Web of Knowledge): 1956–21 April 2015

Searched: 23 April 2015
Indexes=BIOSIS Previews Timespan=2005–2015

#7 (1282) #6 OR #5 OR #4 OR #3 OR #2 OR #1

#6 (81) TS=(Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX")

#5 (9) TS=(multi NEAR/3 compon* NEAR/3 assay*)

#4 (202) TS=(compon* NEAR/3 resolv* NEAR/3 diagnos*)

#3 (22) TS=(Immuno* NEAR/3 solid* NEAR/3 phase* NEAR/3 allerg* NEAR/3 chip*)

#2 (230) TS=(ISAC)

#1 (914) TS=(ImmunoCAP or Immuno-CAP or "Thermo Scientific")

LILACS: 1982–22 April 2015

http://regional.bvsalud.org/php/index.php?lang=en

Searched: 22 April 2015

Terms	Records
ImmunoCAP or "Immuno-CAP" or "Thermo Scientific" or ISAC or Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX"	156
Total	**156**

NIHR HTA programme (internet): up to 23 April 2015

www.hta.ac.uk/

Searched: 23 April 2015

Browsed with the following terms.

Terms	Records
ImmunoCAP	0
Immuno-CAP	0
Thermo Scientific	0
ISAC	0
Allerwatch	0
ComforTen	0
MultiTest	0
True test	0
Microtest DX	0
Micro Test DX	0
Total	**0**

FDA (internet): up to 23 April 2015

www.fda.gov/

Searched: 23 April 2015

Searched Medical Devices.

Search terms	Records
ImmunoCAP OR Immuno-CAP OR Thermo Scientific	15
ISAC	13
Allerwatch OR ComforTen OR MultiTest OR true test OR Microtest DX OR Micro Test DX	16
Total	**44**

OpenGrey: up to 22 April 2015

www.opengrey.eu

Searched: 22 April 2015

Search terms	Records
ImmunoCAP OR "Immuno-CAP" OR "Thermo Scientific"	3
ISAC	8
Allerwatch OR ComforTen OR "MultiTest" OR "true test" OR "Microtest DX" OR "Micro Test DX"	4
Total	**15**

ClinicalTrials.gov (internet): up to 22 April 2015

http://clinicaltrials.gov/ct2/search/advanced

Searched: 22 April 2015

Advanced search option – search terms box.

Search terms	Records
ImmunoCAP OR Immuno-CAP OR Thermo Scientific	27
ISAC	5
Allerwatch OR ComforTen OR "MultiTest" OR "true test" OR "Microtest DX" OR "Micro Test DX"	8
Total	**40**

ISRCTN Registry (internet): up to 22 April 2015

www.isrctn.com/

Searched: 22 April 2015

Advanced search – Text Search.

Search terms	Records
ImmunoCAP OR "Immuno-CAP" OR "Thermo Scientific"	2
ISAC	1
Allerwatch OR ComforTen OR "MultiTest" OR "true test" OR "Microtest DX" OR "Micro Test DX"	1
Total	**4**

WHO ICTRP (internet): up to 22 April 2015

www.who.int/ictrp/en/

Searched: 22 April 2015

Advanced search option.

Title		Intervention	Records
ImmunoCAP OR Immuno-CAP OR Thermo Scientific	OR	ImmunoCAP OR Immuno-CAP OR Thermo Scientific	1
ISAC	OR	ISAC	0
Allerwatch OR ComforTen OR MultiTest OR true test OR Microtest DX OR Micro Test DX	OR	Allerwatch OR ComforTen OR MultiTest OR true test OR Microtest DX OR Micro Test DX	13
Total			**14**

Conference searches

AAAAI Annual Meeting

Searched: 19 May 2015

Searched for last 5 years.

Used "search within this issue" option and exported results for articles only:

2015: www.jacionline.org/issue/S0091-6749%2814%29X0003-5

2014: www.jacionline.org/issue/S0091-6749%2813%29X0015-6

2013: www.jacionline.org/issue/S0091-6749%2813%29X0013-2

2012: www.jacionline.org/issue/S0091-6749%2812%29X0002-2

2011: www.jacionline.org/issue/S0091-6749%2811%29X0002-7

Search terms	2011	2012	2013	2014	2015
ImmunoCAP ISAC	8	2	8	7	4
Immuno-CAP ISAC	5	6	9	6	3
Microtest DX	0	0	0	0	0
Micro Test DX	0	0	0	0	0
Total	13	8	17	13	7
Total before deduplication	**58**				
Total after deduplication	**52**				

EAACI

Searched: 19 May 2015

2015: www.professionalabstracts.com/eaaci2015/programme-eaaci2015.pdf

2014: www.sessionplan.com/eaaci2014/

2013: http://onlinelibrary.wiley.com/doi/10.1111/all.2013.68.issue-s97/issuetoc

2012: http://onlinelibrary.wiley.com/doi/10.1111/all.2012.67.issue-s96/issuetoc

2011: http://onlinelibrary.wiley.com/doi/10.1111/all.2011.66.issue-s94/issuetoc

Search terms	2011	2012	2013	Search terms	2014	2015 (June 2015)
ImmunoCAP	78	38	104	ImmunoCAP ISAC	18	NA
Immuno-CAP	6	7	8	Immuno-CAP ISAC	0	
Microtest	0	0		Microtest	1	
Micro Test	0	0		Micro Test	0	
Total	**84**	**45**	**112**		**19**	NA
Total	**260**					

NA, not applicable.

BSACI

Searched: 19 May 2015

2015: NA – conference had not yet taken place at time of searching

2014: http://onlinelibrary.wiley.com/doi/10.1111/cea.12456/epdf

2013: http://onlinelibrary.wiley.com/doi/10.1111/cea.12197/epdf

2012: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2222.2012.012033.x/epdf

2011: http://onlinelibrary.wiley.com/wol1/doi/10.1111/j.1365-2222.2011.03897.x/abstract

Please note: Unable to access 2011 online without payment.

Search terms	2011	2012	2013	2014	2015
ImmunoCAP	NA	2	4	7	NA
Immuno-CAP		1	0	0	
Microtest		0	0	0	
Micro Test		0	0	0	
Total		3	4	7	
Total	**14**				

NA, not applicable.

FAAM

Searched: 19 May 2015

Searched for last 5 years.

Used 'Control F' to search within saved PDFs.

2015: NA – conference not yet taken place at time of search

2014: www.ctajournal.com/supplements/5/S3

2013: www.ctajournal.com/supplements/3/S3

2012: NA – No record on website of having run in that year

2011: www.ctajournal.com/supplements/1/S1

Search terms	2011	2012	2013	2014	2015
ImmunoCAP ISAC	3	NA	5	3	NA
Immuno-CAP ISAC	0		0	0	
Microtest DX	0		0	0	
Micro Test DX	0		0	0	
Total	3		5	3	
Total before deduplication	**11**				

NA, not applicable.

ISMA

Searched: 20 May 2015

Searched for last 5 years.

Used 'Control F' to search within saved PDFs.

2015: Sixth conference had not yet taken place at time of search

2014: NA

2013: www.ctajournal.com/supplements/4/S2/all (5th conference)

2012: NA

2011: NA (Fourth conference 2010)

Search terms	2011	2012	2013	2014	2015
ImmunoCAP ISAC	NA	NA	5	NA	Not yet run
Immuno-CAP ISAC			0		
Microtest DX			0		
Micro Test DX			0		
Total			5		
Total	**5**				

NA, not applicable.

AAD Meeting

Searched: 26 May 2015

Searched for last 5 years.

2015: http://onlinedigitalpublishing.com/publication/?m=20143&l=1

2014: http://onlinedigitalpublishing.com/publication/?i=199001

2013: http://onlinedigitalpublishing.com/publication/?i=146375

2012: https://s3.amazonaws.com/aad-meetings/AM12_Program.pdf

2011: www.nxtbook.com/nxtbooks/aad/annualmeeting2011/#/0

Search terms	2011	2012	2013	2014	2015
ImmunoCAP	0	0	0	0	0
Immuno-CAP	0	0	0	0	0
Microtest DX	0	0	0	0	0
Micro Test DX	0	0	0	0	0
Total	0	0	0	0	0
Total before deduplication	**0**				

BAD

Searched: 26 May 2015

Searched for last 5 years.

Used "Search within this issue".

2015: Conference had not yet taken place at time of search

2014: http://onlinelibrary.wiley.com/doi/10.1111/bjd.2014.171.issue-s1/issuetoc

2013: http://onlinelibrary.wiley.com/doi/10.1111/bjd.2013.169.issue-s1/issuetoc

2012: http://onlinelibrary.wiley.com/doi/10.1111/bjd.2012.167.issue-s1/issuetoc

2011: http://onlinelibrary.wiley.com/doi/10.1111/bjd.2011.165.issue-s1/issuetoc

Search terms	2011	2012	2013	2014	2015
ImmunoCAP	0	0	0	0	
Immuno-CAP	0	0	0	0	
Microtest DX	0	0	0	0	
Micro Test DX	0	0	0	0	
Total	0	0	0	0	
Total before deduplication	**0**				

Cost-effectiveness

EMBASE (via OvidSP): 1974–20 May 2015

Searched: 21 May 2015

1. allergy rapid test/ (381)
2. (ImmunoCAP or Immuno-CAP or Thermo Scientific or phadia).af. (2718)
3. ISAC.ti,ab,ot. (517)
4. (Immuno$ adj3 solid$ adj3 phase$ adj3 allerg$ adj3 chip$).af. (50)
5. (compon$ adj3 resolv$ adj3 diagnos$).af. (567)
6. (multi adj3 compon$ adj3 assay$).af. (14)
7. 23$ allerg$.ti,ab,ot,hw. (52)
8. 26$ allerg$.ti,ab,ot,hw. (53)
9. 103$ allerg$.ti,ab,ot,hw. (35)
10. 112$ allerg$.ti,ab,ot,hw. (22)
11. (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX").af. (810)
12. or/1-11 (4290)
13. exp microarray analysis/ or (microarray$ or micro array$ or nanoarray$).ti,ab,ot,hw. (140,563)
14. (multiplex adj3 (test$ or assay$)).ti,ab,ot,hw. (6050)
15. or/13-14 (146,303)
16. exp hypersensitivity/ or (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (578,447)
17. 15 and 16 (2794)
18. 12 or 17 (6704)
19. health-economics/ (34,457)
20. exp economic-evaluation/ (226,212)
21. exp health-care-cost/ (217,693)
22. exp pharmacoeconomics/ (173,447)
23. or/19-22 (506,020)
24. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (670,947)
25. (expenditure$ not energy).ti,ab. (26,222)
26. (value adj2 money).ti,ab. (1530)

27. budget$.ti,ab. (26,297)
28. or/24-27 (696,870)
29. 23 or 28 (978,855)
30. letter.pt. (887,374)
31. editorial.pt. (477,247)
32. note.pt. (599,443)
33. or/30-32 (1964064)
34. 29 not 33 (886,862)
35. (metabolic adj cost).ti,ab. (989)
36. ((energy or oxygen) adj cost).ti,ab. (3348)
37. ((energy or oxygen) adj expenditure).ti,ab. (22,162)
38. or/35-37 (25,637)
39. 34 not 38 (881,415)
40. **18 and 39 (197)**

Economics terms based on Costs filter

Centre for Reviews and Dissemination. Search strategies: NHS EED EMBASE using OvidSP (economics filter) (internet). York: CRD; 2014 (accessed 2 June 2014).

Available from www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase

MEDLINE (via OvidSP): 1946–week 3 May 2015

Searched: 21 May 2015

1. (ImmunoCAP or Immuno-CAP or Thermo Scientific).af. (471)
2. ISAC.ti,ab,ot. (116)
3. (Immuno$ adj3 solid$ adj3 phase$ adj3 allerg$ adj3 chip$).af. (9)
4. (compon$ adj3 resolv$ adj3 diagnos$).af. (225)
5. (multi adj3 compon$ adj3 assay$).af. (11)
6. 23$ allerg$.ti,ab,ot,hw. (33)
7. 26$ allerg$.ti,ab,ot,hw. (34)
8. 103$ allerg$.ti,ab,ot,hw. (9)
9. 112$ allerg$.ti,ab,ot,hw. (5)
10. (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX").af. (520)
11. or/1-10 (1335)
12. exp Microarray Analysis/ or (microarray$ or micro array$ or nanoarray$).ti,ab,ot,hw. (105,216)
13. (multiplex adj3 (test$ or assay$)).ti,ab,ot,hw. (3540)
14. or/12-13 (108,548)
15. exp Hypersensitivity/ or (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (375,235)
16. 14 and 15 (1439)
17. 11 or 16 (2675)
18. economics/ (26,620)
19. exp "costs and cost analysis"/ (187,805)
20. economics, dental/ (1859)
21. exp "economics, hospital"/ (20,266)
22. economics, medical/ (8615)
23. economics, nursing/ (3914)
24. economics, pharmaceutical/ (2572)
25. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (445,087)

26. (expenditure$ not energy).ti,ab. (18,132)
27. (value adj1 money).ti,ab. (24)
28. budget$.ti,ab. (17,825)
29. or/18-28 (571,847)
30. ((energy or oxygen) adj cost).ti,ab. (2735)
31. (metabolic adj cost).ti,ab. (818)
32. ((energy or oxygen) adj expenditure).ti,ab. (16,789)
33. or/30-32 (19,615)
34. 29 not 33 (567,494)
35. letter.pt. (847,644)
36. editorial.pt. (356,900)
37. historical article.pt. (316,205)
38. or/35-37 (1,505,328)
39. 34 not 38 (538,417)
40. **17 and 39 (67)**

Costs filter

Centre for Reviews and Dissemination. NHS EED Economics Filter: MEDLINE (via Ovid) monthly search (internet). York: CRD; 2010 (cited 28 September 2010).

Available from: www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

MEDLINE In-Process & Other Non-Indexed Citations (via OvidSP): up to 20 May 2015; MEDLINE Daily Update (via OvidSP): up to 20 May 2015

Searched: 21 May 2015

1. (ImmunoCAP or Immuno-CAP or Thermo Scientific).af. (95)
2. ISAC.ti,ab,ot. (39)
3. (Immuno$ adj3 solid$ adj3 phase$ adj3 allerg$ adj3 chip$).af. (4)
4. (compon$ adj3 resolv$ adj3 diagnos$).af. (33)
5. (multi adj3 compon$ adj3 assay$).af. (0)
6. 23$ allerg$.ti,ab,ot,hw. (2)
7. 26$ allerg$.ti,ab,ot,hw. (2)
8. 103$ allerg$.ti,ab,ot,hw. (2)
9. 112$ allerg$.ti,ab,ot,hw. (1)
10. (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX").af. (24)
11. or/1-10 (176)
12. exp Microarray Analysis/ or (microarray$ or micro array$ or nanoarray$).ti,ab,ot,hw. (7501)
13. (multiplex adj3 (test$ or assay$)).ti,ab,ot,hw. (453)
14. or/12-13 (7944)
15. exp Hypersensitivity/ or (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (11,612)
16. 14 and 15 (89)
17. 11 or 16 (248)
18. economics/ (0)
19. exp "costs and cost analysis"/ (128)
20. economics, dental/ (0)
21. exp "economics, hospital"/ (8)
22. economics, medical/ (1)
23. economics, nursing/ (1)
24. economics, pharmaceutical/ (0)

25. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (60,839)
26. (expenditure$ not energy).ti,ab. (1828)
27. (value adj1 money).ti,ab. (3)
28. budget$.ti,ab. (2518)
29. or/18-28 (63,427)
30. ((energy or oxygen) adj cost).ti,ab. (312)
31. (metabolic adj cost).ti,ab. (101)
32. ((energy or oxygen) adj expenditure).ti,ab. (1452)
33. or/30-32 (1820)
34. 29 not 33 (62,936)
35. letter.pt. (32,097)
36. editorial.pt. (21,356)
37. historical article.pt. (131)
38. or/35-37 (53,569)
39. 34 not 38 (62,298)
40. **17 and 39 (8)**

Costs filter

Centre for Reviews and Dissemination. NHS EED Economics Filter: MEDLINE (via Ovid) monthly search (internet). York: CRD; 2010 (cited 28 September 2010).

