NICE National Institute for Health and Care Excellence

NICE guidance

ImmunoCAP ISAC 112 for multiplex allergen testing

Diagnostics guidance
Published: 18 May 2016

www.nice.org.uk/guidance/dg24

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 There is currently insufficient evidence to recommend the routine adoption of multiplex allergen testing with ImmunoCAP ISAC 112 to help diagnose allergy and predict the risk of an allergic reaction in people with allergy that is difficult to diagnose, when used with standard clinical assessment. **[2020]**

1.2 The ImmunoCAP ISAC 112 shows promise and further research is recommended on the clinical effectiveness of using it in people with allergy that is difficult to diagnose (see section 6.1).

1.3 An allergy healthcare professional with appropriate expertise is needed to ensure the results of multiplex allergen tests are interpreted correctly.

2 Clinical need and practice

The problem addressed

2.1 The risk of an allergic reaction to an allergen varies between people. Multiplex allergen testing allows a clinician to test for multiple allergens at the same time and may help to determine a person's sensitisation profile. The resulting allergen profile may help clinicians to recognise genuine sensitisation, predict the risk of a local or systemic allergic reaction, help with avoidance advice, and identify allergy-triggering components before starting immunotherapy. Multiplex allergen testing may be most appropriate for helping to diagnose more complex allergy cases, such as those where a trigger cannot be identified based on patient history or with conventional testing (such as in idiopathic anaphylaxis), or where polysensitisation makes it difficult to interpret conventional allergen testing results.

2.2 The purpose of this assessment is to assess the clinical and cost effectiveness of using ImmunoCAP ISAC 112 and Microtest to help diagnose allergy and predict the risk of an allergic reaction in people with allergy that is difficult to diagnose.

The condition

2.3 Allergy is a form of exaggerated sensitivity (hypersensitivity) to a 'foreign' substance, called an allergen, that is either inhaled, swallowed, injected, or comes into contact with the skin, eyes or mucosa. Examples of allergens include: pollen from grass, weeds and trees; proteins excreted by house dust mite; food proteins; and insect venoms. Immunoglobulin E (IgE) is a type of antibody that is normally present in very small amounts in the blood but may be increased in allergy. Exposure to an allergen starts a complex set of cellular events leading to the production of a specific IgE antibody to a specific allergen, but no clinical reaction – a process known as sensitisation. Upon re-exposure, the allergen binds to the specific antibody and the immune system starts

a more aggressive and rapid reaction resulting in an inflammatory response with clinical symptoms. When a person is sensitised to 2 or more allergens (polysensitisation), the cause of allergy can be difficult to diagnose because of cross-reactivity, that is, the immune system reacts to other allergens because they are similar in molecular shape and structure to the causal allergen.

2.4 Hypersensitivity reactions are divided into 2 categories: IgE-mediated reactions and non-IgE-mediated reactions. IgE-mediated reactions are usually rapid in onset, and cause symptoms ranging from mild to moderate reactions (such as hives), to severe systemic reactions (anaphylaxis). Non-IgE-mediated reactions are less well understood and are mediated by other parts of the immune system. They usually have a delayed onset, and can happen up to 72 hours after exposure to an allergen.

2.5 In severe cases of allergy, a person may have anaphylaxis: an acute, potentially fatal, multi-organ system, allergic reaction. It is characterised by rapidly developing life-threatening airway, breathing and circulation problems. Certain foods, insect venoms, drugs and latex are common causes of IgE-mediated allergic anaphylaxis. Co-factors such as exercise can also contribute to triggering an anaphylactic event. Food is a very common trigger in children, whereas medicines are much more common triggers in adults. If the cause of anaphylaxis cannot be identified, this is known as idiopathic anaphylaxis.

2.6 Multiple and complex allergies are becoming more common (Allergy UK). In 2008, it was estimated that 16.1% of children in the UK have 2 diagnosed allergies and 2.5% have 3 diagnosed allergies (Punekar and Sheikh 2009). Often these are eczema, asthma and rhinitis. The younger the child is when the first allergic condition appears, the more likely they are to develop multiple allergic conditions (the Parliamentary Office of Science and Technology 2014). Food allergy, one of the most common allergic disorders and a major paediatric health problem in western countries, may be confused with food intolerance. NICE's guideline on food allergy in under 19s notes that only 25–40% of self-reported food allergy is confirmed as true clinical food allergy by an oral food challenge.

