

National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

ImmunoCAP ISAC and Microtest for multiplex allergen testing

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. This document is intended to be read in conjunction with the final scope issued by NICE for the assessment and the diagnostics assessment report. A glossary of terms can be found in Appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to assess the clinical and cost effectiveness of using the molecular allergy tests, ImmunoCAP ISAC and Microtest, in combination with standard clinical assessment to help inform allergy diagnosis and to predict the grade of allergic reaction.

In people with allergic disease the presence of an allergen causes antibodies to be produced in an immune response called sensitisation. Different allergens stimulate the production of corresponding allergen-specific IgE antibodies.

Standard clinical assessment in specialist regional allergy centres in the UK (around 12 centres) involves skin-prick testing and measuring levels of IgE antibodies against a single allergenic molecule (single specific IgE). The

individual allergenic molecules to be tested are selected by the clinician based on the clinical history of the patient.

ImmunoCAP ISAC and Microtest are molecular diagnostic multiplex allergen tests which can simultaneously measure sensitisation to multiple allergens in a single blood test to enable a person's individual sensitisation profile to be determined. Multiplex allergen tests are especially suitable for people with complex sensitisation patterns or symptoms.

It is claimed that using multiplex allergen testing could improve health outcomes by improving allergy management, more appropriately targeting specific immunotherapy, and reducing the number of investigative diagnostic tests and hospital visits. These improvements could also lead to potential savings to the NHS from reducing the number of diagnostic tests and avoiding the use of unnecessary immunotherapy.

Provisional recommendations on the use of these technologies will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 1 December 2015.

1.2 Scope of the evaluation

Table 1 scope of the evaluation

Decision questions	What is the clinical and cost effectiveness of using ImmunoCAP ISAC or Microtest, in combination with current clinical assessment to help inform allergy diagnosis and to predict the grade of allergic reaction?
Populations	People with allergy that is difficult to manage
Interventions	<ul style="list-style-type: none"> • Clinical assessment and ImmunoCAP ISAC • Clinical assessment and Microtest
Comparator	Clinical assessment comprising: <ul style="list-style-type: none"> • Clinical history • Skin prick testing • Singleplex specific IgE
Healthcare setting	Secondary/tertiary care
Outcomes	Intermediate measures for consideration may include:

	<ul style="list-style-type: none"> • Diagnostic accuracy • Discordant results • Test failure rate • Number of specific IgE tests • Number of specific immunotherapies • Number of healthcare attendances and admissions • Use of corticosteroids • Prescription of rescue medicines in anaphylaxis • Number of allergy diagnoses • Number of challenge tests • Change in patient management <p>Clinical outcomes for consideration may include:</p> <ul style="list-style-type: none"> • Allergy symptoms • Incidence of acute exacerbations • Adverse effects of testing and treatment • Morbidity and mortality • Health-related quality of life including patient anxiety <p>Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:</p> <ul style="list-style-type: none"> • Cost of equipment, reagents and consumables • Cost of staff and associated training • Medical costs arising from testing, treatment and care • Medical costs arising from adverse events including those associated with false test results and inappropriate treatment <p>The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.</p>
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details including descriptions of the interventions, comparators, care pathway and outcomes can be found in the [final scope](#).

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group (EAG).

2.1 *Clinical Effectiveness*

The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of ImmunoCAP ISAC and Microtest in people with difficult to manage allergic disease in secondary and tertiary care settings.

Full details of the systematic review can be found starting on page 36 of the diagnostics assessment report.

Overview of the studies

The External Assessment Group identified 20 publications of 15 studies that met the inclusion criteria for the systematic review. Evidence on all versions of ImmunoCAP was considered because it may provide additional information on current versions. No studies of Microtest were identified.

All of the included studies evaluated versions of ImmunoCAP ISAC. ImmunoCAP ISAC is named according to its version, with the difference between versions being the number of allergen components tested. The number of components corresponds to the number at the end of the name. ImmunoCAP ISAC 112 is the most recent version of the ImmunoCAP ISAC array and tests for 112 allergen components. Of the 15 included studies:

- 1 study evaluated ImmunoCAP ISAC 112,
- 5 studies evaluated ImmunoCAP ISAC 103,
- 1 study evaluated ImmunoCAP ISAC 96,
- 1 study evaluated ImmunoCAP ISAC 89,
- 1 study evaluated ImmunoCAP ISAC 51,
- 1 study evaluated ImmunoCAP ISAC 50,
- 5 studies did not specify the version of ImmunoCAP ISAC evaluated

Of the 15 included studies:

- 8 studies compared the diagnostic accuracy of ImmunoCAP ISAC to that of other testing options (single specific IgE testing or skin prick test) to predict clinical reactivity as defined by skin prick test or oral food challenge testing
- 1 study assessed the effects on clinical diagnosis of adding ImmunoCAP ISAC 103 to the standard diagnostic work-up
- 1 study assessed the effects on clinical diagnosis, specific immunotherapy prescription and the value of the additional information provided by adding ImmunoCAP ISAC 103 to the standard diagnostic work-up
- 4 studies assessed the effects on patient management of adding ImmunoCAP ISAC to the standard diagnostic work-up (skin prick test or single specific IgE testing /single specific IgE)
- 1 study looked at the levels of IgE using ImmunoCAP ISAC before and after specific immunotherapy

In addition, 2 studies that used ImmunoCAP ISAC to determine sensitisation rates to various allergens were identified. These studies did not meet the inclusion criteria for the systematic review but are described here for completeness.

Two of the included studies were conducted in the UK, 12 were conducted in other European countries and 1 study did not report location. Of the 15 included studies, 4 were funded by, or received reagents consumables, or testing services, from the company. Five studies were publicly funded, and 6 did not report funding sources.

The EAG did not identify any studies that reported clinical outcomes (i.e. allergy symptoms, incidence of acute exacerbations, mortality, adverse events of testing and treatment, healthcare presentations or admissions, HRQoL, patient anxiety/preferences).

Details of the individual studies can be found starting on page 41 of the diagnostics assessment report. The data extraction tables are presented in Appendix 2, starting on page 166 of the diagnostics assessment report.

Studies were generally of unclear quality because of limitations in reporting, and 6 studies were reported as conference abstracts only. All studies in the review are considered to be at 'high' or 'unclear' risk of bias. The main areas of bias 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). Further details of the quality assessment can be found on page 45 of the diagnostics assessment report.

It was not possible to conduct a meta-analysis of the studies because of the heterogeneity of the included studies and lack of reported data. Details of results of the diagnostic accuracy of ImmunoCAP ISAC, the effects on patient management of adding ImmunoCAP ISAC to the standard diagnostic work-up (skin prick test/single specific IgE) and the effects on clinical diagnosis of adding ImmunoCAP ISAC to the standard diagnostic work-up are presented as a narrative summary.

Evidence on diagnostic accuracy of ImmunoCAP ISAC

Of the 8 studies identified, 6 studies compared the accuracy of ImmunoCAP ISAC to existing diagnostic tests (skin prick test or single specific IgE tests) in people with food allergies and 2 studies in people with allergies to aeroallergens. None of the studies used ISAC 112, 2 used ISAC 103, 1 used ISAC 89, 2 used ISAC 50/51 and 3 used unknown ISAC versions. The results of the comparative diagnostic accuracy studies are summarised in Table 7 starting on page 67 of the diagnostics assessment report.