Available from www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

NHS EED (via Wiley): 2015/April/Iss2

Searched: 21 May 2015

#1 (ImmunoCAP or Immuno-CAP or Thermo Scientific) (48)

#2 ISAC (20)

#3 (Immuno* near/3 solid* adj3 phase* near/3 allerg* near/3 chip*) (0)

#4 (compon* near/3 resolv* near/3 diagnos*) (5)

#5 (multi near/3 compon* near/3 assay*) (0)

#6 23* near/1 allerg* (46)

#7 26* near/1 allerg* (7)

#8 103* near/1 allerg* (2)

#9 112* near/1 allerg* (1)

#10 (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX") (56)

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 (175)

#12 MeSH descriptor: [Microarray Analysis] explode all trees 280)

#13 (microarray* or micro array* or nanoarray*) (586)

#14 (multiplex near/3 (test* or assay*)) (66)

#15 #12 or #13 or #14 (761)

#16 MeSH descriptor: [Hypersensitivity] explode all trees (15,764)

#17 (allerg* or anaphyla* or hypersensiti* or hyper-sensiti* or poly-sensiti* or polysensiti* or paucisensiti*) (25,504)

#18 #16 or #17 (32,705)

#19 #15 and #18 (39)

#20 #11 or #19 (210)

NHS EED search retrieved 1 record.

*Please note: records ceased to be added to the NHS EED resource on 31 March 2015; this search was for archival material only.

EconLit (via EBSCOhost): 1886–21 May 2015

Searched: 21 May 2015
S13 S7 OR S12 (18)

S12 S10 AND S11 (0)

S11 TX(allerg* or anaphyla* or hypersensiti* or hyper-sensiti* or poly-sensiti* or polysensiti* or paucisensiti*) (49)

S10 S8 OR S9 (103)

S9 TX(multiplex N3 (test* or assay*)) (1)

S8 TX(microarray* or micro array* or nanoarray*) (102)

S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 (18)

S6 TX (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX") (13)

S5 TX (multi N3 compon* N3 assay*) (0)

S4 TX (compon* N3 resolv* N3 diagnos*) (0)

S3 TX (Immuno* N3 solid* N3 phase* N3 allerg* N3 chip*) (0)

S2 TX (ISAC) (5)

S1 TX (ImmunoCAP or Immuno-CAP or "Thermo Scientific") (0)

Research Papers in Economics (RePEc) (internet): up to 26 May 2015

http://repec.org/

Searched: 26 May 2015

IDEAS search interface

#1 (ImmunoCAP | Immuno-CAP | "Thermo Scientific") (Results 1)

#2 (Allerwatch | ComforTen | "MultiTest" | "true test" | "Microtest DX" | "Micro Test DX") (Results 17)

RePEc search retrieved 18 records.

Health-related quality of life/utilities searches

EMBASE (via OvidSP): 1974–29 June 2015

Searched: 30 June 2015

1. (food$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (27,518)
2. ((Cereal$ or wheat or rye or barley or oat or oats or rice or maize or spelt or buckwheat or soybean or millet or sorghum or corn or Kamut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (2562)
3. ((Gluten or (glutenin adj3 gliadin) or prolamins) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1408)
4. ((Dairy or milk or yog?urt$ or cream or butter$ or cheese$ or ice cream$ or kefir) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (6786)
5. ((Casein or whey or lactose) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (4128)
6. (Egg$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (2858)
7. ((Peanut$ or arachid or Arachis hypog?ea or groundnut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (3239)
8. ((ground or earth or monkey) adj3 nut$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1)
9. (arachis oil adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (0)
10. ((Nut or nuts or hazelnut$ or cashew$ or walnut$ or pecan$ or almond$ or Macadamia$ or pistachio$ or chestnut$ or coconut$ or Candlenut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1338)

11. ((Brazil or pine or hickory or betel) adj3 nut$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (91)
12. ((Crustacea$ or Mollusc$ or mollusk$ or shellfish or seafood or sea food or Lobster or crab$ or shrimp$ or prawn$ or squid$ or oyster$ or crayfish or cuttlefish or abalone or limpet$ or mussel$ or scallop$ or clam or clams or whelk$ or scampi or octopus or langoustine$ or cockle$ or winkles or krill) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1046)
13. ((Fish or finfish or sole or mackerel$ or hake or whiting or dab or plaice or Anchov$ or Catfish or Eel$ or Haddock or Halibut or Sardine$ or Scad or Snapper or Tilapia or Trout or shark or swordfish or cod or tuna or herring$ or flounder or mullet or salmon or kipper$ or caviar or seer or mackerel or tilefish or Pollock or whitebait or flatfish or john dory or carp) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1799)
14. (Fish adj3 roe adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (7)
15. ((Surimi or sashimi or sushi or cerviche or gravlax) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (2)
16. ((Snail$ or frog$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (221)
17. ((Sulfites or sulphites) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (55)
18. (((sulphiting adj2 agents) or (sulphur adj2 dioxide)) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (13)
19. ((Lentil$ or chickpea$ or pea or peas or garbanzo or bengal gram or chana or channa or leblebi) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (132)
20. ((poppy or sunflower or cotton or flax) adj3 seed$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (59)
21. ((fruit or fruits or vegetable$ or legume$ or kiwi or melon or banana$ or Carrot$ or apple$ or tomato$ or Apricot$ or pepper$ or Cabbage$ or Celery or Celeriac or Cherry or cherries or Courgette$ or zucchini or Aubergine$ or Dates or Fig or figs or plum or plums or garlic$ or grape$ or Lettuce$ or Lychee$ or Mango$ or Peach$ or Pear or pears or Pineapple$ or Pomegranate or Potato$ or Pumpkin$ or Strawberry or strawberries or Turnip$ or Avocado$ or Persimmon) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (2435)
22. ((Acerola or Aniseed or Camomile or Castor bean$ or Cocoa or linseed or Lupin$ or Lupine or Sesame or soy$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1227)
23. ((Condiment$ or spice$ or Mustard$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$, or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (230)
24. or/1-23 (42,706)
25. exp food allergy/ (24,867)
26. exp food allergen/ (4698)
27. or/25-26 (26,399)

28. 24 or 27 (42,706)
29. exp Food/ (721,540)
30. food additive/ (8744)
31. crab meat/ or crab/ or crayfish/ or lobster/ or shrimp/ or mollusc/ or fish/ or fish meat/ (111,052)
32. or/29-31 (822,648)
33. exp allergen/ (54,384)
34. exp hypersensitivity/ (498,826)
35. anaphylaxis/ (34,246)
36. anaphylactic shock/ (4751)
37. (allerg$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (479,818)
38. or/33-37 (649,918)
39. 32 and 38 (35,162)
40. 28 or 39 (58,974)
41. pollen allergy/ or hay fever/ (14,584)
42. ((Pollen or seasonal) adj3 (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (13,145)
43. (hayfever or hay fever or pollinosis or pollinoses).ti,ab,ot,hw. (11,916)
44. or/41-43 (21,333)
45. rhinitis/ or rhiniti$.ti,ab,ot,hw. (47,359)
46. (season$ or spring or summer or pollen$ or grass$ or birch or ragweed or tree$ or weed$ or mugwort or willow or alder).ti,ab,ot,hw. (397,576)
47. 45 and 46 (9392)
48. 44 or 47 (24,956)
49. 40 or 48 (79,964)
50. quality adjusted life year/ or quality of life index/ (16,036)
51. Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (16,212)
52. "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (1859)
53. (sf36 or sf 36 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 thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (26,380)
54. (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1612)
55. (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (5102)
56. (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (855)
57. (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (352)
58. (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (492)
59. "health related quality of life".ti,ab,ot. (34,378)
60. (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (10,293)
61. "assessment of quality of life".ti,ab,ot. (1910)
62. (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (8735)
63. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (17,838)
64. (hye or hyes).ti,ab,ot. (98)
65. health$ year$ equivalent$.ti,ab,ot. (39)
66. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2295)
67. (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (837)

68. (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (2463)
69. (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (13,192)
70. (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (6245)
71. 15d.ti,ab,ot. (1802)
72. (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (340)
73. (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (11,429)
74. (utilities or disutili$).ti,ab,ot. (7194)
75. or/50-74 (108,471)
76. letter.pt. (896,144)
77. editorial.pt. (482,372)
78. note.pt. (606,238)
79. or/76-78 (1,984,754)
80. 75 not 79 (105,171)
81. **49 and 80 (433)**

Health-related quality of life free-text terms based on:

- Figure 4 Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health-state utility values from the literature (internet), 2011 (accessed 18 August 2011). Available from: www.nicedsu.org.uk.

MEDLINE (via OvidSP): 1946–week 3 June 2015

Searched: 30 June 2015

1. (food$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (16,959)
2. ((Cereal$ or wheat or rye or barley or oat or oats or rice or maize or spelt or buckwheat or soybean or millet or sorghum or corn or Kamut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1605)
3. ((Gluten or (glutenin adj3 gliadin) or prolamins) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (876)
4. ((Dairy or milk or yog?urt$ or cream or butter$ or cheese$ or ice cream$ or kefir) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (3865)
5. ((Casein or whey or lactose) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (3292)
6. (Egg$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1416)
7. ((Peanut$ or arachid or Arachis hypog?ea or groundnut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1419)

8. ((ground or earth or monkey) adj3 nut$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (0)
9. (arachis oil adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (0)
10. ((Nut or nuts or hazelnut$ or cashew$ or walnut$ or pecan$ or almond$ or Macadamia$ or pistachio$ or chestnut$ or coconut$ or Candlenut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (643)
11. ((Brazil or pine or hickory or betel) adj3 nut$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (63)
12. ((Crustacea$ or Mollusc$ or mollusk$ or shellfish or seafood or sea food or Lobster or crab$ or shrimp$ or prawn$ or squid$ or oyster$ or crayfish or cuttlefish or abalone or limpet$ or mussel$ or scallop$ or clam or clams or whelk$ or scampi or octopus or langoustine$ or cockle$ or winkles or krill) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (636)
13. ((Fish or finfish or sole or mackerel$ or hake or whiting or dab or plaice or Anchov$ or Catfish or Eel$ or Haddock or Halibut or Sardine$ or Scad or Snapper or Tilapia or Trout or shark or swordfish or cod or tuna or herring$ or flounder or mullet or salmon or kipper$ or caviar or seer or mackerel or tilefish or Pollock or whitebait or flatfish or john dory or carp) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1154)
14. (Fish adj3 roe adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (2)
15. ((Surimi or sashimi or sushi or cerviche or gravlax) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (2)
16. ((Snail$ or frog$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)). ti,ab,ot,hw. (173)
17. ((Sulfites or sulphites) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)). ti,ab,ot,hw. (36)
18. (((sulphiting adj2 agents) or (sulphur adj2 dioxide)) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (3)
19. ((Lentil$ or chickpea$ or pea or peas or garbanzo or bengal gram or chana or channa or leblebi) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (84)
20. ((poppy or sunflower or cotton or flax) adj3 seed$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (27)
21. ((fruit or fruits or vegetable$ or legume$ or kiwi or melon or banana$ or Carrot$ or apple$ or tomato$ or Apricot$ or pepper$ or Cabbage$ or Celery or Celeriac or Cherry or cherries or Courgette$ or zucchini or Aubergine$ or Dates or Fig or figs or plum or plums or garlic$ or grape$ or Lettuce$ or Lychee$ or Mango$ or Peach$ or Pear or pears or Pineapple$ or Pomegranate or Potato$ or Pumpkin$ or Strawberry or strawberries or Turnip$ or Avocado$ or Persimmon) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1449)

22. ((Acerola or Aniseed or Camomile or Castor bean$ or Cocoa or linseed or Lupin$ or Lupine or Sesame or soy$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot, hw. (743)
23. ((Condiment$ or spice$ or Mustard$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$, or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (166)
24. or/1-23 (27,183)
25. exp Food Hypersensitivity/ (15,608)
26. exp Food/ (1,100,276)
27. exp Food Additives/ (239,057)
28. or/26-27 (1,101,303)
29. allergens/ or exp Hypersensitivity/ (288,187)
30. (allerg$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (324,188)
31. or/29-30 (442,055)
32. 28 and 31 (28,934)
33. 24 or 25 or 32 (45,050)
34. Rhinitis, Allergic, Seasonal/ (12,580)
35. ((Pollen or seasonal) adj3 (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (15,942)
36. (hayfever or hay fever or pollinosis or pollinoses).ti,ab,ot,hw. (3989)
37. (rhiniti$ adj3 (season$ or spring or summer or pollen$ or grass$ or birch or ragweed or tree$ or weed$ or mugwort or willow or alder)).ti,ab,ot,hw. (12,979)
38. or/34-37 (17,192)
39. 33 or 38 (60,503)
40. quality-adjusted life years/ or quality of life/ (133,433)
41. (sf36 or sf 36 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 thirty six or short form thirtysix or short form thirty six).ti, ab,ot. (16,140)
42. (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti, ab,ot. (1038)
43. (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (2869)
44. (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (460)
45. (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (336)
46. (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (265)
47. "health related quality of life".ti,ab,ot. (22,368)
48. (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (6465)
49. "assessment of quality of life".ti,ab,ot. (1174)
50. (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (4266)
51. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (10,537)
52. (hye or hyes).ti,ab,ot. (54)
53. health$ year$ equivalent$.ti,ab,ot. (38)
54. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (901)
55. (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (617)
56. (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (1788)

57. (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (7212)
58. (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (3886)
59. 15d.ti,ab,ot. (1173)
60. (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (238)
61. (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (6934)
62. (utilities or disutili$).ti,ab,ot. (4124)
63. or/40-62 (158,071)
64. letter.pt. (854,881)
65. editorial.pt. (359,484)
66. historical article.pt. (317,628)
67. or/64-66 (1,516,490)
68. 63 not 67 (150,867)
69. **39 and 68 (739)**

Health-related quality of life free-text terms based on:

- Figure 4 Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (internet), 2011 (accessed 18 August 2011). Available from: www.nicedsu.org.uk.