2.7 The frequency of anaphylaxis from all causes in the UK is unknown, and because people with anaphylaxis present mainly in emergency departments and outpatient settings, few estimates of prevalence are available from NHS sources. Anaphylaxis may not be recorded, or may be misdiagnosed as another condition, for example, asthma. One study in the UK suggested that about 1 in 1,333 people in England have had anaphylaxis (Stewart and Ewan 1996). About 20 deaths from anaphylaxis are reported each year in the UK (Pumphrey 2000).

The diagnostic and care pathways

Diagnosis

2.8 The first step if an allergy is suspected should be an allergy-focused clinical history. Getting a clinical history and asking specific allergy-focused questions is extremely important for diagnosis. NICE's guideline on food allergy in under 19s states that this can be done by GPs or other primary healthcare professionals with the appropriate competencies, and indicates what should be included when taking a clinical history.

2.9 The Royal College of Paediatrics and Child Health's Allergy Care Pathways Project includes a set of specific questions for taking an allergy-focused clinical history. It recommends several questions grouped into themes. The first set contains 3 screening questions used to identify a person who might need more detailed allergy questioning. If allergy is suspected, a further set of questions is recommended. If the expertise needed to take an allergy-focused clinical history is not available in primary care, a referral to secondary care is recommended. Further history taking is presented across 6 areas; questioning will partly depend on the responses of the child, young person, or parent or carer.

2.10 NICE's guideline on atopic eczema in under 12s recommends that healthcare professionals should try to identify potential triggers during clinical assessment, including irritants, skin infections, contact allergens and inhalant allergens. The guideline also provides guidance on considering a diagnosis of food or inhalant allergy, or allergic contact

dermatitis in children with atopic eczema.

2.11 Based on the results of the allergy-focused clinical history, if IgE-mediated allergy is suspected, NICE's guideline on food allergy in under 19s recommends that the child or young person should be offered a skin prick test or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens. It recommends that these tests should only be carried out by healthcare professionals with the appropriate competencies to select, perform and interpret the results and should only be done where there are facilities to deal with an anaphylactic reaction. The choice between a skin prick test and a specific IgE-antibody blood test should be based on:

- the results of the allergy-focused clinical history
- whether the test is suitable for, safe for and acceptable to the child or young person and
- the available competencies of the healthcare professionals doing the test and interpreting the results.

  It is recommended that information from the allergy-focused clinical history is used to interpret the results of the tests.

2.12 An allergen challenge or provocation test is done by giving a person a suspected allergen to see if they react to it. This is considered the gold standard in allergy diagnosis because it shows a clinical response to the allergen. Oral food challenges are done either because a diagnosis of food allergy is not supported by the clinical history or there is a discrepancy between history and test results. NICE's guideline on food allergy in under 19s states that information should be given to the child or young person and their parent or carer on when, where and how an oral food challenge or food reintroduction procedure may be done. However, they should not be done in primary care, and should only be done in a setting that is fully equipped for emergency treatment if anaphylaxis occurs.

Management and treatment

2.13 Management depends on the type and severity of the allergy. Mild allergies can be managed in primary care, more severe allergies and more complex allergies may need additional management and referral to specialist services. NICE's guideline on food allergy in under 19s gives guidance on when to refer to secondary or specialist care. NICE's guideline on atopic eczema in under 12s and NICE's quality standard on atopic eczema in under 12s recommend that children with a suspected food allergy should be referred for specialist investigation and management by a paediatric allergist or paediatric dermatologist.

2.14 Mild allergies can be treated using over-the-counter medications such as antihistamines and simple avoidance of the allergen. NICE's guideline on food allergy in under 19s recommends that once an allergy is suspected based on clinical history, information and support should be given, particularly on eliminating the food from their diet.

2.15 NICE's guideline on anaphylaxis recommends that after emergency treatment for suspected anaphylaxis, people should be offered an appropriate adrenaline injector as an interim measure before the specialist allergy service appointment.

2.16 NICE's guideline on atopic eczema in under 12s recommends that healthcare professionals should use a stepped approach for managing atopic eczema in children and should adapt the treatment to the severity of the atopic eczema.

2.17 Some people may need allergen-specific immunotherapy, in which allergen extracts are repeatedly given subcutaneously or sublingually for desensitisation so that the response to the allergen decreases. The British Society for Allergy and Clinical Immunology's guidelines on immunotherapy for allergic rhinitis (Walker et al. 2011) recommend that allergy specialists supervise the start and monitoring of all immunotherapy. Immunotherapy should only be given by physicians and nurses with specialist knowledge of allergy and specific immunotherapies.