Diagnosis of food allergy

De Swert et al. (2012) investigated soy flour allergy. The diagnostic accuracy of an unknown ISAC version to measure the soy flour component rGly m4

was compared to the single specific IgE test for the same component and to a skin prick test for soy flour. Cut-off values were reported separately for each test and oral food challenge 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 specific IgE test and skin prick test had similar sensitivity (75%) and specificity (100%).

Alessandri et al. (2011) 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 to the accuracy of single specific IgE tests (egg yolk or egg white) and compared to the accuracy of skin prick tests (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 oral food challenge testing was used as the reference standard. Skin prick test had the highest sensitivity for prediction of allergic response to raw egg white, 88% (95% CI: 71.8 to 96.6%), whilst 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 specific IgE performed similarly to skin prick test, (both measured whole extracts), whilst 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.

D'Urbano et al. (2010) compared the accuracy of ISAC 89, used to measure two individual components (Gal d1 or Bos d8), to the accuracy of single specific IgE tests (egg white or cow's milk). Cut-off values were reported separately for each test and oral food challenge 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 specific 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 specific IgE tests (41% for cow's milk and 27% for egg white). When whole allergen single specific IgE tests and ISAC 89 were used in series (i.e. ISAC 89 results were only

considered in single specific IgE negative participants), the combined sensitivity was greater than that for single specific IgE alone (84% compared to 41% for cow's milk allergy and 73% compared to 27% for hen's egg allergy); specificity was 92% in both cases.

Ott et al. (2008) 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) to the accuracy of single specific IgE tests (hen's egg or cow's milk extract) and to the accuracy of skin prick tests (native hen's egg or native cow's milk). Cut-off values were reported separately for each test and oral food challenge testing was used as the reference standard. The results were very variable between tests. Skin prick test 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 skin prick test 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.

Sokolova et al. (2009) 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 K, Bos d lactoferrin, Bos d 5.0101), was compared to the accuracy of single specific IgE tests for four allergens (whole milk, α -lactoalbumin, β -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. Oral food challenge testing was used as the reference standard. Both combined ISAC testing and combined single specific IgE testing had 100% sensitivity, however, ISAC testing had much higher specificity, 91.7% (95%CI: 73 to 99%) than the single specific IgE testing, 37.5% (95%CI: 18.8 to 59.4%).

Albarini et al. 2013 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 specific IgE tests (hazelnut) and to skin prick test. Cut-off values were not reported for the ISAC test. Oral food challenge testing was used as the reference standard. Both the skin prick test and the single specific IgE test had 100% sensitivity, whilst 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 specific IgE (21.1%) or skin prick testing (52.6%).

Diagnosis of aeroallergy

Wohrl et al. (2006) investigated five different aeroallergens (house dust mite, cat dander, birch pollen, grass pollen and mugwort pollen). The diagnostic accuracy of ISAC 50, used to measure the presence of one or more aeroallergen (up to five), was compared to the accuracy of single specific 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-offs 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% to 98.1%), and, with the exception of mugwort pollen, was comparable to the specificity estimate for the corresponding whole allergen single specific IgE test for all aeroallergens investigated (see Table 7 page 73 of the diagnostics assessment report). The sensitivity of ISAC 50 was lower than that of single specific IgE tests for house

dust mite, cat and mugwort pollen. The sensitivities and specificities of the individual components ISAC 50 components were not reported.

Cabrera-Freitag et al. (2011) investigated two different pollens (grass pollen or *P. pratense* and cypress pollen or *C. arizonica*). Two cut-off points (manufacturers' recommended and ROC optimised) were reported per test and skin prick test was used as the reference standard. The diagnostic accuracy of ISAC 103, when used to measure the eight components for grass pollen (rPhl p 1, rPhl p 2, nPhl p 4, rPhl p 5, rPhl p 6, rPhl p 7, rPhl p 11, rPhl p 12) was compared to the accuracy of a single specific 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 specific 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 to the accuracy of single specific IgE tests to measure *C. arizonica*. The sensitivity estimates for the two tests were equal at both cut-offs (91.7%), however, specificity was higher for ISAC 103 at both cut-offs (91.3% and 95.6%) than for the single specific IgE test (80.4% to 89.1%).

Evidence on clinical diagnosis using ImmunoCAP ISAC

Heaps et al. (2014) investigated 110 people who had a diagnosis of idiopathic anaphylaxis (based on clinical assessment, skin prick test, single specific IgE testing and mast cell tryptase), from five UK specialist allergy centres. Study participants were re-assessed using ImmunoCAP ISAC 103 and clinicians were asked to score the additional information provided. Information 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 in these 22 people, 168 sensitisations which were not thought to be associated with anaphylaxis were also identified (see Table 6 page 60 of the diagnostics assessment report for full details). In addition, for a further 35 (32%) of

participants the information provided by ImmunoCAP ISAC was deemed to have identified only additional sensitisations(322 in total) which were not thought to be associated with anaphylaxis.

Evidence on clinical diagnosis and patient management using ImmunoCAP ISAC

Passalacqua et al. (2013) investigated 318 consecutive polysensitised (at least two positive skin prick tests) people with respiratory allergy in six allergy units in Italy. Participants were initially investigated using clinical history, skin prick test and single specific 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 to provide a judgement of the value of any additional information provided (see Table 5 page 55 of the diagnostics assessment report). 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 specific immunotherapy prescription. The study reported that new information related to patient management was classified as “remarkable” in 299 (95%) of cases and “to some extent” (not defined) in 232 (73%) of cases. The study did not report the details of the new information.

This study also reported detailed information on changes to diagnostic category using five classifications when ImmunoCAP ISAC 103 testing was used (see Table 6 page 60 of the diagnostics assessment report). The number of people who are classified as:

- polysensitised with only one clinically relevant sensitisation decreased from 56 to 33,
- true polysensitised with greater than 1 clinically relevant sensitisation decreased from 176 to 117,

- polysensitised with suspected cross-reactivity increased from 44 to 99
- sensitised to inhalants and foods increased from 34 to 69 and
- non-classifiable decreased from 8 to 0.

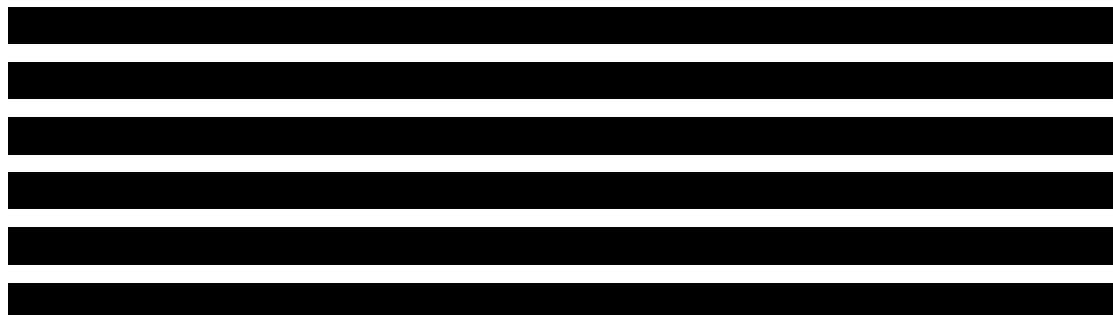
The study also reported changes in specific immunotherapy prescriptions (Table 5 page 56 of the diagnostics assessment report). 85 people with respiratory allergy, who would not have received specific immunotherapy based on standard diagnostic work-up (skin prick test/single specific IgE), were given a new prescription for specific immunotherapy following testing with ImmunoCAP ISAC 103. In addition, the existing specific immunotherapy prescription was changed in a further 3 people with respiratory allergy, following ImmunoCAP ISAC 103 testing. No details of which specific immunotherapy prescriptions were actually used, or any subsequent clinical outcomes were reported.