MEDLINE In-Process & Other Non-Indexed Citations (via OvidSP): up to 29 June 2015; MEDLINE Daily Update (via OvidSP): up to 29 June 2015

Searched: 30 June 2015

1. (food$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1007)
2. ((Cereal$ or wheat or rye or barley or oat or oats or rice or maize or spelt or buckwheat or soybean or millet or sorghum or corn or Kamut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (204)
3. ((Gluten or (glutenin adj3 gliadin) or prolamins) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (115)
4. ((Dairy or milk or yog?urt$ or cream or butter$ or cheese$ or ice cream$ or kefir) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (229)
5. ((Casein or whey or lactose) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (76)
6. (Egg$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (126)
7. ((Peanut$ or arachid or Arachis hypog?ea or groundnut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (155)
8. ((ground or earth or monkey) adj3 nut$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (0)

9. (arachis oil adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (0)
10. ((Nut or nuts or hazelnut$ or cashew$ or walnut$ or pecan$ or almond$ or Macadamia$ or pistachio$ or chestnut$ or coconut$ or Candlenut) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (51)
11. ((Brazil or pine or hickory or betel) adj3 nut$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (5)
12. ((Crustacea$ or Mollusc$ or mollusk$ or shellfish or seafood or sea food or Lobster or crab$ or shrimp$ or prawn$ or squid$ or oyster$ or crayfish or cuttlefish or abalone or limpet$ or mussel$ or scallop$ or clam or clams or whelk$ or scampi or octopus or langoustine$ or cockle$ or winkles or krill) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (44)
13. ((Fish or finfish or sole or mackerel$ or hake or whiting or dab or plaice or Anchov$ or Catfish or Eel$ or Haddock or Halibut or Sardine$ or Scad or Snapper or Tilapia or Trout or shark or swordfish or cod or tuna or herring$ or flounder or mullet or salmon or kipper$ or caviar or seer or mackerel or tilefish or Pollock or whitebait or flatfish or john dory or carp) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (83)
14. (Fish adj3 roe adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1)
15. ((Surimi or sashimi or sushi or cerviche or gravlax) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1)
16. ((Snail$ or frog$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (4)
17. ((Sulfites or sulphites) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (0)
18. (((sulphiting adj2 agents) or (sulphur adj2 dioxide)) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (1)
19. ((Lentil$ or chickpea$ or pea or peas or garbanzo or bengal gram or chana or channa or leblebi) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (9)
20. ((poppy or sunflower or cotton or flax) adj3 seed$ adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (3)
21. ((fruit or fruits or vegetable$ or legume$ or kiwi or melon or banana$ or Carrot$ or apple$ or tomato$ or Apricot$ or pepper$ or Cabbage$ or Celery or Celeriac or Cherry or cherries or Courgette$ or zucchini or Aubergine$ or Dates or Fig or figs or plum or plums or garlic$ or grape$ or Lettuce$ or Lychee$ or Mango$ or Peach$ or Pear or pears or Pineapple$ or Pomegranate or Potato$ or Pumpkin$ or Strawberry or strawberries or Turnip$ or Avocado$ or Persimmon) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (130)
22. ((Acerola or Aniseed or Camomile or Castor bean$ or Cocoa or linseed or Lupin$ or Lupine or Sesame or soy$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (65)

23. ((Condiment$ or spice$ or Mustard$) adj4 (allerg$ or sensitivit$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$, or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (8)
24. or/1-23 (1826)
25. exp Food Hypersensitivity/ (16)
26. exp Food/ (1220)
27. exp Food Additives/ (177)
28. or/26-27 (1220)
29. allergens/ or exp Hypersensitivity/ (201)
30. (allerg$ or hypersensitiv$ or hyper-sensiti$ or intolerance$ or adverse reaction$ or anaphyla$ or pseudoanaphyla$ or poly-sensiti$ or polysensiti$ or paucisensiti$).ti,ab,ot,hw. (15,177)
31. or/29-30 (15,275)
32. 28 and 31 (28)
33. 24 or 25 or 32 (1845)
34. Rhinitis, Allergic, Seasonal/ (1)
35. ((Pollen or seasonal) adj3 (allerg$ or anaphyla$ or hypersensiti$ or hyper-sensiti$ or poly-sensiti$ or polysensiti$ or paucisensiti$)).ti,ab,ot,hw. (324)
36. (hayfever or hay fever or pollinosis or pollinoses).ti,ab,ot,hw. (194)
37. (rhiniti$ adj3 (season$ or spring or summer or pollen$ or grass$ or birch or ragweed or tree$ or weed$ or mugwort or willow or alder)).ti,ab,ot,hw. (97)
38. or/34-37 (502)
39. 33 or 38 (2301)
40. quality-adjusted life years/ or quality of life/ (282)
41. (sf36 or sf 36 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 thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (1709)
42. (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (448)
43. (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (418)
44. (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (50)
45. (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (14)
46. (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (39)
47. "health related quality of life".ti,ab,ot. (3142)
48. (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (927)
49. "assessment of quality of life".ti,ab,ot. (121)
50. (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (723)
51. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (1442)
52. (hye or hyes).ti,ab,ot. (2)
53. health$ year$ equivalent$.ti,ab,ot. (1)
54. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (109)
55. (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (48)
56. (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (331)
57. (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (1076)
58. (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (541)

59. 15d.ti,ab,ot. (116)
60. (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (21)
61. (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (832)
62. (utilities or disutili$).ti,ab,ot. (552)
63. or/40-62 (8337)
64. letter.pt. (30,812)
65. editorial.pt. (22,136)
66. historical article.pt. (227)
67. or/64-66 (53,144)
68. 63 not 67 (8298)
69. **39 and 68 (20)**

Health-related quality of life free-text terms based on:

- Figure 4 Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (internet), 2011 (accessed 18 August 2011). Available from: www.nicedsu.org.uk.

NHS EED (via Wiley): 2015/April/Iss2

Searched: 1 July 2015

#1 food* near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (1044)

#2 (Cereal* or wheat or rye or barley or oat or oats or rice or maize or spelt or buckwheat or soybean or millet or sorghum or corn or Kamut) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (103)

#3 (Gluten or glutenin or prolamins) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (24)

#4 (Dairy or milk or yog*urt* or cream or butter* or cheese* or ice cream* or kefir) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (532)

#5 (Casein or whey or lactose) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (278)

#6 Egg* near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (266)

#7 (Peanut* or arachid or "Arachis hypog*ea" or groundnut) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (150)

#8 "arachis oil" near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (1)

#9 (Nut or nuts or hazelnut* or cashew* or walnut* or pecan* or almond* or Macadamia* or pistachio* or chestnut* or coconut* or Candlenut) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (55)

#10 (Crustacea* or Mollusc* or mollusk* or shellfish or seafood or "sea food" or Lobster or crab* or shrimp* or prawn* or squid* or oyster* or crayfish or cuttlefish or abalone or limpet* or mussel* or scallop* or clam or clams or whelk* or scampi or octopus or langoustine* or cockle* or winkles or krill) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (22)

#11 (Fish or finfish or sole or mackerel* or hake or whiting or dab or plaice or Anchov* or Catfish or Eel* or Haddock or Halibut or Sardine* or Scad or Snapper or Tilapia or Trout or shark or swordfish or cod or tuna or herring* or flounder or mullet or salmon or kipper* or caviar or seer or mackerel or tilefish or Pollock or whitebait or flatfish or "john dory" or carp) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (89)

#12 roe near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (1)

#13 (Surimi or sashimi or sushi or cerviche or gravlax) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (0)

#14 (Snail* or frog*) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (0)

#15 (Sulfites or sulphites) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (6)

#16 (sulphating or sulphur) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (5)

#17 (Lentil* or chickpea* or pea or peas or garbanzo or "bengal gram" or chana or channa or leblebi) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (8)

#18 (poppy or sunflower or cotton or flax) near/3 seed* near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (0)

#19 (fruit or fruits or vegetable* or legume* or kiwi or melon or banana* or Carrot* or apple* or tomato* or Apricot* or pepper* or Cabbage* or Celery or Celeriac or Cherry or cherries or Courgette* or zucchini or Aubergine* or Dates or Fig or figs or plum or plums or garlic* or grape* or Lettuce* or Lychee* or Mango* or Peach* or Pear or pears or Pineapple* or Pomegranate or Potato* or Pumpkin* or Strawberry or strawberries or Turnip* or Avocado* or Persimmon) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (101)

#20 (Acerola or Aniseed or Camomile or "Castor bean*" or Cocoa or linseed or Lupin* or Lupine or Sesame or soy*) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti*) (83)

#21 (Condiment* or spice* or Mustard*) near/4 (allerg* or sensitivit* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla*, or "poly-sensiti*" or polysensiti* or paucisensiti*) (8)

#22 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 (2007)

#23 MeSH descriptor: [Food Hypersensitivity] explode all trees (618)

#24 MeSH descriptor: [Food] explode all trees (22,580)

#25 MeSH descriptor: [Food Additives] explode all trees (545)

#26 #24 or #25 (22,598)

#27 MeSH descriptor: [Allergens] explode all trees (1554)

#28 MeSH descriptor: [Hypersensitivity] explode all trees (15,778)

#29 allerg* or hypersensitiv* or "hyper-sensiti*" or intolerance* or "adverse reaction*" or anaphyla* or pseudoanaphyla* or "poly-sensiti*" or polysensiti* or paucisensiti* (36,164)

#30 #27 or #28 or #29 (43,237)

#31 #26 and #30 (1384)

#32 #22 or #23 or #31 (2743)

#33 MeSH descriptor: [Rhinitis, Allergic, Seasonal] explode all trees 1611)

#34 (Pollen or seasonal) near/3 (allerg* or anaphyla* or hypersensiti* or "hyper-sensiti*" or "poly-sensiti*" or polysensiti* or paucisensiti*) (3657)

#35 hayfever or "hay fever" or pollinosis or pollinoses (951)

#36 rhiniti* near/3 (season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder) (2962)

#37 #33 or #34 or #35 or #36 (4095)

#38 #32 or #37 (6656)

#39 MeSH descriptor: [Quality-Adjusted Life Years] this term only (3930)

#40 MeSH descriptor: [Quality of Life] this term only (15,292)

#41 sf36 or sf 36 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 thirty six" or "short form thirtysix" or "short form thirty six" (6646)

#42 sf6 or "sf 6" or sf-6 or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six" (137)

#43 sf12 or "sf 12" or "sf-12" or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve" (975)

#44 sf6D or "sf 6D" or "sf-6D" or "short form 6D" or "shortform 6D" or "sf six D" or sfsixD or "shortform six D" or "short form six D" (186)

#45 sf20 or "sf 20" or "sf-20" or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty" (74)

#46 sf8 or "sf 8" or "sf-8" or "short form 8" or "shortform 8" or "sf eight" or sfeight or "shortform eight" or "short form eight" (58)

#47 "health related quality of life" (6922)

#48 "Quality adjusted life" or "Quality-adjusted-life" (6557)

#49 "assessment of quality of life" (318)

#50 euroqol or "euro qol" or eq5d or "eq 5d" (2744)

#51 hql or hrql or hqol or "h qol" or hrqol or "hr qol" (2599)

#52 hye or hyes (53)

#53 "health* year* equivalent*" (5)

#54 hui or hui1 or hui2 or hui3 or hui4 or "hui-4" or "hui-1" or "hui-2" or "hui-3" (1262)

#55 "quality time" or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" (231)

#56 "Disability adjusted life" or "Disability-adjusted life" or "health adjusted life" or "health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost" (350)

#57 QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL* (5218)

#58 timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "Standard gamble*" or "willingness to pay" (1916)

#59 15d (107)

#60 HSUV* or "health state* value*" or "health state* preference*" or HSPV* (83)

#61 utilit* near/3 ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*) (4632)

#62 utilities or disutili* (1656)

#63 #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 (33,724)

#64 #38 and #63 (393)

NHS EED search retrieved 34 records.*

*Please note: Records ceased to be added to the NHS EED resource on 31 March 2015, this search was for archival material only.

CEA Registry (internet): up to 1 July 2015

https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx

Searched: 1 July 2015

Basic search for 'articles'.

Search term	Hits
Allergy	16
Allergies	0
Allergens	0
Allergic	20
Intolerance	6
Intolerances	0
Hypersensitivity	4
Hypersensitivities	0
Hyper-sensitivity	0
Hyper-sensitivities	0
Anaphylaxis	4
Anaphylactic	1
Pollen	5
Rhinitis	9
Hay fever	0
Hayfever	0
pollinosis	0
pollinoses	0
Total	**65 (including duplicates)**

PROQOLID (internet): up to 1 July 2015

www.proqolid.org/

Searched: 1 July 2015

Basic search

Search term	Hits
Allergy	0
Allergies	0
Allergens	0
Allergic	0
Intolerance	0
Intolerances	0
Hypersensitivity	0
Hypersensitivities	0
Hyper-sensitivity	0
Hyper-sensitivities	0
Anaphylaxis	0
Anaphylactic	0
Pollen	0
Rhinitis	9
Hay fever	0
Hayfever	0
pollinosis	0
pollinoses	0
Total	**9**

Appendix 2 Data extraction tables

A Baseline details (studies of change to management, treatment or diagnostic classification)

Study details	Selection criteria	Participant details (allergic)	Participant details (healthy controls)
Gay-Crosier 2010[36] *Country*: NR *Funding*: NR *Study design*: Observational before-and-after study *Recruitment*: Participants undergoing subcutaneous immunotherapy. No further details reported *No. of participants*: 9	*Inclusion criteria*: Participants undergoing subcutaneous immunotherapy *Exclusion criteria*: None reported	*n*: 9 Mean age, *years* (SD): NR Male (%): NR Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with gastrointestinal symptoms (%): NR *n* with respiratory symptoms (%): NR *n* with urticaria (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): NR	NA
Heaps 2014,[39] 2010[35] *Country*: UK *Funding*: Reagents and consumables provided by Thermo Fisher Scientific *Study design*: Prospective, observational before-and-after study *Recruitment*: Participants recruited from five specialist allergy centres. No further details reported *No. of participants*: 110	*Inclusion criteria*: Adult patients diagnosed with idiopathic anaphylaxis *Exclusion criteria*: None reported	*n*: 110 Mean age, years (range): 42 (20–76) Male (%): 37 (33.6) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with gastrointestinal symptoms (%): NR *n* with respiratory symptoms (%): NR *n* with urticaria (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): 110 (100)	NA

Study details	Selection criteria	Participant details (allergic)	Participant details (healthy controls)
Hermansson 2014[33,34] *Country*: Finland *Funding*: NR *Study design*: Prospective, observational *Recruitment*: Database of 2317 primary school children used to identify 199 children who were on restrictive diets, of whom 85 agreed to participate in the study and were still classified as allergic following nurse interview *No. of participants*: 85	*Inclusion criteria*: Children who were on a restrictive diet in school catering *Exclusion criteria*: Coeliac disease	*n*: 85 Mean age, years (range): NR Male (%): NR Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with gastrointestinal symptoms (%): NR *n* with respiratory symptoms (%): NR *n* with urticaria (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): NR	NA
Luengo 2010[37] *Country*: Spain, 'Mediterranean population' *Funding*: NR *Study design*: observational before-and-after study *Recruitment*: No details reported *No. of participants*: 55	*Inclusion criteria*: Well characterised, multisensitised, allergic patients *Exclusion criteria*: None reported	*n*: 55 Mean age, years (range): NR Male (%): NR Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with gastrointestinal symptoms (%): NR *n* with respiratory symptoms (%): NR *n* with urticaria (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): NR	NA
Noimark 2012[40] *Country*: UK *Funding*: NR *Study design*: Case series, abstract only, no details reported *Recruitment*: Selected participants from a specialist allergy centre. No further details reported *No. of participants*: 12	*Inclusion criteria*: Children with moderate to severe eczema and multiple food allergies *Exclusion criteria*: None reported	*n*: 12 Mean age, years (range): NR Male (%): NR Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with gastrointestinal symptoms (%): NR *n* with respiratory symptoms (%): NR *n* with urticaria (%): NR *n* with atopic eczema (%): 12 (100) *n* with anaphylaxis (%): NR	NA

Study details	Selection criteria	Participant details (allergic)	Participant details (healthy controls)
Passalacqua 2013[38] *Country*: Italy *Funding*: Phadia AB/Thermo Fisher Scientific *Study design*: Prospective, observational before-and-after study *Recruitment*: Participants recruited from six allergy centres. No further details reported *No. of participants*: 409 (318 allergy patients and 91 healthy controls)	*Inclusion criteria*: Patients referred for respiratory allergic diseases who had at least two positive SPTs. Controls had negative SPTs *Exclusion criteria*: None reported	*n*: 318 Mean age, years (range): 37 (12–78) Male (%): 148 (46.5) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): 51 (16) *n* with gastrointestinal symptoms (%): 14 (4.4) *n* with respiratory symptoms (%): 318 (100) *n* with urticaria (%): 36 (11.3) *n* with atopic eczema (%): 4 (1.3) *n* with anaphylaxis (%): 6 (1.9)	*n*: 91 Mean age, years (range): 40 (15–83) Male (%): 19 (20.9) Median duration of allergy, years (range): NA *n* with oral allergy syndrome (%): 0 (0) *n* with gastrointestinal symptoms (%): 0 (0) *n* with respiratory symptoms (%): 0 (0) *n* with urticaria (%): 0 (0) *n* with atopic eczema (%): 0 (0) *n* with anaphylaxis (%): 0 (0)
Sastre 2012[30–32,59] *Country*: Spain *Funding*: CIBER de Enfermedades Respiratorias and Instituto de Salud Carlos III of the Ministry of Science and Information, Spain *Study design*: Observational before-and-after study *Recruitment*: Participants attending an outpatient allergy clinic. No further details reported *No. of participants*: 141	*Inclusion criteria*: Patients with allergic rhinoconjunctivitis and/or asthma who were sensitised to pollen, with or without concomitant food allergy *Exclusion criteria*: None reported	*n*: 141 Mean age, years (SD): 31 (13.6) Male (%): 58 (41) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with gastrointestinal symptoms (%): NR *n* with respiratory symptoms (%): 141 (100) *n* with urticaria (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): NR	NA

NA, not applicable; NR, not reported; SD, standard deviation.