3 The diagnostic tests

The interventions

ImmunoCAP ISAC

3.1 The ImmunoCAP Immuno-Solid phase Allergy Chip (ISAC) is a CE-marked molecular diagnostic test that can test for IgE antibodies to 112 components from 51 allergen sources at the same time. It is a miniaturised immunoassay platform that uses a single sample (30 microlitres) of serum, plasma or capillary blood.

3.2 Each slide contains 4 microarrays giving results for 4 samples per slide. ImmunoCAP ISAC is a 2-step assay. IgE antibodies from the patient sample bind to immobilised allergen components spotted in triplets on polymer-coated slides. An enzyme-labelled antibody detects the IgE-allergen complex. The results are measured using a biochip scanner. Confocal laser scanning devices, in particular the CapitalBio LuxScan 10K microarray scanner, are recommended. The results are evaluated using the proprietary Microarray Image Analysis software, which, like the ImmunoCAP ISAC, is also produced by Phadia.

3.3 ImmunoCAP ISAC is a semi-quantitative test and results are reported in ISAC standard units (ISU) indicating specific IgE-antibody levels; the operating range is 0.3–100 ISU-E. This range is about the same as a concentration range of 0.3–100 kilo international units of allergen-specific antibody per unit volume of sample (kUA/litre) of IgE (1 kUA/litre is equal to 2.4 nanograms/ml). The assay takes 4 hours to give a result, including sample processing and incubation time.

Microtest

3.4 Microtest is a CE-marked, in vitro diagnostic test, which uses microarray technology to measure specific antibodies to 22 allergen extracts and 4 allergen components at the same time. It is a miniaturised

immunoassay platform and uses a single sample (100 microlitres) of serum or plasma. IgE antibodies from the patient sample bind to immobilised allergen extracts and components spotted on the Microtest biochip.

3.5 Each slide contains 1 matrix microarray. Up to 5 microarrays can be assayed at the same time on the platform. Microtest is semi-automated and includes a 3-step reaction. The sample is incubated on the slide, during which time the IgE antibodies from the sample bind to the immobilised allergens. An enzyme-labelled antibody detects the IgE-allergen complex and a detection solution is used to develop the fluorescence. Once the chips have been washed and dried, the platform automatically reads and analyses the signal. The fluorescent signal is processed using the Microtest software. The Microtest platform can process up to 5 samples in each run.

3.6 Microtest is a semi-quantitative test and results are calculated in kU/litre (kilo international units of allergen specific antibody per unit volume of sample) and reported in IgE classes (class 0: <0.35 kU/litre; class 1: 0.35–1 kU/litre; class 2: 1.01–15 kU/litre; class 3: >15 kU/litre) giving specific-IgE-antibody levels. The operating range is 0.3–100 kU/litre; 1 kU/litre is equal to 2.4 nanograms/ml. The Microtest procedure is reported to take about 4 hours to give a result.

The comparator

3.7 The comparator for this assessment was current standard clinical assessment, which should always include an allergy-focused clinical history and can additionally involve single specific-IgE testing, skin prick testing, oral-food-challenge testing or a combination of these approaches.

4 Outcomes

The diagnostics advisory committee (section 9) considered evidence from a number of sources (section 10). Full details of all the evidence are in the committee papers.

How outcomes were assessed

4.1 The assessment consisted of a systematic review of the evidence on test performance and clinical-effectiveness data for ImmunoCAP ISAC, Microtest and standard clinical assessment (comparator).

4.2 Different versions of the ImmunoCAP ISAC tests are named according to the number of allergen components tested, indicated by the number at the end of the name. For example, ImmunoCAP ISAC 112, the most recent version, tests for 112 allergen components. All 15 of the studies included in the review evaluated versions of ImmunoCAP ISAC:

- ImmunoCAP ISAC 112: 1 study
- ImmunoCAP ISAC 103: 5 studies
- ImmunoCAP ISAC 96: 1 study
- ImmunoCAP ISAC 89: 1 study
- ImmunoCAP ISAC 51: 1 study
- ImmunoCAP ISAC 50: 1 study
- ImmunoCAP ISAC version unspecified: 5 studies.

4.3 In the included studies, 'standard diagnostic work-up' includes a combination of an allergy-focused clinical history, and single specific-IgE testing, skin prick testing or oral-food-challenge testing. The combination used in each study varies by study setting and design.

4.4 Of the 15 included studies:

- 8 studies compared the diagnostic accuracy of ImmunoCAP ISAC with other testing options (single specific-IgE testing or skin prick testing) to predict clinical reactivity as defined by clinical history, and skin prick test alone or with 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 gained by adding ImmunoCAP ISAC 103 to the standard diagnostic work-up.
- 4 studies assessed the effects on managing the patient's condition by adding ImmunoCAP ISAC to the standard diagnostic work-up.
- 1 study looked at the levels of IgE using ImmunoCAP ISAC before and after specific immunotherapy.