Evidence on patient management using ImmunoCAP ISAC

Discontinuation of restrictive diets

Two studies investigated the use of ImmunoCAP ISAC to guide decisions on the discontinuation of restrictive diets in children with food allergies [Hermansson et al. (2014), Noimark et al. (2014)]. Both studies were reported as conference abstracts only and hence provided only limited study details and results.

Hermansson et al. (2014) used a database to identify 199 school children in Härkätie, Finland, receiving special diets in school catering;



████████████████████ No information on clinical outcomes following changes to dietary management was reported.

Noimark et al. (2012) investigated 12 children selected from people attending an East London allergy clinic (no details of the selection criteria were reported). Participants were investigated using skin prick test and/or single specific IgE, and an un-specified 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 specific IgE alone; the numbers of potential re-introductions based on standard diagnostic work-up (skin prick test and/or single specific IgE) were not reported. No details were reported of which single specific IgE/skin prick test tests were conducted or which ISAC components were assessed. The number of food reintroductions that occurred following testing, or clinical outcomes of any changes to dietary management were not reported.

Value of additional information

Luengo et al. (2010) performed ImmunoCAP ISAC 103 testing in 55 well characterised, poly-sensitised people (as assessed by skin prick test and single specific 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%) of cases. The added value was in the ability of ImmunoCAP ISAC to differentiate between protein homologues and hence to aid in the discrimination of allergens which were cross-immunoreactive rather than those which were responsible for sensitisation. In 34 (62%) of cases the clinicians considered that it would have been useful to perform ImmunoCAP ISAC 103 testing before skin prick test, since several protein homologues can be investigated at once using ImmunoCAP ISAC.

Changes in specific immunotherapy prescriptions

Sastre et al. (2012) investigated 141 people with respiratory allergy (with or without concomitant food allergy) in one allergy outpatient clinic in Spain. Specific immunotherapy indications were initially assessed based on clinical history and skin prick test (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). Clinicians then re-assessed specific immunotherapy indications based on all diagnostic information, including ImmunoCAP ISAC 96 results. Disagreements on the specific immunotherapy prescription based on standard diagnostic work-up and that based on all information, including ImmunoCAP ISAC, occurred for 79 (54%) of study participants; details are reported in Table 5 page 57 of the diagnostics assessment report. No details of which specific immunotherapy prescriptions were actually used, or any subsequent clinical outcomes were reported.

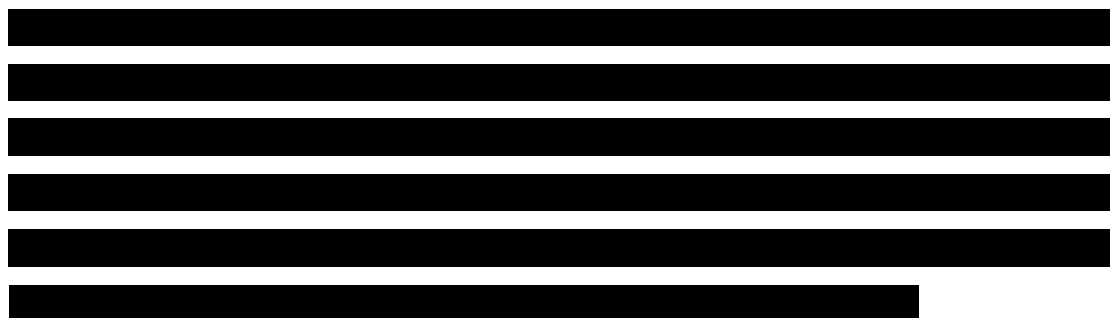
Evidence on assessment of IgE levels before and after specific immunotherapy

Gay-Crosier et al. (2010) assessed the relationship between change in IgE levels, measured by ImmunoCAP single specific IgE and change in IgE levels measured by an un-specified version of ImmunoCAP ISAC before and after a three year course of specific immunotherapy, and the clinicians' evaluation of the benefit of specific immunotherapy. This study included only nine participants who received a total of 31 courses of specific immunotherapy (no details of diagnosis were reported). The median specific IgE levels, measured by ISAC, decreased from 5.6 ISU/ml at the beginning of specific immunotherapy to 0.01 ISU/ml at the end of specific immunotherapy and this change correlated with clinical benefit of specific immunotherapy (evaluated by clinicians), Spearman $r=0.46$, $p=0.0236$. Conversely, allergen-specific single specific IgE measurements did not show a decrease from the beginning to the end of specific immunotherapy.

Additional studies reporting sensitisation rates that did not meet inclusion criteria

Two studies, conducted in Spain, that did not meet the original inclusion criteria for the systematic review looked at sensitisation rates to various plant food allergens in allergic and tolerant individuals and have been included as they provide additional useful information. The studies are described in detail on pages 114 and 115 of the diagnostics assessment report.

Pedrosa et al. (2012) assessed 123 children with food allergy, of whom 55 were classified as peanut-allergic and 68 as peanut tolerant (skin prick test and single specific IgE) and used ImmunoCAP ISAC 103 to assess sensitisation to a range of allergenic components. 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 h 8, Act d 8, Cor a 1, Gly m4, Mal d 1, Pru p 1), profilins (Bet v 2, Ole e 2, Hev b 8, Mer a 1, Phl p 12), some lipid transfer proteins lipid transfer proteins (Par j 2, Pru p 3), cross-reactive carbohydrate determinate Ana c 2, or pollens (Ole e 1, Phl p 1).



2.2 Costs and cost effectiveness

The EAG conducted a search to identify existing studies investigating the cost effectiveness of ImmunoCAP ISAC and Microtest, in combination with current clinical assessment to help inform allergy diagnosis and predict the grade of allergic reaction. As a result of lack of long term clinical effectiveness data a de novo economic model could not be developed.

Systematic review of cost effectiveness evidence

Full details of the review can be found starting on page 75 the diagnostics assessment report. Nine publications of 4 studies were considered eligible for inclusion in the systematic review. The results of the studies are summarised in Table 8 page 79 of the diagnostics assessment report. All 4 included studies are authored by Hermansson (affiliated with Thermo Fischer Scientific). All included studies were only reported as conference abstracts, so the methods and assumptions used were largely unclear. Fundamental inputs to the models in the studies were based on expert opinion, inaccessible references, or no references were reported. The results of the quality assessment are presented in Table 9 on page 81 of the diagnostics assessment report.

Hermansson et al. (2014) (2 publications) considered the cost-effectiveness of using ImmunoCAP ISAC in addition to standard diagnostic work-up compared with standard diagnostic work-up alone, for Finnish school children with a restricted diet because of suspected food allergy (community setting). The analysis was informed by 24 children from a larger database (including a total of 2,317 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 compared to standard diagnostic work-up alone.