B Baseline accuracy study details (diagnostic case–control)

Study details	Selection criteria	Participant details (allergic)	Participant details (tolerant)
Alessandri 2011[42] *Country*: Italy *Funding*: Italian Ministry of Health, Programma Ricerca Corrente 2008–2010 *Recruitment*: January 2008 to September 2010 *No. of participants*: 68	*Inclusion criteria*: Children referred for suspected hen's egg allergy (based on history of reactions after ingestion and positive SPT or IgE to hen's egg white extracts). All patients were following a hen's egg elimination diet *Exclusion criteria*: Steroid treatment *Recruitment* site: Centre for Molecular Allergology, IDI-IRCCS, Rome, Italy	*n*: 19 Median age, years (range): 4.3 (NR) Male (%): 15 (79) Median duration of allergy, years (range): NR *n* with atopic eczema (%): NR *n* with oral allergy syndrome (%): 3 (16)[a] *n* with asthma (%): 7 (37)[a] *n* with anaphylaxis (%): 1 (5) *n* with gastritis/vomiting (%): 11(58) *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR	*n*: • 14 (tolerant to boiled, not raw) • 35 (tolerant to raw and boiled) Median age, years (range): • 3.17 (NR) (tolerant to boiled, not raw) • 4.42 (NR) (tolerant to raw and boiled) Male (%): • 9 (64) (tolerant to boiled, not raw) • 23 (66) (tolerant to raw and boiled) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): • 3 (21) (tolerant to boiled, not raw)[a] • 0 (0) (tolerant to raw and boiled)[a] *n* with asthma (%): • 3 (21) (tolerant to boiled, not raw)[a] • 0 (0) (tolerant to raw and boiled)[a] *n* with anaphylaxis (%): • 0 (0) (tolerant to boiled, not raw)[a] • 0 (0) (tolerant to raw and boiled)[a] *n* with gastritis/vomiting (%): • 10 (71) (tolerant to boiled, not raw)[a] • 0 (0) (tolerant to raw and boiled)[a] *n* with atopic eczema (%): NR *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR

Study details	Selection criteria	Participant details (allergic)	Participant details (tolerant)
Cabrera-Freitag 2011,[43] 2010,[94] 2011[48] *Country*: Spain *Funding*: Spanish Society of Allergy and Clinical Immunology Foundation; Spanish Research Network on Adverse Reactions to Allergens and Drugs *Recruitment*: March 2008 to May 2009 *No. of participants*: 173	*Inclusion criteria*: Allergic patients had (1) an allergen-specific history (rhinitis, rhinoconjunctivitis and/or bronchial asthma) during the season of pollinisation of grass pollen and/or cypress pollen and (2) a positive SPT to the corresponding pollen, *P. pratense* and/or *C. arizonica*. Controls had no pollen allergen-specific history and had negative SPT to the corresponding pollen *Exclusion criteria*: Patients showing clinical history during the season of pollinisation of grass pollen and showing SPT-positive to grass pollen and to other pollen that pollinated in the same season (i.e. olive) *Recruitment* site: Clínica Universidad de Navarra, Pamplona, Spain	• *n*: 43 (grass), 12 (cypress) Mean age, years (25th–75th percentile): • Grass 29 (20–37) • Cypress 32 (21–44) Male (%): • Grass 21 (49) • Cypress 4 (33.3) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): • Grass 15 (35) • Cypress 3 (25) *n* with anaphylaxis (%): NR *n* with gastritis/vomiting (%): NR *n* with atopic eczema (%): NR *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR	• *n*: 26 (grass), 92 (cypress) Control definition: Negative history and SPT Mean age, years (25th–75th percentile): • Grass 27 (17–35) • Cypress 29 (20–38) Male (%): • Grass 10 (39) • Cypress 46 (50) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): • Grass 7 (27) • Cypress 2 (35) *n* with anaphylaxis (%): NR *n* with gastritis/vomiting (%): NR *n* with atopic eczema (%): NR *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR
De Swert 2012[41] *Country*: Belgium *Funding*: NR *Recruitment*: NR *No. of participants*: 15	*Inclusion criteria*: Subjects with birch pollen allergy (typical allergic symptoms during the birch pollen season in combination with a positive IgE response to birch or rBet v1), suspected of also being soy allergic *Exclusion criteria*: NR *Recruitment* site: Outpatient allergy clinic, Paediatric Department, University Hospital Gasthuisberg, Leuven, Belgium	*n*: 8 Median age, years (range): 10.3 (4.8–15.6) Male (%): NR Median duration of allergy, years (range): tree 3.7 (1–9) *n* with oral allergy syndrome (%): 7 (88) *n* with asthma (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): NR *n* with gastritis/vomiting (%): NR *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR	*n*: 7 Median age, years (range): 10.1 (4.7–16) Male (%): NR Median duration of allergy, years (range): tree 3.5 (1–10) *n* with oral allergy syndrome (%): 4 (57) *n* with asthma (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): NR *n* with gastritis/vomiting (%): NR *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR

Study details	Selection criteria	Participant details (allergic)	Participant details (tolerant)
Sokolova 2009[46] *Country*: Portugal *Funding*: Phadia, Portugal *Recruitment*: NR *No. of participants*: 41	*Inclusion criteria*: Patients from Food Allergy Outpatient Clinic who, at the time of diagnosis, had a clinical picture compatible with IgE-mediated CMPA, documented by SPT and positive specific IgE (> 0.35 kU/l) to whole milk and/or its protein fractions (α-LA, β-LG and casein). Control group consisted of four atopic individuals with no history of CMPA and who ingested cow's milk daily *Exclusion criteria*: NR *Recruitment* site: Food Allergy Outpatient Clinic, Centro Hospitalar Lisboa Norte, Lisbon, Portugal	*n*: 17 Mean age, years (range): 9.25 (2–19) Male (%): 10 (58.5) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): NR *n* with anaphylaxis (%): NR *n* with gastritis/vomiting (%): NR *n* with atopic eczema (%): 2 (12) *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR	*n*: 20 Control definition: Negative OFC Mean age, years (range): 6.15 (2–22) Male (%): 7 (65) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): NR *n* with anaphylaxis (%): NR *n* with gastritis/vomiting (%): NR *n* with atopic eczema (%): 6 (30) *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR

CMPA, cow's milk protein allergy; kU/l, kilo International Unit per litre; NR, not reported.
a After oral challenge.

C Baseline accuracy study details (diagnostic cohort studies)

Study details	Selection criteria	Participant details
Albarini 2013[47] *Country*: NR *Funding*: NR *Recruitment*: April 2007 to May 2012 *No. of participants*: 35	*Inclusion criteria*: Children with immediate reaction to hazelnut ingestion *Exclusion criteria*: NR *Recruitment* site: NR	*n*: 35 Median age, years (range): 8.3 (2.2–14.2) Male (%): 26 (74) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): NR *n* with anaphylaxis (%): NR *n* with gastritis/vomiting (%): NR *n* with atopic eczema (%): NR *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR

Study details	Selection criteria	Participant details
D'Urbano 2010[44] *Country*: Italy *Funding*: IRCCS Children's Hospital Bambino Gesù *Recruitment*: NR *No. of participants*: 104 (58 cow's milk and 46 hen's egg)	*Inclusion criteria*: Infants and children referred for evaluation of suspected IgE-mediated food hypersensitivity (history related to cow's milk or hen's egg consumption, of severe and/or immediate reactions) *Exclusion criteria*: Atopic eczema as the only indication for suspected allergy *Recruitment* site: Department of Paediatric Medicine–Allergy Unit, IRCCS Children's Hospital Bambino Gesù, Rome, Italy	*n*: 104 Median age, years (range): 4.9 (0.7–15.1) Male (%): 62 (60) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): NR *n* with atopic eczema (%): NR *n* with skin symptom (%): 44 (42) *n* with respiratory symptoms (%): 6 (96) *n* with gastrointestinal symptoms (%): 33 (32) *n* with anaphylaxis (%): 4 (4)
Ott 2008[49] *Country*: Germany *Funding*: START programme of the Medical Faculty of the Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen *Recruitment*: NR *No. of participants*: 130	*Inclusion criteria*: Children referred for evaluation of suspected IgE-mediated food hypersensitivity *Exclusion criteria*: NR *Recruitment* site: Charité Allergy Center, Universitätsmedizin Berlin, Germany	*n*: 130 Median age, months (range): NR [total = 14 (5–150)] Male (%): 70 (54) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): NR *n* with atopic eczema (%): NR *n* with anaphylaxis (%): NR *n* with vomiting (%): 23 (16) *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR
Wohrl 2006[45] *Country*: Austria *Funding*: ISAC and IgE were performed in the laboratories of VBC-GENOMICS, Vienna, Austria *Recruitment*: September to October 2004 *No. of participants*: 120 patients with allergic rhinitis	*Inclusion criteria*: Adults at the end of the pollen season *Exclusion criteria*: Total serum IgE > 1000 kU/l (to minimise non-specific binding in the ImmunoCAP system) *Recruitment* site: Allergy Outpatient Clinic of the Division of Immunology, Allergy and Infectious Diseases, Medical University of Vienna, and at a private outpatient allergy clinic FAZ–Floridsdorf Allergy Center, Vienna	*n*: 120 Mean age, years (SD): 35.9 (14.4) Male (%): 50 (42) Median duration of allergy, years (range): NR *n* with oral allergy syndrome (%): NR *n* with asthma (%): NR *n* with atopic eczema (%): NR *n* with skin symptom (%): NR *n* with respiratory symptoms (%): NR *n* with gastrointestinal symptoms (%): NR *n* with anaphylaxis (%): NR

CMPA, cow's milk protein allergy; kU/l, kilo International Unit per litre; NR, not reported; SD, standard deviation.

D Index test and comparator details (studies of change to management, treatment or diagnostic classification)

Study details	Index test details	Standard care details
Heaps 2014[39]	*Version*: ImmunoCAP ISAC 103 *Manufacturer*: Phadia/Thermo Fisher Scientific, Milan, Italy *Method*: 'According to the manufacturer's instructions.' Slides were scanned using a GenePix 4000B microarray scanner (Molecular Devices, Sunnyvale, CA, USA). Image analysis was performed using the Microarray Image Analyser (MIA: Thermo Fisher Scientific/Phadia, Uppsala, Sweden). All new positive ISAC results were retested for confirmation *Allergens (components) assessed*: NR *Definition of a positive result*: 'According to the manufacturer's instructions' ISU > 0.3 *Positive control*: NR *Negative control*: NR	*Method*: SPT and clinical history, and sIgE and MCT *SPT*: NR *sIgE and MCT*: FEIA auto-analyser, ImmunoCAP 250 platform (Thermo Fisher Scientific/Phadia AB, Uppsala, Sweden), 'according to the manufacturer's instructions'
Hermansson 2014[33,34]	*Version*: ImmunoCAP ISAC 112 *Manufacturer:* NR *Method*: NR *Allergens (components) assessed*: NR *Definition of a positive result*: NR *Positive control*: NR *Negative control*: NR	*Method*: Clinical history/parental report, and sIgE *sIgE*: RAST
Luengo 2010[37]	*Version*: ImmunoCAP ISAC 103 *Manufacturer*: NR *Method*: NR *Allergens (components) assessed*: NR *Definition of a positive result*: NR *Positive control*: NR *Negative control*: NR	*Method*: SPT and sIgE *SPT*: NR *sIgE*: NR

Study details	Index test details	Standard care details
Noimark 2012[40]	*Version*: ImmunoCAP ISAC unspecified version *Manufacturer*: NR *Method*: NR *Allergens (components) assessed*: NR *Definition of a positive result*: NR *Positive control*: NR *Negative control*: NR	*Method*: SPT and/or sIgE *SPT*: NR *sIgE*: NR
Passalacqua 2013[38]	*Version*: ImmunoCAP ISAC 103 *Manufacturer*: Thermo Fisher Scientific, Milan, Italy *Method*: According to the manufacturer's instructions. Slides were read automatically using a Laser Scan Confocal microarray reader (LuxScan 10K/A, CapitalBio, Beijing, China) *Allergens (components) assessed*: NR *Definition of a positive result*: ≥ 0.35 ISU *Positive control*: NR *Negative control*: NR	*Method*: SPT and clinical history, with sIgE as required *SPT*: Standard panel of commercial extractive preparations (ALK-Abelló, Milan, Italy), including mites, grass, olive, *Parietaria*, birch, cypress, ragweed, mugwort, cat and dog dander, *Alternaria* and *Aspergillus*. A positive result was defined as a weal reaction of ≥ 3 mm in diameter. 1% histamine was used as a positive control and diluent as a negative control *sIgE*: Commercial immunoenzymatic method (Thermo Fisher Scientific/Phadia AB, Uppsala, Sweden). A positive result was defined as > 0.35 kU/l
Sastre 2012[32]	*Version*: ImmunoCAP ISAC 96 *Manufacturer*: Phadia, Sweden *Method*: 'According to the manufacturer's instructions' *Allergens (components) assessed*: Olive (Ole 1); cypress (Cup s 1); plane (pla a1, Pla a2); grass (Phl p1, phl p5); cynodon (Cyn d1) *Definition of a positive result*: 'According to the manufacturer's instructions' *Positive control*: NR *Negative control*: NR	*Method:* SPT and clinical history, taking into consideration the time of year of respiratory symptoms and European Academy of Allergy and Clinical Immunology guidelines *SPT*: Standard panel of commercial inhalants (ALK-Abelló, Madrid, Spain), including Olea e, Platanus a, Cupressus a, grass mix, Cynodon d, Phragmites c, Artemisia v, Salsola k, and Plantago l. A positive result was defined as a weal reaction ≥ 3 mm more than negative control. Histamine (10 mg/ml) was used as a positive control and glycerol–saline solution as a negative control

FEIA, fluoroenzyme immunoassay; kU/l, kilo International Unit per litre; NR, not reported; RAST, radioallergosorbent test.