4.5 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 as examples of studies in which positive results do not always link with clinical reactivity.

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

4.7 The external assessment group did not identify any studies that reported clinical outcomes (that is, allergy symptoms, incidence of acute exacerbations, mortality, adverse events of testing and treatment, healthcare presentations or admissions, health-related quality of life, patient anxiety, or patient preferences).

4.8 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).

4.9 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.

Evidence on diagnostic accuracy of ImmunoCAP ISAC

4.10 Of the 8 studies identified, 6 compared the accuracy of ImmunoCAP ISAC with commonly used diagnostic tests (skin prick tests 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.

Diagnosis of food allergy

4.11 De Swert et al. (2012) investigated soy flour allergy. The diagnostic accuracy of an unknown ImmunoCAP ISAC version to measure the soy flour component rGly m 4 was compared with the single specific-IgE test for the same component and with 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. ImmunoCAP ISAC had the highest sensitivity (86%; 95% confidence interval [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%).

4.12 Alessandri et al. (2011) investigated allergy to boiled or raw egg. The diagnostic accuracy of ISAC 103, when used to measure 3 individual egg components (Gal d 1, Gal d 2 or Gal d 3), was compared with the accuracy of single specific-IgE tests (egg yolk or egg white) and compared with the accuracy of skin prick tests (egg white extract, raw egg white, boiled egg white, egg yolk extract, raw egg yolk and boiled egg yolk). Cut-off values were reported separately for each test and

oral-food-challenge testing was used as the reference standard. The skin prick test had the highest sensitivity for prediction of allergic response to raw egg white (88%; 95% CI 71.8% to 96.6%), whereas Gal d 3 measured using ImmunoCAP 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 tests worked the same as a skin prick test, (both measured whole extracts), whereas ImmunoCAP ISAC 103 gave much more variable results for the 3 different components measured. No measure of the overall diagnostic performance of ImmunoCAP ISAC 103 (all components combined) was reported.

4.13 D'Urbano et al. (2010) compared the accuracy of ImmunoCAP ISAC 89, used to measure 2 individual components (Gal d 1 or Bos d 8), with 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 ImmunoCAP ISAC 89 components and for cow's milk and egg white single specific-IgE tests. Sensitivity values were higher for ISAC 89 components (78% for Bos d 8 and 73% for Gal d 1) 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 ImmunoCAP ISAC 89 were used in series (that is, ImmunoCAP ISAC 89 results were only considered in people with single specific-IgE negative results), the combined sensitivity was greater than that for single specific-IgE tests 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. (2008) compared the accuracy of ImmunoCAP ISAC 51, used to measure 8 individual components (alpha casein, beta casein, kappa casein, Bos d 4, Bos d 5, Gal d 1, Gal d 2, Gal d 4) with the accuracy of single specific-IgE tests (hen's egg or cow's milk extract) and with 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 highly variable between tests. The skin prick test had the highest sensitivity for cow's milk allergy (93.6%; 95% CI 78.5% to 99%). The ImmunoCAP ISAC 51 components all had low sensitivity for cow's milk allergy (ranging from 23.9% to 50% for the 5 components assessed). Conversely, all 5 ImmunoCAP ISAC 51

components had high specificity for cow's milk allergy (ranging from 88.4% to 97.7%), whereas the skin prick test had low specificity (48.2%; 95% CI 28.7% to 68%). Single specific-IgE testing had the highest sensitivity for hen's egg allergy (71.1%; 95% CI 55.7% to 83.6%). All 3 ImmunoCAP 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 ImmunoCAP ISAC 51 components were 100% for Gal d 4, 86.7% for Gal d 1 and 80% for Gal d 2). Single specific-IgE testing and skin prick testing had comparable specificity (86.7% and 100% respectively). No measure of the overall diagnostic performance of ImmunoCAP ISAC 51 (all relevant components combined) was reported for either cow's milk or hen's egg allergy.

4.14 Sokolova et al. (2009) investigated milk allergy. The diagnostic accuracy of an unknown ISAC version, used to measure 9 individual components (Bos d 4, Bos d 6, Bos d 7, Bos d 8, casein alpha-S1, casein beta and casein kappa, Bos d lactoferrin, Bos d 5.0101), was compared with the accuracy of single specific-IgE tests for 4 allergens (whole milk, alpha-lactalbumin, beta-lactoglobulin and casein). For both methods, a positive result was defined as positive for at least 1 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 ImmunoCAP ISAC testing and combined single specific-IgE testing had 100% sensitivity, but ImmunoCAP 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%).