Another study by Hermansson and colleagues (Hermansson et al. 2013 and Hermansson et al. 2012) examined the cost-effectiveness of ImmunoCAP ISAC compared to double blind placebo controlled food challenge (DBPCFC) and skin prick testing (SPT) for children with suspected peanut allergy. For this purpose, a Markov model was constructed with a five 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 United States and China. The results indicated that ImmunoCAP ISAC is least expensive while skin prick test is most expensive for all three countries. Moreover, ImmunoCAP ISAC was also found to be most effective leading to

3.97 QALYs gained while the DBPCFC strategy was least effective (2.54 QALYs). Consequently, ImmunoCAP ISAC dominated both the skin prick test and DBPCFC strategies.

Glaumann et al. (2013) examined the cost-effectiveness of ImmunoCAP ISAC compared to DBPCFC, open(non-blinded)oral food challenge (OFC) and skin prick test for children with suspected peanut allergy in Sweden. A Markov model with a five 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 while skin prick test is most expensive. Furthermore, ImmunoCAP ISAC was also found to be most effective leading to 4.34 QALYs while the oral food challenge strategy was considered least effective (2.23 QALYs). Consequently, ImmunoCAP ISAC dominated all three alternative strategies.

Mascialino et al. (2013) (2 publications) and Hermansson et al. (2012) examined the cost-effectiveness of ImmunoCAP ISAC with skin prick test compared to skin prick test only for Spanish people sensitised to pollen in a complex pollen area. The analysis was based on a Markov model with a nine year time horizon and the assumption that people on specific immunotherapy (specific immunotherapy) continue this treatment for 3 years and remain healthy for the subsequent 6 years or discontinue specific immunotherapy and move to symptom management treatment until year 9. The analysis was informed by a dataset of 141 people with allergic rhino-conjunctivitis and/or asthma sensitised to pollen. The results indicated that the addition of ImmunoCAP ISAC to skin prick test reduces specific immunotherapy prescriptions and hence results in cost savings compared to skin prick test only (€2,538 versus €2,608). ImmunoCAP ISAC with skin prick test was also found to be more effective (7.03 QALYs) compared with skin prick test only (6.88 QALYs), hence ImmunoCAP ISAC with skin prick test dominated skin prick test only.

The study by Rogriguez-Ferran et al. (2011), reported in a conference abstract, was originally excluded from the review as it did not include effectiveness outcomes, but a description is included for completeness. The study considered the costs of skin prick test, Phadiatop and ImmunoCAP Rapid for screening respiratory allergy in children in primary care. Their results showed that skin prick testing is least expensive (€10-€15), followed by ImmunoCAP Rapid (€30) and Phadiatop (€36-€67). The authors stated that they believe skin prick testing is cost-effective.

Economic analysis

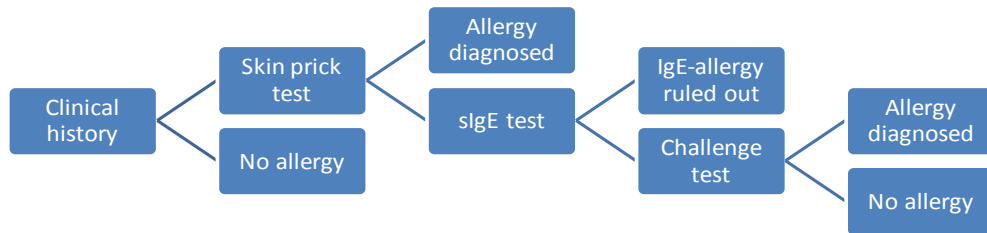
Arising from the lack of data on the clinical consequences of adding multiplex allergen testing to current clinical practice the External Assessment Group were unable to develop a de novo economic model. Instead of developing a long-term cost-effectiveness model, current and potential diagnostic pathways were explored and a concept model structure was developed.

Current and potential diagnostic pathways

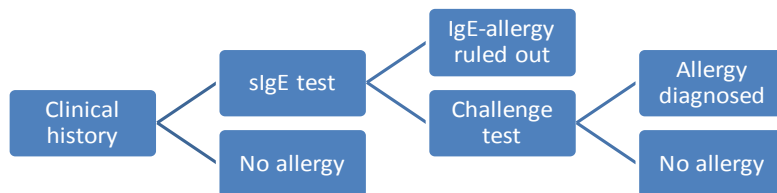
Current clinical diagnostic pathways for people referred for specialist allergy investigation in secondary or tertiary care settings may include skin prick test, single specific IgE testing and an oral food challenge test where appropriate, combined with clinical history. Skin prick test is often the first investigation performed in allergy diagnostics. Based on consultations with clinical experts, it is assumed that single specific IgE testing will be performed in cases where the results of the skin prick test are not consistent with the clinical history of a patient. Inconsistency can occur if the skin prick test for the most likely allergen (based on clinical history) is negative, or if a skin prick test is positive for an allergen that does not seem to explain the symptoms completely. Additionally, an oral food challenge test is usually performed to confirm or rule-out allergy to a specific food-related allergen or allergens. If skin prick test is not considered acceptable or practical (e.g. in children with atopic eczema), single specific IgE testing might be the first-line investigation, using confirmatory oral food challenge or skin prick test as necessary. Moreover, it might be possible to proceed to oral food challenge based on skin prick test

(and patient history) alone. Figure 1 provides an overview of the possible diagnostic pathways with and without skin prick test. It should be noted that it is unclear whether this theoretical diagnostic pathway (based on clinical expertise and literature) is representative of current UK clinical practice in all secondary or tertiary care settings.

A: Current diagnostic pathway (with skin prick test)



B: Current diagnostic pathway (without skin prick test)



C: Current diagnostic pathway (with skin prick test and without single specific IgE test)

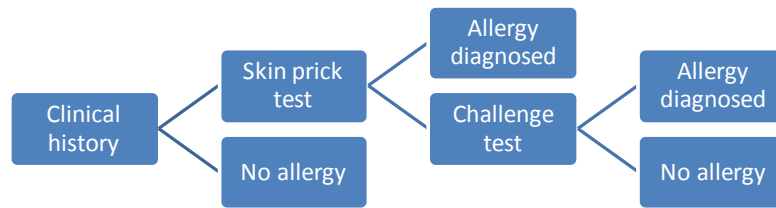
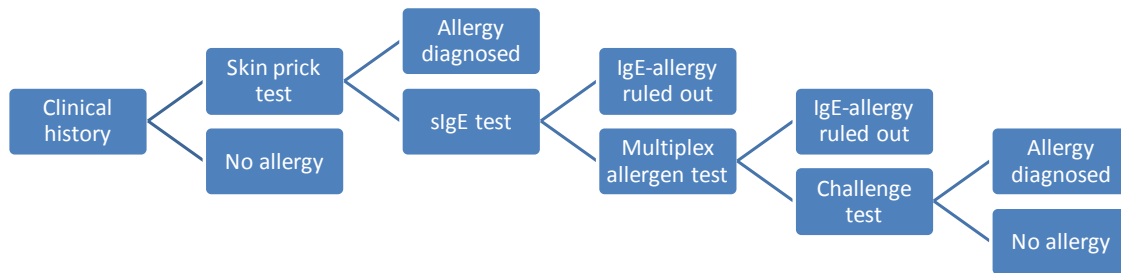


Figure 1. Current diagnostic pathways

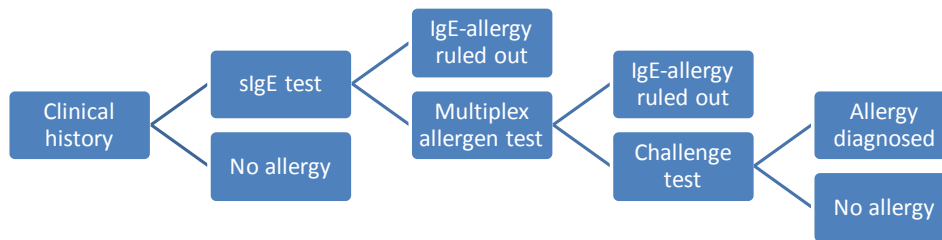
In these pathways it is assumed that *no* further testing will be performed if IgE-mediated allergic response can be ruled-out as an explanation for the observed symptoms. In all other cases it is assumed that further testing will be performed.