E Index test and reference standard details (accuracy studies)

Study details	Index test details			Reference standard details: oral challenge
	ImmunoCAP/Microtest	Specific IgE tests	SPT	
Albarini 2013[47]	*Version*: ImmunoCAP ISAC unspecified version *Manufacturer*: NR *Method*: NR *Definition of positive result*: NR *Positive control*: NR *Negative control*: NR	*Version*: ImmunoCAP *Manufacturer*: NR *Method*: NR *Definition of positive result*: > 0.35 kUI/l *Positive control*: NR *Negative control*: NR	*Method*: NR Allergen: NR *Positive result*: Mean weal diameter > 3 mm *Positive control*: NR *Negative control*: NR	DBPCFC
Alessandri 2011[42]	*Version*: ImmunoCAP ISAC 103 *Manufacturer*: Phadia AB, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of a positive result*: Thresholds for each allergen/ component derived from ROC analyses, but not reported *Positive control*: NR *Negative control*: NR	*Version*: ImmunoCAP *Manufacturer*: Phadia AB, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of a positive result*: Thresholds for each allergen/ component derived from ROC analyses, but not reported *Positive control*: NR *Negative control*: NR	*Method*: Performed in duplicate on the volar surface of the forearm by the same investigator, following European Academy of Allergy and Clinical Immunology recommendations, using 1-mm-tipped lancets. Weal reactions were recorded after 15 minutes, by outlining with pen onto paper sheets, which were scanned to digitally measure areas *Allergen*: Commercial extracts (Allergopharma, Reinbek, Germany) and freshly prepared egg reagents *Positive result*: Mean weal diameter of ≥ 7 mm *Positive control*: Histamine diphosphate (10 mg/ml) *Negative control*: Glycerol–saline solution	Double-blind placebo-controlled hen's egg challenges were carried out using commercially available eggs *Boiled egg*: Administering an initial dose of 0.1 ml, and, in case of no reactions in the next 20 minutes, by progressively increasing the egg amount by a factor 5 (0.5, 2, 10 and 50 ml) up to the ingestion of one egg (approximately 6 g) Patients tolerating boiled egg were then challenged with raw egg in a similar way

Study details	Index test details			Reference standard details: oral challenge
	ImmunoCAP/Microtest	Specific IgE tests	SPT	
De Swert 2012[41]	*Version*: ImmunoCAP ISAC unspecified version *Manufacturer*: Phadia AB, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of a positive result*: ≥ 0.3 ISU, ≥ 1.0 ISU for rGly m4 *Positive control*: NR *Negative control*: NR	*Version*: ImmunoCAP FEIA *Manufacturer*: Phadia AB, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of a positive result*: ≥ 0.10 kU/l, ≥ 17.6 kU/l for rGly m4 *Positive control*: NR *Negative control*: NR	*Method*: Performed using a microlance. Weal reactions were recorded after 15 minutes; orthogonal diameters were measured and mean diameters were calculated Allergen: 1/10 w/v dilution of soy flour (Sojameel, Biofresh, Genk, Belgium) *Positive result*: Mean weal diameter ≥ 3 mm, (cut-off point ≥ 7 mm rGly m4) *Positive control*: Histamine diphosphate (1 mg/ml) *Negative control*: Coca solution in 50% glycerol	Subjects were on a soy-free diet for at least 8 weeks Challenge performed with Alpro soya natural drink; one drop of soy drink at the inner side of the lower lip If no reaction occurred within 15 minutes, increasing doses of 1, 2, 5, 10, 20, 40 and 80 ml of soy drink were given at 20-minute intervals, until appearance of objective allergic symptoms (or until 158 ml) If no symptoms after 2 hours, the parents were asked to give the child daily volumes of 120 ml of soy drink in the next 2 weeks, while continuing their diet otherwise unchanged Re-evaluation was provided after 2 weeks or earlier if required
D'Urbano 2010[44]	*Version*: ImmunoCAP ISAC 89 *Manufacturer*: Phadia AB, Uppsala, Sweden *Method*: 'according to the manufacturer's instructions' *Definition of positive result*: NR *Positive control*: NR *Negative control*: NR	*Version*: ImmunoCAP *Manufacturer*: Phadia AB, Uppsala, Sweden *Method*: 'according to the manufacturer's instructions' *Definition of positive result*: NR *Positive control*: NR *Negative control*: NR	*Method*: The response was read 15 min after puncture and results were expressed as the mean weal diameter (mm) *Allergen*: Natural food and commercial natural extracts to milk, α-lactalbumin, β-lactoglobulin, casein, egg white, egg yolk (Lofarma, Milan, Italy) *Positive result*: Mean weal diameter of > 3 mm with erythema *Positive control*: Histamine hydrochloride *Negative control*: Sodium chloride (0.9%)	Performed in an open fashion The material was pasteurised cow's milk and cooked egg (boiled for 10 minutes) or raw egg in the case of negative result to cooked egg When the patient tolerated the first dose, the subsequent doses were given every 15 minutes until objective symptoms developed or when the entire dose was ingested (equivalent to one egg; or up to 250 ml of milk) *Positive result* was scored if anaphylactic shock or two or more of the following objective clinical reactions were noted: bronchial asthma, lips/periorbital oedema, urticaria/angioedema, rhinitis, conjunctivitis, diarrhoea and repetitive vomiting

Study details	Index test details			Reference standard details: oral challenge
	ImmunoCAP/Microtest	Specific IgE tests	SPT	
Ott 2008[49]	*Version*: ImmunoCAP ISAC 51 *Manufacturer*: VBC Genomics Bioscience Research, Vienna, Austria *Method*: 'According to the manufacturer's instructions' *Definition of positive result*: Cut-off points used for analyses derived from ROC analyses *Positive control*: NR *Negative control*: NR	*Version*: UniCAP® *Manufacturer*: Phadia AB, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of positive result*: > 0.35 kU/l (derived from ROC analyses) *Positive control*: NR *Negative control*: NR	*Method*: One drop of either milk or native hen's egg was applied to the patient's forearm with 1-mm single-peak lancets (ALK, Copenhagen, Denmark) *Allergen*: Fresh cow's milk (3.5% fat) or native hen's egg (whisked white of egg and yolk). *Definition of positive result*: Mean weal diameter > 3 mm, or greater than negative control. Cut-off points used for analyses derived from ROC analyses *Positive control*: Histamine hydrochloride (1%) *Negative control*: Saline	OFCs with either cow's milk and/or hen's egg The food challenges were scored as positive by a paediatric allergologist if one or more of the following objective clinical reactions were noted: urticaria, flushing, pruritus, angioedema, exacerbation of AE, vomiting, diarrhoea, stridor or other respiratory symptoms

FEIA, fluoroenzyme immunoassay; kU/l, kilo International Unit per litre; w/v, weight/volume.

Study details	Index test details		Reference standard details
	ImmunoCAP®/Microtest	Specific IgE tests	Oral challenge
Sokolova 2009[46]	*Version*: ImmunoCAP ISAC NR *Manufacturer*: VBC Genomics Bioscience Research, Vienna, Austria *Method*: 'According to the manufacturer's instructions' *Definition of positive result*: Cut-off points NR *Positive control*: NR *Negative control*: NR	*Version*: UniCAP *Manufacturer*: Phadia, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of positive result*: > 0.35 kU/l *Positive control*: NR *Negative control*: NR	Patients complaining of anaphylaxis after accidental ingestion of milk or its derivatives were considered persistent A diagnosis of persistent CMPA was confirmed in the remaining patients via a positive oral challenge test, performed following current recommendations. The initial dose administered was 0.1 ml with posterior duplication of the doses and administration at 30-minute intervals. It was considered positive if cutaneous (urticaria/angioedema), respiratory or gastrointestinal (vomiting, diarrhoea) symptoms occurred. A negative open oral challenge to cow's milk was defined as a cumulative dose of 200 ml The control group consisted of four atopic individuals with no history of CMPA and who ingested cow's milk daily

CMPA, cow's milk protein allergy; FEIA, fluoroenzyme immunoassay; kU/l, kilo International Unit per litre; NR, not reported; w/v, weight/volume.

Study details	Index test details: ImmunoCAP/Microtest	Index test details: Specific IgE tests	Reference standard details: SPT + allergen-specific history
Cabrera-Freitag 2011[43]	*Version*: ImmunoCAP ISAC 103 *Manufacturer*: Phadia, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of positive result*: ≥ 0.3 ISU. Thresholds for each allergen/component derived from ROC analyses, but not clearly reported *Positive control*: NR *Negative control*: NR	*Version*: ImmunoCAP FEIA *Manufacturer*: Phadia, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of positive result*: > 0.35 kU/l. Thresholds for each allergen/component derived from ROC analyses, but not clearly reported *Positive control*: NR *Negative control*: NR	*Method*: 1-mm-tip lancet (ALK-Abelló) on the volar side of the forearm. Read after 20 minutes. Performed by the same experienced nurses *Allergen*: Commercial, natural extracts (ALK-Abelló, Madrid, Spain) *Definition of positive result*: Mean weal diameter of > 3 mm *Positive control*: Histamine hydrochloride (10 mg/ml) *Negative control*: Sodium chloride (0.9%) *Allergen history*: Rhinoconjunctivitis and/or bronchial asthma Controls had no pollen allergen-specific history and had negative SPT to the corresponding pollen
Wohrl 2006[45]	*Version*: ImmunoCAP ISAC CRD 50 *Manufacturer*: Genomics Bioscience Research, Vienna, Austria *Method*: 'According to the manufacturer's instructions'. Slides were scanned in an Affymetrix 428 microarray scanner (Affymetrix, Santa Clara, CA, USA). Images were analysed using the GenePix image analysis software (version 3.0.6.89; Axon Instruments, Union City, CA, USA) *Definition of a positive result*: Thresholds for each allergen/component derived from ROC analyses, but not reported *Positive control*: NR *Negative control*: NR	*Version*: ImmunoCAP *Manufacturer*: Phadia, Uppsala, Sweden *Method*: 'According to the manufacturer's instructions' *Definition of a positive result*: Thresholds for each allergen/component derived from ROC analyses, but not reported *Positive control*: NR *Negative control*: NR	*Method*: SPTs were read after 20 minutes. Weals and flares were pen-marked, transferred to a paper with transparent adhesive tape and analysed with an investigator-independent system calculating the weal size in mm^2 *Allergen*: Commercial extracts (HAL Allergie GmbH, Germany, and ALK, Hørsholm, Denmark) *Positive result*: Mean weal area of ≥ 7 mm^2 or > 3 mm diameter *Positive control*: Histamine hydrochloride (ALK) *Negative control*: Sodium chloride (0.9%) *Allergen history*: Obtained in all subjects using a questionnaire that gave special regard to the clinical relevance of the sensitisation to each allergen (e.g. clinical relevance of the sensitisation to birch pollen was affirmed by asking for an oral allergy syndrome to apple and other Rosaceae fruits) All subjects without allergen-specific history (atopics) and those with additional negative SPTs (non-allergic) served as controls

FEIA, fluoroenzyme immunoassay; kU/l, kilo International Unit per litre; NR, not reported.

Appendix 3 Table of excluded studies with rationale

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Ackerbauer 2015[95]	Food	Yes	ImmunoCAP ISAC 112	Other	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by single ImmunoCAP sIgE and ImmunoCAP ISAC 112, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Acosta Rivera 2012[96]	Food	Yes	ImmunoCAP ISAC 103	SPT	No relevant outcomes	Insufficient information for accuracy
Alessandri 2011[97]	Food	Yes	ImmunoCAP ISAC 103	OFC	No relevant outcomes	Insufficient information for accuracy
Alonso 2014[98]	Food		ImmunoCAP ISAC 112	Other	No relevant outcomes	Method of diagnosis not adequately reported; insufficient information for accuracy
Alvarado 2013[99]	Food	Yes	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Antonicelli 2014[100]	Food	Unclear	Other	Other	No relevant outcomes	Microarray and reference standard not specified and no relevant outcomes
Araujo 2012[101]	Pollen	Unclear	ImmunoCAP ISAC other	Other	No relevant outcomes	Unspecified version ISAC, diagnosis according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines; insufficient information for accuracy
Asero 2014[102]	Pollen	Unclear	Other	NA	No relevant outcomes	Not ISAC or Microtest
Bauermeister 2009[103]	Food	Unclear	Other	NA	No relevant outcomes	ImmunoCAP® 250 – not ISAC or Microtest
Berneder 2013[104]	Food	Unclear	ImmunoCAP ISAC 112	NA	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by single ImmunoCAP sIgE and ImmunoCAP ISAC 112, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Blankestijn 2014[105]		Yes	ImmunoCAP ISAC other	NA	No relevant outcomes	Unspecified version ISAC, prevalence only

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Bokanovic 2013[106]	Pollen	Yes	ImmunoCAP ISAC 103	SPT	Accuracy only	Comparative accuracy: whole panel ISAC vs. sIgE vs. inhaled challenge. Some patients tested with ISAC 112. However, sIgE were reported as measured with ImmunoCAP component assays and ISAC, and accuracy data appeared to relate to the component measured rather than the test (i.e. included participants could have been tested using either method)
Bonini 2010[107]	Other	Unclear	ImmunoCAP ISAC 103	SPT	No relevant outcomes	Insufficient information for accuracy
Bonini 2010[108]	Other	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Bonini 2012[109]	Other	Yes	ImmunoCAP ISAC 103	NA	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by single ImmunoCAP sIgE and ImmunoCAP ISAC 103, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Brans 2012[110]	Food	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Concordance only, FEIA vs. single IgE derived from ISAC Comparison of levels of sIgE against omega-5-gliadin, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Cabrera-Freitag 2011[111]		Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	Technical reproducibility data only
Caimmi 2011[112]	Food		ImmunoCAP ISAC other	SPT	No relevant outcomes	Unspecified version ISAC, insufficient information for accuracy or concordance
Caimmi 2011[113]	Other	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Unspecified version ISAC, insufficient information for concordance or accuracy
Caimmi 2013[114]	Other	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Carter 2012[115]	Other	Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Cavagni 2009[116]	Food	Unclear	ImmunoCAP ISAC 89	OFC	No relevant outcomes	Insufficient information for accuracy
Cavagni 2010[117]	Food	Unclear	ImmunoCAP ISAC 89	OFC	No relevant outcomes	Insufficient information for accuracy

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Chambel 2011[118]	Pollen	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Unspecified version ISAC; insufficient information for accuracy or concordance
Chambel 2012[119]	Pollen	Yes	ImmunoCAP ISAC 103	SPT	No relevant outcomes	Insufficient information for accuracy; includes only patients with a positive reference standard diagnosis
Charalambous 2014[120]	Other	Yes	ImmunoCAP ISAC other	NA	No relevant outcomes	Exclude 'Audit' of clinical records information on patients previously tested with ISAC; no details of test results or their effects on decision-making
Chevallier 2013[121]	Food	Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Chia 2013[122]	Food	Unclear	Other	Other challenge test	No relevant outcomes	Intervention was unspecified version ISAC or ImmunoCAP; not enough detail for accuracy data
Cho 2014[123]	Pollen	Yes	Other	NA	Concordance only	No relevant outcomes Comparison of positive rates between SPT, AdvanSure and ImmunoCAP sIgE
Choi 2014[124]	Other	Yes	ImmunoCAP ISAC other	SPTs	No relevant outcomes	Unspecified version ISAC; insufficient information for patient level accuracy
Choi 2014[125]	Other	Unclear	ImmunoCAP ISAC other	SPTs	No relevant outcomes	Unspecified version ISAC; insufficient details for accuracy
De Amici 2014[126]	Other	Unclear	ImmunoCAP ISAC 112	NA	No relevant outcomes	Comparison with ISAC 103, outcome was described as 'diagnostic utility' and 'therapeutic utility' scores, but no further details were reported
De Boer 2012[127]	Other	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	Technical reproducibility and limit of detection only, using a single pooled QC sample. Intra-assay and inter-assay variation
De Boer 2013[128]	Other	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
De Boer 2013[128]	Food	Yes	ImmunoCAP ISAC 112	NA	No relevant outcomes	No relevant outcomes
De Knop 2011[129]	Food	Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Doyen 2011[130]		Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	Interference of omalizunab with ISAC and ImmunoCAP
Ebo 2010[131]	Latex	Yes	ImmunoCAP ISAC 103	SPT	No relevant outcomes	Insufficient information for accuracy