When considering people with difficult to manage allergic disease that 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 the allergens of interest are included). Its role would be to identify which allergens a patient is sensitive to. Any allergens identified would have to be confirmed by skin prick test or oral food challenge. The potential advantage of the multiplex testing 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 oral food challenge. It is likely that multiplex allergen testing would replace single specific IgE testing, although some single specific IgE testing might still be required e.g. if all suspected allergens are not included. Figure 2 provides an overview of potential diagnostic pathways including multiplex allergen testing. In some pathways (Figure 2 A and B) it is assumed, based on clinical opinion, that single specific IgE testing will always be performed before multiplex allergen testing (if single specific IgE testing is applicable). However, this might not always be the case, as multiplex allergen testing may also be performed instead of single specific IgE testing (Figure 2 C and D). The most important point is that multiplex allergen testing would be likely to reduce the number of single specific IgE tests, by ruling out particular allergens thereby reducing the need for oral food challenge.

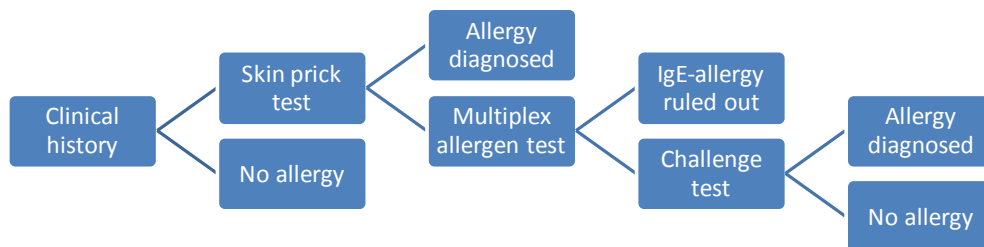
A: Multiplex allergen test *in addition to* single specific IgE testing (*with* skin prick test)



B: Multiplex allergen test *in addition to* single specific IgE testing (*without* skin prick test)



C: Multiplex allergen test *instead of* single specific IgE testing (*with* skin prick test)



D: Multiplex allergen test *instead of* single specific IgE testing (*without* skin prick test)

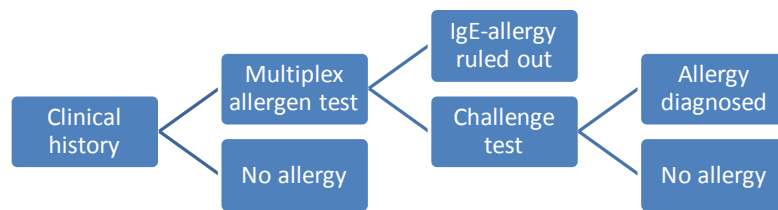


Figure 2. Proposed diagnostic pathway

^a 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.

Concept 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)', 'not at risk of allergic reaction (untreated)'. Moreover, potential adverse events of testing can be considered in the decision tree. The decision tree is shown in Figure 3.

The long-term consequences in terms of costs and QALYs can be estimated using a state-transition cohort model (Figure 4) 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

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 e.g. those suspected of having clinical reactivity to an inhaled versus an ingested allergen.

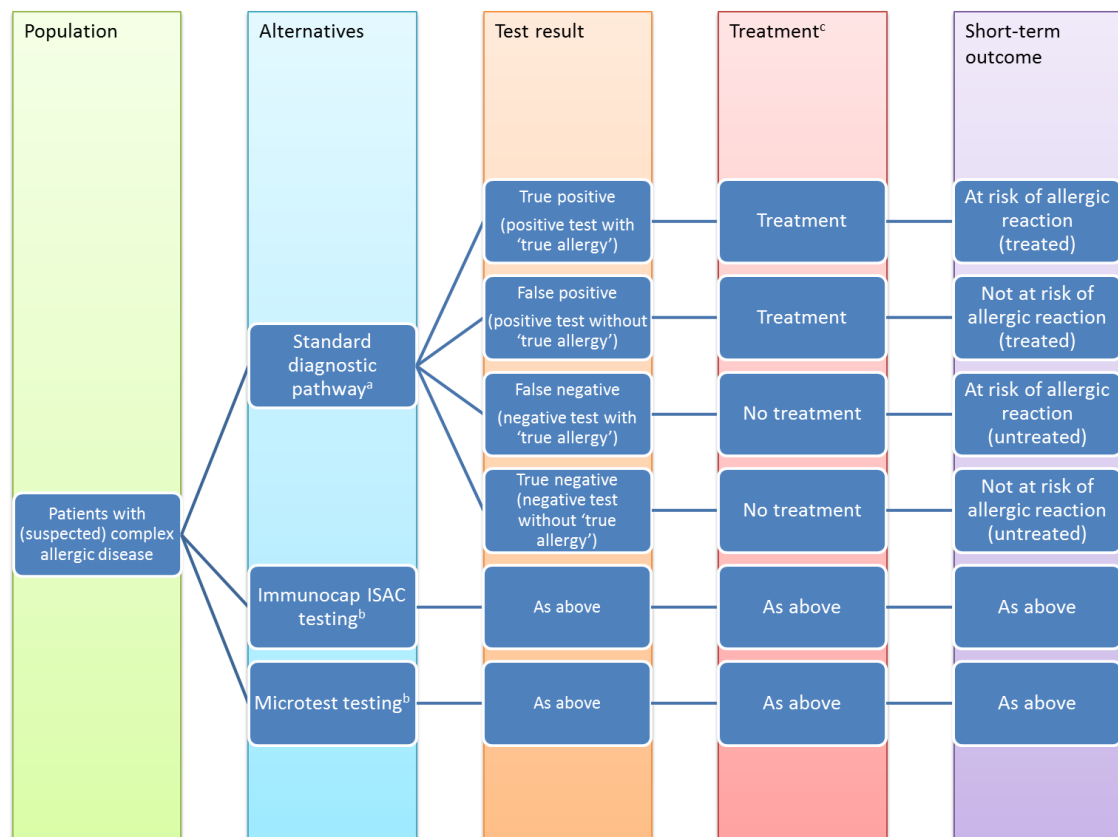


Figure 3. Potential decision tree for the diagnostic pathway

^aStandard diagnostic pathway may consist of skin prick tests, single specific IgE testing and/or food challenge (see Figure 1)

^bMultiplex allergen testing might be performed in addition to the standard diagnostic pathway or instead of (part of) the standard diagnostic pathway (see Figure 2)

^cTreatment 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

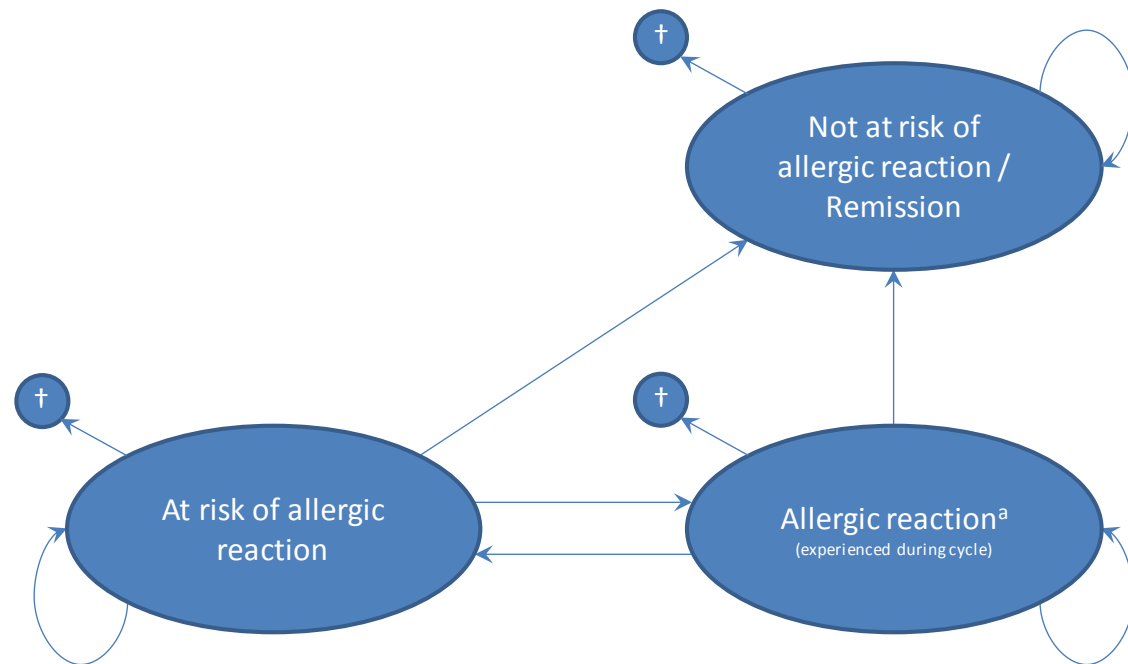


Figure 4. Transition Model

^aDifferent types and severities of allergic reactions can be separately included in the model.

†Death

Model inputs

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

- proportion of people who receive a particular test (i.e. skin prick test, single specific IgE test, multiplex allergen test and/or oral food challenge test) as well as the number of skin prick test and/or single specific 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 skin prick test, single specific IgE and/or multiplex testing);

- the treatment decision.

However, data on the above parameters was not available.

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.

However, no long-term consequences for multiplex allergen testing were identified in the systematic review.

Health state utilities

The systematic review of health state utilities identified 14 studies reporting health state utilities for allergic conditions. The results are summarised in Table 10 and Table 11 starting on page 89 of the diagnostics assessment report. Ten studies, reported in 13 publications, used the EuroQol instrument, and reported either the EQ-5D utility score or the visual analogue scale (VAS) score. One study reported utilities obtained by the HUI Mark III instrument. Three studies used a direct utility elicitation technique. Ten studies reported on 28 populations; 14 with rhinitis/rhinosinusitis/rhinoconjunctivitis/asthma, 11 with eczema, 2 with food allergy, and 1 with mixed allergies except food allergies.

Six studies describing 10 populations comparing health state utility scores for people with and without allergic disease were found. 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, (2004) or EQ-5D scores from a European

study (Poole et al. (2004), Bachert et al. (2007) and Currie et al. (2014)) could be taken. Stephens et al (2004) used standard gamble to obtain utility values for atopic eczema in UK children. Only in the study by Stephens et al. (2004) were utilities reported per degree of severity of the allergic conditions (see Tables 10 and 11 on page 89 and 91 of the diagnostics assessment report). 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. (2013) that the impact of anaphylactic shock on quality of life was equal to zero utility for a duration of nine days at maximum.

Resource use and costs

To estimate the costs of the individual tests, a detailed cost calculation (see Appendix 7 page 224 of the diagnostics assessment report) 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 1. For ImmunoCAP ISAC and Microtest testing 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 Microtest Dx where the test would be performed (most conservative scenario) while 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. Capital costs are annuitized using a cost discount rate of 3.5%.

Table 1. Results of the test cost calculation

	£ per patient tested
Skin prick test	£62.28
IgE test	£136.37
Oral food challenge test	£570.00
ImmunoCAP ISAC	£219.51
Microtest	£156.85

Additional costs that would be considered in a long-term cost(-effectiveness) analysis may include the costs of specific immunotherapy, 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 specific immunotherapy might be provided within a specific population. Hence the specific type(s) of specific immunotherapy prescribed and the specific immunotherapy duration would be required to calculate these costs.

Base-case results

In the base case a cost comparison of 3 diagnostic strategies is assessed: with ImmunoCAP ISAC versus with Microtest versus the standard diagnostic pathway without multiplex allergen testing.

As the proportion of people receiving single specific IgE and oral food challenge tests in addition to ImmunoCAP ISAC or Microtest is unclear, the cost analyses are performed using two-way threshold analysis for these parameters. Specifically, in pairwise comparisons of two test strategies, the minimal reduction (i.e. threshold) in proportions of single specific IgE and oral food challenge 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 people receive eight single specific IgE tests on average and all people receiving on average one oral food challenge test (see Appendix 7 of the diagnostics assessment report starting page 224). Therefore, for example, if it was assumed that the use of multiplex allergen testing would result in no single specific IgE testing then this would imply a 100% reduction in single specific IgE testing compared to the standard diagnostic pathway. Given that multiplex allergen testing is more costly than single specific IgE testing, threshold analysis could then show what percentage reduction in oral food challenge 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 was no reduction in single specific IgE testing by use of multiplex allergen then this would result in a different threshold for the percentage reduction in oral food challenge tests required to give the multiplex allergen pathway the same cost as the standard diagnostic pathway.

The following assumptions are made:

- everything except the number of single specific IgE tests and the number of oral food challenge tests remains equal
- the proportion of people receiving any skin prick test is equal for all test strategies.

Although, this assumption is debatable, it might be justified given that skin prick test is a simple, safe and quick test (providing results within 15-20 minutes) that is often the first-line investigation in allergy diagnostics. Moreover, 1 clinician, with experience with ImmunoCAP ISAC testing, indicated that all people would receive skin prick test when using ImmunoCAP ISAC.

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 oral food challenge 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 specific IgE tests (i.e. from 100% to 0%). On the other hand, if there is no reduction in the proportion of single specific IgE tests (assuming an average of 8 per person), the reduction in oral food challenge tests should be at least 39% and 28% for ImmunoCAP ISAC and Microtest respectively. Moreover, for ImmunoCAP ISAC compared with Microtest, the proportion of oral food challenge tests for ImmunoCAP ISAC should be reduced by at least 11% if there is no reduction in the proportion of single specific IgE tests. When assuming no reduction in the proportion of oral food challenge tests, the proportion of people receiving an average of 8 single specific IgE tests for ImmunoCAP ISAC should be reduced by at least 44% (Figure 10 on page 103 of the diagnostics assessment report).