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Ebo 2010[132]	Pollen	Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Eller 2013[133]	Food	Yes	Other	SPT	Accuracy only	ImmuoCAP sIgE only
Fernandez 2011[134]	Pollen	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Unspecified version ISAC, insufficient information for concordance
Flores 2014[135]	Pollen	Yes	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Fung 2012[136]	Food	Unclear	ImmunoCAP ISAC other	Other	No relevant outcomes	No relevant outcomes
Gadisseur 2009[137]	Other	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	Insufficient information for concordance or accuracy
Gadisseur 2011[138]	Other	Unclear	ImmunoCAP ISAC 103	NA	Concordance only	No relevant outcomes Reports agreement on allergen source between specific serum IgE levels measured by single ImmunoCAP sIgE and ImmunoCAP ISAC 103, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Gadisseur 2011[138]	Other	Yes	ImmunoCAP ISAC 103	NA	Concordance only	No relevant outcomes Reports agreement between sIgE and ImmunoCAP ISAC 103, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Gadisseur 2012[139]	Food	Unclear	ImmunoCAP ISAC 112	NA	No relevant outcomes	Refers to additional information provided by ISAC, but no details given
Garriga Baraut 2010[140]	Pollen	Unclear	ImmunoCAP ISAC other	SPT	No relevant outcomes	Unspecified version ISAC; insufficient information for accuracy
Goikoetxea 2013[141]		No	Other	NA	No relevant outcomes	Review article
Goikoetxea 2015[142]		Yes	ImmunoCAP ISAC 112	NA	No relevant outcomes	No relevant outcomes
Hermansson 2012[60]	Pollen		ImmunoCAP ISAC other	Other	Economics only	No relevant outcomes
Hoffmann 2014[143]	Pollen	Unclear	Other	NA	No relevant outcomes	Intervention was SIT: use of ISAC and IgE/IgG4 to measure response to SIT
Hong 2011[144]	Food	Unclear	ImmunoCAP ISAC 103	Other	No relevant outcomes	Insufficient information for accuracy
Hong 2012[145]	Food	Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Javaloyes 2012[146]	Food	Yes	ImmunoCAP ISAC 103	Other	No relevant outcomes	No relevant outcomes
Jung 2012[147]	Pollen	Unclear	ImmunoCAP ISAC other	SPT	No relevant outcomes	Insufficient information for accuracy or concordance and unspecified version of ISAC
Kattan 2013[148]	Food	Yes	ImmunoCAP ISAC 112	OFC	No relevant outcomes	Insufficient information for accuracy
Kattan 2014[149]	Food	Yes	ImmunoCAP ISAC 112	OFC	Accuracy only	Accuracy of components of ISAC for peanut allergy only (no comparative data)
Kim 2015[150]	Pollen	Unclear	ImmunoCAP ISAC other	SPT	No relevant outcomes	Insufficient detail on accuracy data
Klemans 2013[151]	Food	Yes	ImmunoCAP ISAC 103	SPT	No relevant outcomes	No relevant outcomes, incomplete accuracy data
Klemans 2014[152]	Food	Yes	ImmunoCAP ISAC 112	OFC	Accuracy only	ISAC only, no comparative accuracy data
Konradsen 2015[153]	Other	Unclear	Microtest	NA	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by Microtest, single ImmunoCAP sIgE and ImmunoCAP ISAC 112, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the three methods
Lee 2013[154]	Food	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Liso 2011[155]		Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Experimental ISAC with omalizumab added and no relevant outcomes
Liu 2011[156]	Food	Unclear	ImmunoCAP ISAC other	OFC	Accuracy only	Accuracy reported for the allergen component (measured by a variety of methods). Data reported only for ISAC; no comparative accuracy data
Lizaso 2011[157]	Pollen	Yes	ImmunoCAP ISAC 89	NA	Concordance only	No relevant outcomes Reports percentage agreement between single ImmunoCAP sIgE, ImmunoCAP ISAC 89, and an Avida-Centaur component resolved assay, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Lohman 2013[158]			Other	NA	No relevant outcomes	Not ISAC, development of a microarray

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Luengo 2011[159]	Food	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	Insufficient outcome information
Mailhol 2013[160]		Unclear	ImmunoCAP ISAC 112	NA	No relevant outcomes	No relevant outcomes
Martinez-Aranguren 2013[161]		Unclear	ImmunoCAP ISAC 112	NA	No relevant outcomes	Technical reproducibility only, wrong comparator
Martinez-Aranguren 2014[162]	Other	Unclear	ImmunoCAP ISAC 112	NA	Concordance only	No relevant outcomes Reports agreement on sensitisations between single ImmunoCAP sIgE, ImmunoCAP ISAC112 and SPT, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Martinez-Aranguren 2014[163]	Food	Yes	ImmunoCAP ISAC 112	SPT	Accuracy only	ISAC only, no comparative accuracy
Martinez-Aranguren 2014[164]	Other	Yes	ImmunoCAP ISAC 112	NA	No relevant outcomes	Technical data, assay reproducibility only
Mascialino 2013[59]	Pollen	Yes	ImmunoCAP ISAC other	NA	Economics only	No relevant outcomes
Mascialino 2013[58]	Pollen				Economics only	No relevant outcomes
Melioli 2011[165]	Pollen	Yes	ImmunoCAP ISAC 103	NA	Concordance only	No relevant outcomes Reports percentage positive agreement between single ImmunoCAP sIgE and ImmunoCAP ISAC 103, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Microtest DX 2014[166]	Other	Unclear	Microtest	NA	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by Microtest, single ImmunoCAP sIgE and ImmunoCAP ISAC 112, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the three methods
Murng 2011[167]	Other	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Insufficient details of outcomes reported, unspecified version ISAC
Murng 2011[168]	Food	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Insufficient outcome information

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Nanda 2015[169]	Food	Unclear	Other	NA	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by single ImmunoCAP sIgE and an unspecified version of ImmunoCAP ISAC, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Nicaise-Rolland 2010[170]		Unclear	ImmunoCAP ISAC 103	Other	No relevant outcomes	Insufficient information for accuracy
Nicolaou 2010[171]	Food		Other	NA	No relevant outcomes	Not ISAC or Microtest
Nicolaou 2010[171]	Food	Yes	Other	NA	No relevant outcomes	Not ISAC or Microtest
Nystrand 2012[172]		Unclear	ImmunoCAP ISAC 112	NA	No relevant outcomes	Technical reproducibility and limit of detection only
Olivieri 2010 [173]	Food	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Olivieri 2013[174]	Food	Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Onell 2012[175]		Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Ott 2010[176]	Other	Unclear	Other	NA	No relevant outcomes	No relevant outcomes, unspecified microarray
Paes 2010[177]	Food	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Palomba 2013[178]	Other	Unclear	Microtest	NA	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by Microtest and single ImmunoCAP sIgE, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Palomba 2014[179]	Other	Unclear	Microtest	NA	No relevant outcomes	Concordance between Microtest and an unspecified commercially available system, insufficient detail reported
Pascal 2016[93]	Food	Yes	ImmunoCAP ISAC 112	SPT, sIgE	Accuracy only	No comparison results for sIgE or SPT
Passalacqua 2013[52]	Other	Unclear	Other	NA	Treatment change	Insufficient outcome details, but abstract refers to treatment change

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Patelis 2012[180]	Pollen	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Pedrosa 2012[92]	Food	Yes	ImmunoCAP ISAC 103	Other	Accuracy only	Accuracy of various components on ISAC only (no comparison with other index tests, e.g. sIgE or SPT)
Pomponi 2013[181]		Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	Autoimmune disease
Raulf 2014[182]		No	Other	NA	No relevant outcomes	Review article
Röckmann 2014[183]	Food	Yes	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Rodriguez-Ferran 2011[61]		Unclear	Other	NA	No relevant outcomes	Review article
Romano 2012[184]	Food	Unclear	Other	Other	No relevant outcomes	No relevant outcomes
Sanchez-Lopez 2013[185]		Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Unclear whether results were derived from an unspecified version of ISAC or UniCAP sIgE
Santos 2011[186]	Pollen	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Santosa 2015[187]	Other	Yes	ImmunoCAP ISAC 112	NA	No relevant outcomes	No relevant outcomes
Sanz 2010[94]	Pollen	Unclear	ImmunoCAP ISAC 103	SPT	Accuracy only	Accuracy of various components on ISAC only (no comparison with other index tests, e.g. sIgE or SPT)
Sastre 2014[188]	Pollen	Yes	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Scala 2011[189]	Food	Unclear	ImmunoCAP ISAC 103	Other	No relevant outcomes	Method of diagnosis not specified, insufficient information for accuracy
Scala 2011[190]	Other	Unclear	ImmunoCAP ISAC 103	NA	No relevant outcomes	No relevant outcomes
Schuler 2013[191]	Latex	Yes	Other	SPT	No relevant outcomes	Intervention either ImmunoCAP sIgE or ISAC
Seyfarth 2011[192]	Latex	Unclear	ImmunoCAP ISAC 103	Other	No relevant outcomes	Partial accuracy only, no reference standard defined, non-clinical spiked sample
Seyfarth 2011[192]	Latex	Unclear	ImmunoCAP ISAC other	Other	No relevant outcomes	Partial accuracy only, no reference standard defined, non-clinical spiked sample
Seyfarth 2011[193]	Latex	Unclear	ImmunoCAP ISAC 103	Other	No relevant outcomes	Partial accuracy only, no reference standard defined, non-clinical spiked sample
Seyfarth 2014[194]	Latex	Yes	ImmunoCAP ISAC 103	SPT	No relevant outcomes	Partial accuracy only, non-clinical spiked sample
Shibata 2014[195]	Food	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes

Study details	Allergy type	Secondary or tertiary care?	Intervention	Reference	Outcome	Reason for exclusion and comments
Sousa 2009[196]	Pollen	Unclear	ImmunoCAP ISAC other	SPT	Accuracy only	ISAC only, no comparative accuracy
Stringari 2014[51]	Pollen	Yes	Other	NA	Clinical	Not ISAC or Microtest, ImmunoCAP FEIA
Tolkki 2013[197]	Food	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Tolkki 2013[198]	Food	Yes	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Tripathi 2012[199]		Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	Eosinophilic esophagitis and no relevant outcomes
Tripathi 2014[200]	Food	Unclear	ImmunoCAP ISAC 112	NA	No relevant outcomes	Eosinophilic esophagitis and no relevant outcomes
Tripathi 2014[201]	Food		ImmunoCAP ISAC 112	NA	No relevant outcomes	Mixed population
Uriarte 2013[202]	Other	Unclear	Other	NA	No relevant outcomes	Intervention was sIgE ImmunoCAP or ISAC
Vitte 2014[203]	Other	Unclear	ImmunoCAP ISAC other	NA	No relevant outcomes	No relevant outcomes
Weimann 2011[204]		Unclear	ImmunoCAP ISAC other	Other	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by single ImmunoCAP sIgE and an unspecified version of ImmunoCAP ISAC, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Williams[205]	Other	Yes	Microtest	Other	Concordance only	No relevant outcomes Correlation of specific serum IgE levels measured by Microtest and single ImmunoCAP sIgE, but insufficient data to compare diagnostic performance (e.g. sensitivity and specificity) of the two methods
Yadzir 2014[206]	Other	Yes	ImmunoCAP ISAC 112	SPT	No relevant outcomes	Insufficient information for accuracy
Young 2012[207]	Other	Yes	ImmunoCAP ISAC 112	NA	No relevant outcomes	No data

ARIA, Allergic Rhinitis and its Impact on Asthma; FEIA, fluoroenzyme immunoassay; NA, not applicable; QC, quality control.

Appendix 4 Risk-of-bias assessments

A Review-specific assessments of 'diagnostic before-and-after' studies

Study ID: Heaps 2014[35,39]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Patients with idiopathic anaphylaxis (cause could not be established by standard diagnostic work-up) recruited from five specialist allergy centres). No further details reported. No exclusion criteria reported	
Was a consecutive or random sample of patients enrolled?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): The cause of anaphylaxis could not be established using standard diagnostic work-up (including clinical history, SPT, single IgE). The study was conducted in the UK	
Do the included patients match the review question?	**CONCERN: LOW**

DOMAIN 2: INDEX TEST(S)

A. Risk of bias

Describe how the index test was conducted and interpreted: ISAC used 'according to the manufacturer's instructions'	
Was the index test method, including threshold, prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: LOW**

DOMAIN 3: COMPARATOR

A. Risk of bias

Describe the comparator and how it was conducted and interpreted: Standard care, including clinical history, SPT and single IgE. ISAC testing was conducted after routine diagnostic work-up	
Was the diagnostic assessment, based on the comparator, made without knowledge of the results of the index test?	Yes
Could the comparator, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the comparator does not match current standard care, as defined in the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test or comparator: Three patients did not receive MCT testing (part of standard work-up). All patients were included in the analysis	
Describe the time interval and any interventions between index and comparator: Not reported	
Was there an appropriate interval between index test and comparator?	Unclear
Did patients receive the same comparator/standard care?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Luengo 2010[37]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Abstract only, no details reported	
Was a consecutive or random sample of patients enrolled?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Population described as 'well characterised, multi-sensitised' and 'Mediterranean'	
Do the included patients match the review question?	**CONCERN: UNCLEAR**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test was conducted and interpreted: Abstract only, no details reported	
Was the index test method, including threshold, prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: UNCLEAR**

DOMAIN 3: COMPARATOR

A. Risk of bias

Describe the comparator and how it was conducted and interpreted: SPT and single IgE, abstract only, no further details reported	
Was the diagnostic assessment, based on the comparator, made without knowledge of the results of the index test?	Unclear
Could the comparator, its conduct or its interpretation have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Is there concern that the comparator does not match current standard care, as defined in the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, or comparator: All participants appear to have received ISAC and standard diagnostic work-up	
Describe the time interval and any interventions between index and comparator: Not reported	
Was there an appropriate interval between index test and comparator?	Unclear
Did patients receive the same comparator/standard care?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Noimark 2012[40]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Abstract only, no details reported	
Was a consecutive or random sample of patients enrolled?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Children with moderate to severe atopic eczema and multiple food allergies. The study was conducted in a UK secondary care allergy clinic	
Do the included patients match the review question?	**CONCERN: LOW**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test was conducted and interpreted: Abstract only, no details reported	
Was the index test method, including threshold, prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: UNCLEAR**

DOMAIN 3: COMPARATOR

A. Risk of bias

Describe the comparator and how it was conducted and interpreted: SPT and/or single IgE, abstract only, no further details reported	
Was the diagnostic assessment, based on the comparator, made without knowledge of the results of the index test?	Unclear
Could the comparator, its conduct or its interpretation have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Is there concern that the comparator does not match current standard care, as defined in the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, or comparator: All participants appear to have received ISAC and standard diagnostic work-up	
Describe the time interval and any interventions between index and comparator: ISAC was performed 'alongside' SPT and single IgE	
Was there an appropriate interval between index test and comparator?	Yes
Did patients receive the same comparator/standard care?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Passalacqua 2013[38]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Patients with respiratory allergic disease prospectively recruited from six allergy centres. No further details reported. No exclusion criteria were reported	
Was a consecutive or random sample of patients enrolled?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Polysensitised patients (at least two positive SPTs). However, the study was conducted in Italy, where there is likely to be a different pattern of pollen sensitisations to that observed in the UK	
Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test was conducted and interpreted: ISAC 103, using manufacturer's recommended threshold	
Was the index test method, including threshold, prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: LOW**