Analysis of alternative scenarios

1) In the calculation of the base case costs for ImmunoCAP ISAC it is assumed that the LuxScan 10 000k reader (scanner recommended for measuring the fluorescence of ImmunoCAP ISAC) would only be used for ImmunoCAP ISAC testing (on average 386 tests per year). However, the LuxScan 10 000k reader might be used for other purposes. Therefore in the first scenario analysis, it is assumed that the LuxScan 10 000k reader would be fully occupied for 253 days per year. This reduces the ImmunoCAP ISAC testing costs to £201.91 per patient tested, a decrease of £18. At the reduced cost, to be cost-saving compared with the standard diagnostic pathway, the proportion of oral food challenge tests for ImmunoCAP ISAC should be reduced by at least 11% (e.g. from 50% to 39%) if there was a 100% reduction in single specific IgE tests. On the other hand, if there is no reduction in the proportion of single specific IgE tests, the reduction in oral food challenge tests should be at least 35% for ImmunoCAP ISAC.

For ImmunoCAP ISAC compared with Microtest, the proportion of oral food challenge tests for ImmunoCAP ISAC should be reduced by at least 8% if

there is no reduction in the proportion of single specific IgE tests. When assuming no reduction in the proportion of oral food challenge tests, the proportion of single specific IgE tests for ImmunoCAP ISAC should be reduced by at least 33% in order to be cost-saving. (Figure 11 page 104 of the diagnostics assessment report).

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 by £7 to £149.37 per patient tested (see Appendix 8 page 233 of the diagnostics assessment report). At the reduced cost, to be cost-saving compared with the standard diagnostic pathway, the proportion of oral food challenge tests for Microtest should be reduced by at least 2% if there was a 100% reduction in single specific IgE tests. On the other hand, if there is no reduction in the proportion of single specific IgE tests, the reduction in oral food challenge tests should be at least 26% for Microtest. Moreover, for ImmunoCAP ISAC compared with Microtest, the proportion of oral food challenge tests for ImmunoCAP ISAC should be reduced by at least 15% if there is no reduction in the proportion of single specific IgE tests. When assuming no reduction in the proportion of oral food challenge tests, the proportion of single specific IgE tests for ImmunoCAP ISAC should be reduced by at least 39% in order to be cost-saving. (Figure 12 page 104 of the diagnostics assessment report).

3) The third scenario analysis considered the impact of the number of allergens tested using single specific single specific IgE testing (base case value = 8 allergens tested per person). When assuming 1 allergen being tested, for ImmunoCAP ISAC and Microtest to be cost-saving compared with the standard diagnostic pathway, the proportions of oral food challenge tests should be reduced by at least 35% and 24% respectively if there was a 100% reduction in single specific IgE tests. Moreover, for ImmunoCAP ISAC compared with Microtest, the proportion of oral food challenge tests for ImmunoCAP ISAC should be reduced by at least 8% if there is a 100%

reduction in single specific IgE tests. On the other hand when assuming 20 allergies to be tested, for ImmunoCAP ISAC and Microtest to be cost-saving compared with the standard diagnostic pathway, assuming no reduction in oral food challenge tests, the proportion of single specific IgE tests should be reduced by at least 64% and 46% respectively. Moreover, for ImmunoCAP ISAC compared with Microtest, the proportion of single specific IgE tests for ImmunoCAP ISAC should be reduced by at least 18% (assuming no reduction in oral food challenge tests) in order to be cost-saving (Figures 13 and 14 page 105 of the diagnostics assessment report).

4) Finally, decreasing the oral food challenge costs to £256.00 substantially increases the reduction in oral food challenge needed in order for multiplex allergen testing to be cost-saving. More specifically, in order for ImmunoCAP ISAC and Microtest to be cost-saving compared with the standard diagnostic pathway, the proportion of OFC tests should be reduced by at least 32% and 8% respectively if there would be a 100% reduction in single specific IgE tests. On the other hand, if there is no reduction in the proportion of single specific IgE tests, the reduction in oral food challenge tests should be at least 86% and 61% for ImmunoCAP ISAC and Microtest respectively. Moreover, for ImmunoCAP ISAC compared with Microtest, the proportion of oral food challenge tests for ImmunoCAP ISAC should be reduced by at least 24% if there is no reduction in the proportion of single specific IgE tests. When assuming no reduction in the proportion of oral food challenge tests, the proportion of single specific IgE tests for ImmunoCAP ISAC should be reduced by at least 46% in order to be cost-saving (Figure 15 page 106 of the diagnostics assessment report).

Threshold analyses

For the situation where ImmunoCAP ISAC or Microtest are used as replacement test(s) for single specific 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 specific IgE tests in order for single specific IgE testing to be equally or more expensive than multiplex allergen testing,

assuming that everything else remains equal. This analysis was also performed for skin prick test. In these analyses, it is assumed that there is no reduction in oral food challenge testing with multiplex testing. In order for the standard pathway to be as expensive as the ImmunoCAP ISAC and Microtest pathways, the minimum number of allergens tested using single specific Ig E tests were 13 and 10 respectively. This means that, if multiplex testing replaced single specific IgE testing then it would have to replace at least 13 or 10 tests to be cost saving. For skin prick test these numbers were 39 and 27, respectively.

3 Summary of the main findings from the assessment

Clinical effectiveness

Twenty publications of 15 studies met the inclusion criteria for the systematic review and all versions of ImmunoCAP ISAC were included. No studies including Microtest were identified. 8 Studies assessed the diagnostic accuracy of ImmunoCAP, 1 study assessed the effects on clinical diagnosis, 1 study assessed the effects on clinical diagnosis and specific immunotherapy prescription, 4 studies assessed the effect on patient management and 1 study investigated the levels of IgE before and after specific immunotherapy. Two studies were identified that reported sensitisation rates to various allergens as determined by ImmunoCAP ISAC but these did not meet the inclusion criteria of the systematic review.

- All of the studies were considered 'high' or 'unclear' risk of bias
- A meta-analysis of the studies was not possible
- None of the studies reported clinical outcomes
- The diagnostic performance varied considerably between studies but in general, individual components had low sensitivities and high specificities
- The evidence suggests that ImmunoCAP ISAC could be used to discriminate cross-immunoreactive allergen components.

- The evidence suggests that ImmunoCAP ISAC can identify sensitisations but they may not all be clinically relevant
- The evidence suggests that ImmunoCAP ISAC testing may influence a clinician's management decision with regards to recommendations on restriction diets and specific immunotherapy prescriptions. However no data were found for the clinical consequences of these changes in management.

Cost effectiveness

All 4 studies in the systematic review were reported as abstracts and showed that ImmunoCAP ISAC had increased effectiveness and was cost saving; however, the methods, assumptions and strategies used in the studies were unclear and many inputs to the models were based on expert opinion so the findings should be interpreted with caution.

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 utility values could be taken from a number of European studies. One study reported utility values for atopic eczema in children and one study reported the degree of severity of allergic conditions. Utility values for complications of allergies, such as anaphylactic shock, could not be found in the literature.

Data on the probability of an allergic reaction, probability of remission, the probability of dying and the long term consequences of multiplex allergen testing was not found.