DOMAIN 3: COMPARATOR

A. Risk of bias

Describe the comparator and how it was conducted and interpreted: Standard care: SPT and clinical history, with single IgE(s) as required. Diagnosis and treatment plans were formulated based on standard care without ISAC. Decisions were then reviewed with ISAC results available. It was not clear how many participants received single IgE testing as part of standard care	
Was the diagnostic assessment, based on the comparator, made without knowledge of the results of the index test?	Yes
Could the comparator, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the comparator does not match current standard care, as defined in the review question?	**CONCERN: UNCLEAR**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, or comparator: All participants appear to have received both ISAC and standard care. Standard care could include single IgE, but it was not clear in how many participants single IgE assay(s) were performed	
Describe the time interval and any interventions between index and comparator: Not reported	
Was there an appropriate interval between index test and comparator?	Unclear
Did patients receive the same comparator/standard care?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: HIGH**

Study ID: Sastre 2012[30–32]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Patients with allergic rhinoconjunctivitis and/or asthma who were sensitised to pollen, with or without concomitant food allergy. Patients were attending an allergy outpatient clinic. No further details reported. No exclusion criteria were reported	
Was a consecutive or random sample of patients enrolled?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients sensitised to pollen, with or without concomitant food allergy. The study does not specify polysensitised patients or difficult to manage allergic disease. The study was conducted in Spain, where there is likely to be a different pattern of pollen sensitisations to that observed in the UK	
Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

A. Risk Of bias

Describe how the index test was conducted and interpreted: ISAC 96, used according to the manufacturer's instructions	
Was the index test method, including threshold, prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: LOW**

DOMAIN 3: COMPARATOR

A. Risk of bias

Describe the comparator and how it was conducted and interpreted: Standard care: SIT prescriptions were formulated based on clinical history, current guidance and SPT results, without knowledge of ISAC results, then reformulated with access to ISAC results. Standard care did not appear to have included single IgE testing	
Was the diagnostic assessment, based on the comparator, made without knowledge of the results of the index test?	Yes
Could the comparator, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the comparator does not match current standard care, as defined in the review question?	**CONCERN: UNCLEAR**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test or comparator: All participants appear to have received both ISAC and standard care	
Describe the time interval and any interventions between index and comparator: Not reported	
Was there an appropriate interval between index test and comparator?	Unclear
Did patients receive the same comparator/standard care?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

B Critical Appraisal Skills Programme Cohort tool assessment

Gay-Crosier 2010[36]		
(a) *Are the results of the study valid?*	1. Did the study address a clearly focused issue?	Yes 'We compared the clinical responses to SIT with allergen specific IgE levels measured by Immuno-CAP and by a new microarray-based assay'
	2. Was the cohort recruited in an acceptable way?	Unclear Reported as an abstract
	3. Was the exposure accurately measured to minimise bias?	Unclear Reported as an abstract. Subcutaneous immunotherapy but no further details
	4. Was the outcome accurately measured to minimise bias?	Unclear Reported as an abstract. Allergen-specific IgE and IgG4 levels were also measured before and after SIT, both by ImmunoCAP single IgE and by ISAC assays

Gay-Crosier 2010[36]		
	5a. Have the authors identified all important confounding factors?	Unclear
	5b. Have they taken account of the confounding factors in the design and/or analysis?	No
	6a. Was the follow-up of subjects complete enough?	Unclear Reported as an abstract
	6b. Was the follow-up of subjects long enough?	Yes Follow-up was 3 years
(b) *What are the results?*	7. What are the results of this study?	Results clearly reported in relevant section
	8. How precise are the results?	Unclear; no variation reported
	9. Do you believe the results?	Unclear; too little information provided to be clear
(c) *Will the results help locally?*	10. Can the results be applied to the local population?	It is unclear what the specific population was; therefore, it is unclear if the results apply to patients with complex allergy
	11. Do the results of this study fit with other available evidence?	Unclear
	12. What are the implications of this study for practice?	Unclear at present, although conclusions are that 'allergen specific IgE levels and even more the specific IgE/IgG4 ratio measured by a microarray assay (ISAC) is significantly related in this study, to the clinical outcome of SIT'

C QUADAS-2 assessments of comparative accuracy studies

Study ID: Albarini 2013[47]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Not reported. Children reported with immediate reactions to hazelnut ingestion	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients were allergic to hazelnuts (response to ingestion). Patients were given an oral challenge and tests were compared between those who were tolerant and those who were allergic. Did not specify patients with 'difficult to manage' allergic disease or similar classification and only one allergy source was being investigated	
Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: The article was reported as an abstract with little methodological detail. The methods for ImmunoCAP ISAC (cut-off points: NR) and ImmunoCAP (positive result: ≥ 0.35 kU/l) were not provided. SPT method was not reported (positive result: mean weal diameter ≥ 3 mm)

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: UNCLEAR**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: DBPCFC, no further details

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): It appears that all patients were included in the analysis

Describe the time interval and any interventions between index, comparator(s) and reference standard: No time intervals were reported

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Alessandri 2011[42]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Not described	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients had suspected hen's egg allergy (history of reactions after ingestion and positive SPT or IgE to hen's egg white extracts). Patients were given a hen's egg oral challenge and tests were compared between those who were tolerant, partially tolerant (allergic to raw egg but not boiled) and those who were allergic. Did not specify patients with 'difficult to manage' allergic disease or similar classification and only one allergy source was being investigated. The study was not conducted in the UK	
Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: ImmunoCAP ISAC (positive result: NR) and ImmunoCAP FEIA (positive result: NR) performed according to the manufacturer's instructions. Standard SPT was performed (positive result: mean weal diameter $\geq$ 7 mm). All thresholds were optimised based on ROC analyses	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: HIGH**

B. Applicability

Is there concern that the index test, its conduct or interpretation differ from the review question?	**CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: Oral challenge performed with boiled or raw hen's egg. Increased egg amount until there was a reaction (or one egg or 6 g ingested)	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Unclear**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): Unclear if all patients received all index tests (applying reported sensitivity and specificity estimates to the total numbers of participants who were positive to each of the reference standards does not result in whole numbers for 2 × 2 data). All patients received OFC

Describe the time interval and any interventions between index, comparator(s) and reference standard: Timings were not reported; no other interventions were reported

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	No
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: HIGH**

Study ID: Cabrera-Freitag 2011[43]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Not reported. Patients from the Clínica Universidad de Navarra in Pamplona, Spain. Patients with allergies to pollen other than grass or cypress were excluded, thereby excluding complex patients

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	No
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: HIGH**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients were allergic to grass and cypress pollen (clinical history and SPTs). Control patients were negative to history and SPT. Both populations were examined by ISAC 103 or single IgE for components specific to grass and cypress pollen. Did not specify patients with 'difficult to manage' allergic disease or similar classification and only two allergy sources were being investigated. The study was not conducted in the UK

Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: The method for ImmunoCAP ISAC (cut-off points: reported) and ImmunoCAP (cut-off points: reported) were described as per the manufacturer's methods	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: HIGH**

B. Applicability

Is there concern that the target condition as defined by the index test does not match the review question?	**CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: SPT (grass and cypress pollen) and clinical history (rhinoconjunctivitis and/or bronchial asthma)	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): All patients appear to have been included in the analysis	
Describe the time interval and any interventions between index, comparator(s) and reference standard: No time intervals were reported	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: De Swert 2012[41]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Unclear, 'we selected subjects with birch pollen allergy who were suspected of also being soy allergic'

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: HIGH**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients had been diagnosed with birch pollen allergy (clinical history and positive IgE response to birch or rBet v1). Patients were given a soy oral challenge and tests were compared between those who were tolerant and those who were allergic. Did not specify patients with 'difficult to manage' allergic disease or similar classification and only one allergy source was being investigated. The study was not conducted in the UK

Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: The methods section described ImmunoCAP ISAC (positive result: ≥ 0.3 ISU) and ImmunoCAP FEIA (positive result: ≥ 0.1 kU/l) performed according to the manufacturer's instructions. Standard SPT performed (positive result: mean weal diameter ≥ 3 mm). However, the results section reported different cut-off values for all three tests, suggesting that these may have been optimised for the study population

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: HIGH**

B. Applicability

Is there concern that the index test, its conduct or interpretation differ from the review question?	**CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: Oral challenge performed with Alpro soya natural drink. Increased volumes of drink until there was a reaction (or until 158 ml)	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): SPT results for one patient and ISAC results for three patients were not included in the analysis	
Describe the time interval and any interventions between index, comparator(s) and reference standard: Timings were not reported, no other interventions were reported	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: HIGH**

Study ID: D'Urbano 2010[44]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Not described	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: HIGH**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients had suspected hen's egg or cow's milk allergy (history of reactions after ingestion). Patients were given an OFC and tests were compared between those who were tolerant and those who were allergic. Did not specify patients with 'difficult to manage' allergic disease or similar classification and only one allergy source was being investigated. The study was not conducted in the UK

Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: ImmunoCAP ISAC (positive result: NR) and ImmunoCAP FEIA (positive result: NR) performed according to the manufacturer's instructions. Standard SPT performed (positive result: mean weal diameter of ≥ 3 mm). Thresholds for single IgE and ISAC were derived from ROC analysis

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: HIGH**

B. Applicability

Is there concern that the index test, its conduct or interpretation differ from the review question?	**CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: Oral challenge performed with pasteurised cow's milk, boiled or raw hen's egg. Increased egg amount until there was a reaction (or one egg or 6 g ingested or 250 ml milk)

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Unclear**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): All patients appeared to have received both index tests (separate testing for patients with suspected cow's milk and hen's egg allergy). All patients received OFC. All patients appeared to have been included in the analyses (separate for patients with suspected cow's milk and hen's egg allergy)

Describe the time interval and any interventions between index, comparator(s) and reference standard: Timings were not reported, no other interventions were reported

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Ott 2008[49]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Retrospective, but no further methodology

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients had suspected IgE-mediated food hypersensitivity. Patients were given a milk or hen's egg oral challenge and tests were compared between those who were tolerant and those who were allergic. Did not specify patients with 'difficult to manage' allergic disease or similar classification and only one allergy source was being investigated. The study was not conducted in the UK

Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: ImmunoCAP ISAC (positive result: NR) and UniCAP (positive result: > 0.35 kU/l) performed according to the manufacturer's instructions. Standard SPT performed (positive result: mean weal diameter ≥ 3 mm or greater than negative control). Thresholds were derived from ROC analyses for all index tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: HIGH**

B. Applicability

Is there concern that the index test, its conduct or interpretation differ from the review question?	**CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: Oral challenge performed with milk or hen egg	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Unclear**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): Unclear if all patients received all index tests. All patients received OFC (applied separately for suspected cow's milk and suspected hen's egg allergy)	
Describe the time interval and any interventions between index, comparator(s) and reference standard: Timings were not reported, no other interventions were reported	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Sokolova 2009[46]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Not reported. Patients from the food allergy clinic	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: HIGH**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients were allergic to cow's milk protein (SPTs and positive specific IgE). Patients were given an oral milk challenge and those who were positive [cutaneous (urticaria/angioedema), respiratory or gastrointestinal (vomiting, diarrhoea) symptoms] vs. tolerant (no symptoms to 200 ml milk) or were controls (no history of allergy and drank milk) were examined by ISAC or UNICAP. Did not specify patients with 'difficult to manage' allergic disease or similar classification and only one allergy source was being investigated. The study was not conducted in the UK	
Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

A. Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: The method for ImmunoCAP ISAC (cut-off points: NR) and ImmunoCAP (cut-off points: NR) were described as per the manufacturer's methods. Cut-off points were not reported	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. Applicability

Is there concern that the target condition as defined by the index test does not match the review question?	**CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: OFC was described	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): All patients appear to have been included in the analysis. Patients reporting anaphylaxis after accidental ingestion and controls with no history of CMPA who ingested cow's milk daily did not receive OFC testing

Describe the time interval and any interventions between index, comparator(s) and reference standard: No time intervals were reported.

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

CMPA, cow's milk protein allergy.

Study ID: Wohrl 2006[45]

DOMAIN 1: PATIENT SELECTION

A. Risk of bias

Describe methods of patient selection: Not reported. Adults at the end of the pollen season from two allergy clinics. Patients with total serum IgE of > 1000 kU/l were excluded to minimise non-specific binding in the ImmunoCAP system. The system should be able to cope with the full range of patients

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	No
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: HIGH**

B. Applicability

Describe included patients (prior testing, presentation, intended use of index test and setting): Patients were allergic to one or more aeroallergens (house mite, cat, birch pollen, grass pollen or mugwort pollen). Patients were given a SPT and a history was taken. ISAC and single IgE test were used to distinguish between those who were allergic (positive SPT and history) vs. non-allergic (negative SPT and atopic/negative history). Did not specify patients with 'difficult to manage' allergic disease or similar classification and only five allergy sources were being investigated. The study was not conducted in the UK

Do the included patients match the review question?	**CONCERN: HIGH**

DOMAIN 2: INDEX TEST

Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted: The method for ImmunoCAP ISAC (cut-off points: NR) was provided but not for ImmunoCAP (cut-off points: NR). Cut-off points were calculated from ROC curves but were not described for individual components	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: HIGH**

B. Applicability

Is there concern that the target condition as defined by the index test does not match the review question?	**CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted: SPT method was reported (positive result: mean weal diameter of ≥ 3 mm) and details of clinical history were partially reported	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: LOW**

B. Applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of bias

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2 × 2 table(s): All patients appear to have been included in the analysis	
Describe the time interval and any interventions between index, comparator(s) and reference standard: No time intervals were reported	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Appendix 5 Between-system concordance data provided by Microtest Matrices Ltd

Confidential information has been removed.

Appendix 6 Survey to inform the number of patients receiving each test

1. Do you have experience with ImmunoCAP ISAC testing? Yes/No

   Although some of the questions below are related to ImmunoCAP ISAC testing, it would still be greatly appreciated if you could answer as many of the questions as possible.
   For questions 2 and 3, consider patients where the primary presentation is inhalation allergy for whom you would consider testing with ImmunoCAP ISAC.

2. With current standard care:

   - What is the number of IgE tests that you would order? (average, range)
   - What is the proportion of patients that would get a food challenge test? (average, range)
   - What is the proportion of patients that would get a skin prick test? (average, range)
   - In those patients, what is the number of allergens tested (using skin prick testing)? (average, range).

3. With ISAC:

   - For what proportion of patients would you order further IgE tests? (average, range)
   - In those patients, what is the number of IgE tests that you would order? (average, range)
   - What is the proportion of patients that would get a food challenge test? (average, range)
   - What is the proportion of patients that would get a skin prick test? (average, range)
   - In those patients, what is the number of allergens tested (using skin prick testing)? (average, range).

   For questions 4 and 5, consider patients where the primary presentation is food allergy for whom you would consider testing with ImmunoCAP ISAC.

4. With current standard care:

   - What is the number of IgE tests that you would order? (average, range)
   - What is the proportion of patients that would get a food challenge test? (average, range)
   - What is the proportion of patients that would get a skin prick test? (average, range)
   - In those patients, what is the number of allergens tested (using skin prick testing)? (average, range).

5. With ISAC:

   - For what proportion of patients would you order further IgE tests? (average, range)
   - In those patients, what is the number of IgE tests that you would order? (average, range)
   - What is the proportion of patients that would get a food challenge test? (average, range)
   - What is the proportion of patients that would get a skin prick test? (average, range)
   - In those patients, what is the number of allergens tested (using skin prick testing)? (average, range).