As a result of the lack of data on the clinical effectiveness of multiplex allergen testing, a long term economic model could not be developed. A concept model structure that could potentially be used to assess the cost-effectiveness of multiplex allergen testing was described. This model compares testing and current clinical practice with current clinical practice alone for people with difficult to manage allergic disease in secondary or tertiary care settings. The

place of multiplex allergen testing in the diagnostic pathway and the proportion of people receiving a particular test are unclear because of lack of data.

Cost analyses were performed to estimate the short-term cost of diagnostic pathways with and without multiplex allergen testing. A 2-way threshold analysis assessed the minimal reduction (i.e. threshold) in proportions of single specific IgE and oral food challenge tests needed for the most expensive test strategy to become cheaper than the alternative test strategy, assuming that everything else remains equal. The base case results indicated that:

- if multiplex testing replaced single specific IgE testing (assuming 8 tests per person) then a 15% or 4% reduction in oral food challenge would be needed for ImmunoCAP ISAC and Microtest, respectively.
- if there is no reduction in the proportion of single specific IgE tests (assuming an average of 8 per person), the reduction in oral food challenge tests would need to be at least 39% and 28% for ImmunoCAP ISAC and Microtest, respectively.

Scenario analysis showed that the inputs that caused the greatest effect on the results were the assumed number of allergens tested by single specific IgE testing and the cost of an oral food challenge test.

4 Issues for consideration

Clinical effectiveness

The results of the limited number of available studies provide some indication that the addition of multiplex allergen testing (ImmunoCAP ISAC) to standard diagnostic work-up can change the clinicians' views on the diagnosis, management and treatment of people with allergy; no data were available for Microtest. No studies were identified which compare the management of people based on standard diagnostic work-up to management based on standard diagnostic work-up with the addition of multiplex allergen testing and

which reported information on subsequent clinical outcomes. No studies of multiplex allergen testing using Microtest were identified that met the inclusion criteria for this assessment.

The quality assessment of the included studies suggested that the majority of the included studies had an unclear risk of bias because of poor reporting. 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 healthcare settings). Studies which 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 people) were classified as having 'high' concerns regarding applicability. Studies which 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.

There was some indication that the use of ImmunoCAP ISAC testing may guide decisions on the discontinuation of restrictive diets, the content of specific immunotherapy prescriptions, and whether or not people should receive specific immunotherapy. However, importantly, none of the studies that were 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 which 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 un-diagnosed people (Heaps et al. 2014). 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.

The diagnostic performance of ImmunoCAP ISAC in comparison to other tests (single specific IgE and skin prick test) varied considerably between studies, according to the allergens investigated and the way in which ISAC testing was applied. The majority of studies compared the accuracy of testing whole allergens by single specific IgE or skin prick test versus testing allergen components using ImmunoCAP ISAC. The studies only looked at populations in whom there was a clinical suspicion of a specific allergy, for example, in people with suspected cows milk allergy, only cows milk allergens were looked at. In people with difficult to manage allergic disease, their diagnosis is more uncertain, and interpretation of results multiplex allergen testing is more complex. This could lead to greater numbers of false positives.

Overall only one of the diagnostic studies compared the ability of single specific IgE testing and ImmunoCAP ISAC to detect specific antibodies to the same component (rGLy m4). . The two testing methods reported different sensitivities and specificities suggesting that they perform differently. In general, individual ISAC components tended to have high specificity, but low sensitivity relative to whole allergen single specific IgE tests or skin prick test, for the prediction of allergic response. The relatively low sensitivities of individual ISAC components are likely to be indicative of the proportions of people 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 specific 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 which are structurally similar and are recognised by the

same IgE antibody (cross-immunoreactive) may represent clinically useful additional information. Therefore, if the focussed use of groups of ISAC components can achieve equivalent sensitivity and specificity to that of single specific IgE testing, ISAC testing may be preferred.

As none of the included studies investigated the clinical effects of adding multiplex allergen testing to the investigation of people with difficult to manage allergies, the clinical consequences of changes to diagnosis or treatment, and the frequency and relevance of clinically false-positive sensitisations is not known. As a result there was also no evidence on the long term outcomes of the addition of multiplex testing, such as incidence and severity of allergic reactions, mortality, adverse reactions and service use.

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.

All 4 identified cost-effectiveness studies (all abstracts) showed an increased effectiveness when using ImmunoCAP ISAC and three out of four studies also showed cost-savings when using ImmunoCAP ISAC. However, the method, assumptions and strategies investigated 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, inaccessible references, or no references were provided. In addition, 2 assessments focused on the same population, both using a Markov model with a five year time horizon, but the reported QALYs and outcomes differed substantially. Therefore, these findings should be interpreted with extreme caution.

The place of multiplex allergen testing in the diagnostic pathway and the proportions of people receiving a particular test is unclear (for both the current diagnostic pathway and the diagnostic pathway including multiplex allergen testing). The most cost-effective position for multiplex testing in the diagnostic pathway could not be modelled due to insufficient data to inform the model.

The evidence on utility values for allergic conditions in the UK population was limited. For food allergies no utility values were found while 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 skin prick test, single specific IgE and the food challenge test these were £62.29, £136.37 and £570.00. 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 people receiving a particular test are unclear different scenario and threshold analyses were performed. The results of these analyses depend on the effect of multiplex testing on the need for single specific IgE, skin prick test and oral food challenge testing. For example, if multiplex testing replaced single specific IgE testing (assuming 8 tests per person) then a 15% or 4% reduction in oral food challenge would be required for ImmunoCAP ISAC and Microtest respectively to be cost saving. However, if there was no reduction in single specific IgE testing then the number of oral food challenge tests per patient that needed replacing would have to be at least 39% or 28% for ImmunoCAP ISAC and Microtest respectively to be cost saving.

5 Equality considerations

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

There is wide variation in access to allergy specialists and allergy care, including challenge testing, across the UK. There is a reported rise in the incidence of allergies in children.

6 Implementation

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

7 Authors

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October 2015

Appendix A: Sources of evidence considered in the preparation of the overview

- A. The diagnostics assessment report for this assessment was prepared by Kleijnen Systematic Reviews Ltd.

Westwood ME, Ramaekers BLT, Lang SH, Armstrong N, Noake C, de Kock S, Joore MA, Severens JL, Kleijnen J. ImmunoCAP ISAC and Microtest for multiplex allergen testing in people with difficult to manage allergic disease: A systematic review and cost-effectiveness analysis. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd, 2015.

- B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- Thermo Fisher Scientific
- Microtest Dx

Other commercial organisations:

- None

Professional groups and patient/carer groups:

- Royal College of Pathologists
- Royal College of Physicians
- Royal college of Nursing
- UK NEQAS for Immunology, Immunochemistry and Allergy
- British Society for Allergy and Clinical Immunology
- The Anaphylaxis Campaign

Research groups:

- None

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Allergen is a substance that causes an allergic reaction

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

Cross-immunoreactive is when an antibody interacts or binds with more than one antigen

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

Homologous allergens are allergen molecules with very similar molecular structures.

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

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

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

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

Polysensitisation usually refers to sensitisation to two or more allergen sources

Sensitisation is the process of producing a specific IgE antibody from exposure to a specific allergen.

Single specific IgE testing is used to measure IgE antibodies against allergenic molecules. This involves testing a single allergenic molecule at one time and allows the clinician to select the individual allergenic molecules to be tested based on the clinical history. More than 650 allergenic molecules are available for testing.