Appendix 7 Cost calculation for individual tests

SPT costs	Total	Cost per test	Costs per patient tested	Source
Vial costs (includes 80 drops, so can be used for 80 tests)	£17.00	£0.21	£1.70	NICE 2011[86]
Control costs (includes 2 × 80 drops, so can be used for 160 tests)	£12.00	£0.08	£0.60	NICE 2011[86]
Lancet costs (200 pack)	£12.00	£0.06	£0.48	NICE 2011[86]
Capital costs				
None				
Other costs (service, maintenance)				
None				
Personnel costs to perform and interpret test				
Personnel time to interpret test results (hours per test): GP	0.02			NICE 2011[86]
Personnel costs for interpreting test results (per hour): GP	£234.00	£4.88	£39.00	Curtis 2014[88]
Personnel time to perform tests (hours per tests): nurse	0.06			NICE 2011[86]
Personnel costs to perform one batch of 4 tests (per hour): nurse	£41.00	£2.56	£20.50	Curtis 2014[88]
No. of tests				
No. of allergens tested per person	8			NICE 2011[86]
Total costs			**£62.28**	

GP, general practitioner.

APPENDIX 7

IgE test costs	Total	Cost per test	Costs per patient tested	Source
Test costs per allergy	£12.00	£12.00	£96.00	NICE 2011[86]
Capital costs				
None				
Other costs (service, maintenance)				
None				
Personnel costs to perform and interpret test				
Personnel time to interpret test results (hours per test): GP	0.02			NICE 2011[86]
Personnel costs for interpreting test results (per hour): GP	£234.00	£4.88	£39.00	Curtis 2014[88]
Personnel time to perform tests (hours per patient): nurse	0.03			NICE 2011[86]
Personnel costs to perform one batch of four tests (per hour): nurse	£41.00		£1.37	Curtis 2014[88]
No. of tests				
No. of allergens tested per person	8			NICE 2011[86]
Total costs			**£136.37**	

GP, general practitioner.

OFC test costs	Total	Cost per test	Costs per patient tested	Source
Hospital appointment to implement the food elimination diet		£314.00	£314.00	Department of Health 2013–14[89]
Hospital appointment to carry out OFC for diagnosis		£256.00	£256.00	Department of Health 2013–14[89]
Total costs			**£570.00**	

ImmunoCAP ISAC – minimum	Total	Per year (annuitised)	Costs per test (annuitised)	Costs per patient tested (annuitised)	Source
Test costs					
Costs per ImmunoCAP ISAC 112 IgE kit	£2500.00		£125.00	£125.00	Information submitted to NICE by Thermo Fisher Scientific
Wash solution costs	£18.50		£0.34	£0.34	
Capital costs					
Costs of the LuxScan 10k reader	£28,999.00	£2411.73	£6.25	£6.25	Information submitted to NICE by Thermo Fisher Scientific
Resale value	£0.00				
Life time of LuxScan 10k reader (years)	10				
Cost of ImmunoCAP starter kit	£500.00	£41.58	£0.11	£0.11	
Resale value	£0.00				Assumption
Life time of ImmunoCAP starter kit (years)	10				Assumption
Other costs (service, maintenance)					
Single flat fee to cover all eventualities (0–4 kits per month)		£2000.00	£0.00	£0.00	Information submitted to NICE by Thermo Fisher Scientific
Single flat fee to cover all eventualities (4–6 kits per month)		£4000.00	£10.36	£10.36	
Personnel costs to perform/process and interpret test					
Personnel time to interpret test results (hours per test)	0.08				Information submitted to NICE by Thermo Fisher Scientific
Personnel costs for interpreting test results (per hour): immunologist[a]	£140.00		£11.67	£11.67	Curtis 2014[88]
Personnel time to perform one batch of 4 tests (hours per kit)	0.05				Information submitted to NICE by Thermo Fisher Scientific
Personnel costs to perform one batch of 4 tests (per hour): biomedical scientist[b]	£55.16		£0.69	£0.69	Curtis 2014[88]
No. of tests					
No. of kits per year	97				Information submitted to NICE by Thermo Fisher Scientific
No. of tests per kit	4				
Total costs				**£154.41**	

a Costs of a medical consultant was used to reflect the costs of an immunologist.
b Costs of a health-care scientist was used to reflect the costs of a biomedical scientist.

ImmunoCAP ISAC – minimum	Total	Per year (annuitised)	Costs per test (annuitised)	Costs per patient tested (annuitised)	Source
Test costs					
Costs per ImmunoCAP ISAC 112 IgE kit	£2500.00		£125.00	£125.00	Information submitted to NICE by Thermo Fisher Scientific
Wash solution costs	£18.50		£0.34	£0.34	
Capital costs					
Costs of the LuxScan 10k reader	£28,999.00	£3114.65	£8.07	£8.07	Information submitted to NICE by Thermo Fisher Scientific
Resale value	£0.00				
Life time of LuxScan 10k reader (years)	8				
Cost of ImmunoCAP starter kit	£500.00	£53.70	£0.14	£0.14	
Resale value	£0.00				Assumption
Life time of ImmunoCAP starter kit (years)	8				Assumption
Other costs (service, maintenance)					
Single flat fee to cover all eventualities (0–4 kits per month)		£2000.00	£0.00	£0.00	Information submitted to NICE by Thermo Fisher Scientific
Single flat fee to cover all eventualities (4–6 kits per month)		£4000.00	£10.36	£10.36	
Personnel costs to perform/process and interpret test					
Personnel time to interpret test results (hours per test)	1.00				Information submitted to NICE by Thermo Fisher Scientific
Personnel costs for interpreting test results (per hour): immunologist[a]	£140.00		£140.00	£140.00	Curtis 2014[88]
Personnel time to perform one batch of 4 tests (hours per kit)	0.05				Information submitted to NICE by Thermo Fisher Scientific
Personnel costs to perform one batch of 4 tests (per hour): biomedical scientist[b]	£55.16		£0.69	£0.69	Curtis 2014[88]
No. of tests					
No. of kits per year	97				Information submitted to NICE by Thermo Fisher Scientific
No. of test per kit	4				
Total costs				**£284.60**	

a Costs of a medical consultant was used to reflect the costs of an immunologist.
b Costs of a health-care scientist was used to reflect the costs of a biomedical scientist.

Microtest[a] – minimum	Total	Costs per test	Costs per patient tested	Source
Test costs				
Cost of allergy reagents (can be used for 1–5 tests)		£1.00	£1.00	Information submitted to NICE by Microtest DX
Shipping costs		£7.70	£7.70	
Sample handling fee		£20.00	£20.00	
Costs of allergy biochip		£100.00	£100.00	
Capital costs				
None	£0.00		£0.00	
Other costs (service, maintenance)				
None	£0.00		£0.00	Information submitted to NICE by Microtest DX
Personnel costs to perform and interpret test				
Personnel time to interpret test results (hours per test)		0.08		Information submitted to NICE by Microtest DX
Personnel costs for interpreting test results (per hour): immunologist[b]	£140.00	£11.67	£11.67	Curtis 2014[88]
Total costs			**£140.37**	

a This calculation assumed that test samples would be send to Microtest DX, where the test would be performed.
b Costs of a medical consultant was used to reflect the costs of an Immunologist.

Microtest[a] – maximum	Total	Costs per test	Costs per patient tested	Source
Test costs				
Cost of allergy reagents (can be used for 1–5 tests)		£5.00	£5.00	Information submitted to NICE by Microtest DX
Shipping costs		£15.00	£15.00	
Sample handling fee		£30.00	£30.00	
Costs of allergy biochip		£100.00	£100.00	
Capital costs				
None	£0.00		£0.00	
Other costs (service, maintenance)				
None	£0.00		£0.00	Information submitted to NICE by Microtest DX
Personnel costs to perform and interpret test				
Personnel time to interpret test results (hours per test)		0.17		Information submitted to NICE by Microtest DX
Personnel costs for interpreting test results (per hour): immunologist[b]	£140.00	£23.33	£23.33	Curtis 2014[88]
Total costs			**£173.33**	

a This calculation assumed that test samples would be send to Microtest DX, where the test would be performed.
b Costs of a medical consultant was used to reflect the costs of an immunologist.

Appendix 8 Cost calculation for Microtest (performed at service provider laboratory)

Microtest[a] – minimum	Total	Per year (annuitised)	Costs per test (annuitised)	Costs per patient tested (annuitised)	Source
Test costs					
Cost of allergy reagents (can be used for 1–5 tests)			£1.00	£1.00	Information submitted to NICE by Microtest DX
Costs of allergy biochip			£100.00	£100.00	
Capital costs					
Microtest instrument	Confidential information has been removed	£6321.07	£16.38	£16.38	Information submitted to NICE by Microtest DX
Resale value	£0.00				
Life time of Microtest instrument (years)	5				
Other costs (service, maintenance)					
Personnel time for quality control			7.00		Information submitted to NICE by Microtest DX
Personnel costs for quality control	£55.16		£1.00	£1.00	Curtis 2014[88]
Personnel costs to perform and interpret test					
Personnel time to interpret test results (hours per test)			0.08		Information submitted to NICE by Microtest DX
Personnel costs for interpreting test results (per hour): immunologist[b]	£140.00		£11.67	£11.67	Curtis 2014[88]
Personnel time to perform one test (hours per test)			0.17		Information submitted to NICE by Microtest DX
Personnel costs to perform one batch of 4 tests (per hour): biomedical scientist[c]	£55.16		£9.19	£9.19	Curtis 2014[88]
No. of tests					
No. of tests per year	386				Assumption
Total costs				**£139.24**	

a This calculation assumed that test would be performed at the service provider laboratories.
b Costs of a medical consultant was used to reflect the costs of an immunologist.
c Costs of a health-care scientist was used to reflect the costs of a biomedical scientist.

Microtest[a] – minimum	Total	Per year (annuitised)	Costs per test (annuitised)	Costs per patient tested (annuitised)	Source
Test costs					
Cost of allergy reagents (can be used for 1–5 tests)			£5.00	£5.00	Information submitted to NICE by Microtest DX
Costs of allergy biochip			£100.00	£100.00	
Capital costs					
Microtest instrument	£35,000.00	£6,321.07	£16.38	£16.38	Information submitted to NICE by Microtest DX
Resale value	£0.00				
Life time of Microtest instrument (years)	5				
Other costs (service, maintenance)					
Personnel time for quality control			7.00		Information submitted to NICE by Microtest DX
Personnel costs for quality control	£55.16		£1.00	£1.00	Curtis 2014[88]
Personnel costs to perform and interpret test					
Personnel time to interpret test results (hours per test)			0.17		Information submitted to NICE by Microtest DX
Personnel costs for interpreting test results (per hour): immunologist[b]	£140.00		£23.33	£23.33	Curtis 2014[88]
Personnel time to perform one test (hours per test)			0.25		Information submitted to NICE by Microtest DX
Personnel costs to perform one batch of 4 tests (per hour): biomedical scientist[c]	£55.16		£13.79	£13.79	Curtis 2014[88]
No. of tests					
No. of tests per year	386				Assumption
Total costs				**£159.50**	

a This calculation assumed that test would be performed at the service provider laboratories.
b Costs of a medical consultant was used to reflect the costs of an immunologist.
c Costs of a health-care scientist was used to reflect the costs of a biomedical scientist.

Appendix 9 Guidance relevant to difficult to manage allergic disease

National Institute for Health and Care Excellence guidance

Atopic Eczema in Children. NICE Quality Standards, QS44, September 2014.

Omalizumab for Treating Severe Persistent Allergic Asthma (review of technology appraisal guidance 133 and 201). NICE technology appraisals, TA278, April 2013.

Atopic Eczema in Children. NICE Pathway, August 2012.

Pharmalgen for the Treatment of Bee and Wasp Venom Allergy. NICE technology appraisals, TA246, February 2012.

Anaphylaxis. NICE Pathway, December 2011.

Anaphylaxis: Assessment to Confirm an Anaphylactic Episode and the Decision to Refer after Emergency Treatment for a Suspected Anaphylactic Episode. NICE Clinical Guidelines, CG134, December 2011.

Food Allergy in Children and Young People. NICE Pathway, December 2011.

Food Allergy in Children and Young People: Diagnosis and Assessment of Food Allergy in Children and Young People in Primary Care and Community Settings. NICE Clinical Guidelines, CG116, February 2011.

Alitretinoin for the Treatment of Severe Chronic Hand Eczema. NICE technology appraisals, TA177, August 2009.

Inhaled Corticosteroids for the Treatment Of Chronic Asthma in Adults and in Children aged 12 years and over. NICE technology appraisals, TA131, November 2007.

Atopic Eczema in Children: Management of Atopic Eczema in Children from Birth up to the age of 12 years. NICE Clinical Guidelines, CG57, December 2007.

Inhaled Corticosteroids for the Treatment of Chronic Asthma in Children under the age of 12 years. NICE technology appraisals, TA131, November 2007.

Tacrolimus and Pimecrolimus for Atopic Eczema. NICE technology appraisals, TA82, August 2004.

Frequency of Application of Topical Corticosteroids for Atopic Eczema. NICE technology appraisals, TA81, August 2004.

Guidance from other agencies

Patient UK (June 2014) *Skin Prick Allergy Test*.

BUPA (May 2014) *Managing Your Allergies*.

NHS Choices (April 2014) *Allergies*.

NHS Choices (April 2014) *Food allergy*.

Map of Medicine (April 2014) *Anaphylaxis – Suspected*.

British Society for Allergy & Clinical Immunology (April 2014) *Guideline for the Diagnosis and Management of Cow's Milk Allergy*.

Anaphylaxis Campaign (February 2014) *Latex Allergy: The Facts*.

Anaphylaxis Campaign (February 2014) *Food Allergens in Non-food Items*.

World Allergy Organization (October 2013) *A WAO – ARIA – GA²LEN Consensus Document on Molecular-based Allergy Diagnostics*.

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

Anaphylaxis Campaign (April 2013) *Celery Allergy: The Facts*.

Patient UK (December 2012) *Anaphylaxis*.

Patient UK (May 2012) *Food Allergy and Intolerance*.

British Society for Allergy & Clinical Immunology (March 2012) *Standards for Paediatric Allergy Services in Secondary Care*.

Patient UK (March 2012) *Allergy – General Overview*.

Patient UK (March 2012) *Nut Allergy*.

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

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

Royal College of Paediatrics and Child Health (November 2011) *Care Pathway for Food Allergy in Children: an Evidence and Consensus Based National Approach*.

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

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

Quality, Innovation, Productivity and Prevention (QIPP) (October 2011) *Pharmacological Interventions to Prevent Allergic and Febrile Non-haemolytic Transfusion Reactions*.

British Society for Allergy & Clinical Immunology (August 2011) *Diagnosis and Management of Hymenoptera Venom Allergy*.

British Society for Allergy & Clinical Immunology (July 2011) *Immunotherapy for Allergic Rhinitis*.

Scottish Intercollegiate Guidelines Network (SIGN) (March 2011) *Management of Atopic Eczema in Primary Care*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Latex Allergy*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Venom Allergy*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Drug Allergy*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Urticaria, Angio-odema or Mastocytosis*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Eczema*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Asthma and/or Rhinitis*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Food Allergy*.

Royal College of Paediatrics and Child Health (2011) *Care Pathway for Anaphylaxis*.

British Society for Allergy & Clinical Immunology (June 2010) *Guidelines for the Management of Egg Allergy*.

British Society for Allergy & Clinical Immunology (December 2008) *Guidelines for the Management of Drug Allergy*.

Scottish Intercollegiate Guidelines Netwrok (SIGN) (July 2008 updated April 2014) *Antibiotic Prophylaxis in Surgery*.

Royal College of Physicians of London (May 2008) *Latex Allergy: Occupational Aspects of Management*.

Royal College of Physicians of London (March 2008) *Latex Allergy Guideline*.

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

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

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