4.15 Albarini et al. 2013 investigated hazelnut allergy. The diagnostic accuracy of an unknown ImmunoCAP ISAC version, used to measure 4 individual components (Cor a 1 1010, Cor a 1 0401, Cor a 8, Cor a 9), was compared with the accuracy of single specific-IgE tests (hazelnut) and with skin prick testing. Cut-off values were not reported for the ImmunoCAP 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, whereas the ImmunoCAP ISAC components generally had low sensitivity (ranging from 6.3% to 56.3%). However, the ImmunoCAP 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

4.16 Wohrl et al. (2006) investigated 5 different aeroallergens (house dust mite, cat dander, birch pollen, grass pollen and mugwort pollen). The diagnostic accuracy of ImmunoCAP ISAC 50, used to measure the presence of 1 or more aeroallergens (up to 5), was compared with the accuracy of single specific-IgE tests of whole allergens. When multiple ImmunoCAP ISAC components were assessed, a positive result was defined as positive for at least 1 component. The cut-offs for each test were not reported. Skin prick testing was used as the reference standard. The specificity of ImmunoCAP 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, except for mugwort pollen, was comparable with the specificity estimate for the corresponding whole allergen single specific-IgE test for all aeroallergens investigated. The sensitivity of ImmunoCAP 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 ImmunoCAP ISAC 50 components were not reported.

4.17 Cabrera-Freitag et al. (2011) investigated 2 different pollens (grass pollen or *P. pratense* and cypress pollen or *C. arizonica*). Two cut-off points (recommended by the companies and ROC optimised) were reported for each test; skin prick test was used as the reference standard. The diagnostic accuracy of ImmunoCAP ISAC 103, when used to measure the 8 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 with the accuracy of a single specific-IgE test to measure *P. pratense*; a positive result was defined as positive for at least 1 component. The sensitivity and specificity for ImmunoCAP ISAC 103 and the single specific-IgE test were similar, whatever the cut-off point used. Sensitivity and specificity estimates for individual grass pollen ImmunoCAP ISAC 103 components were not reported. The accuracy of ImmunoCAP ISAC 103 was also used to measure the presence of a single component for cypress pollen (nCup a 1) compared with the accuracy of single specific-IgE tests to measure *C. arizonica*. The sensitivity estimates for the 2 tests were equal

at both cut-offs (91.7%), but specificity was higher for ImmunoCAP 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

4.18 Heaps et al. (2014) investigated 110 people with a diagnosis of idiopathic anaphylaxis (based on clinical assessment, skin prick test, single specific-IgE testing and mast cell tryptase), from 5 UK specialist allergy centres. Study participants were re-assessed using ImmunoCAP ISAC 103 and clinicians were asked to score the additional information provided. Information from 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%) participants, but in these 22 people, 168 sensitisations that were not thought to be associated with anaphylaxis were also identified. Also, for a further 35 (32%) participants, the information from ImmunoCAP ISAC was thought to have only identified additional sensitisations that were not thought to be associated with anaphylaxis (322 in total).

Evidence on clinical diagnosis and management using ImmunoCAP ISAC

4.19 Passalacqua et al. (2013) investigated 318 consecutive people with polysensitised (at least 2 positive skin prick tests) respiratory allergy in 6 allergy units in Italy. Participants first gave a clinical history, and had skin prick testing and single specific-IgE testing (including mites, grass, olive, parietaria, birch, cypress, ragweed, mugwort, cat and dog dander, alternaria and aspergillus), and were then assessed using ImmunoCAP ISAC 103 (no details reported of components assessed or interpretation, but cross-immunoreactive allergens were considered). Clinicians were asked to review their diagnosis or treatment based on the ImmunoCAP ISAC 103 results and to judge the value of any additional information gained from the test. New information was classified as 'remarkable' if it could not be obtained using standard diagnostic work-up and could

affect the accuracy of diagnosis or the specific immunotherapy prescription. The authors reported that new information related to managing the patient's condition was classified as 'remarkable' for 299 (95%) participants and 'to some extent' (not defined) in 232 (73%) patients. Details of the new information were not reported.

4.20 Passalacqua et al. (2013) also reported detailed information on changes to diagnostic category using 5 classifications when ImmunoCAP ISAC 103 testing was used. The number of people classified as:

- polysensitised with only 1 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
- non-classifiable decreased from 8 to 0.

4.21 Passalacqua et al. (2013) also reported changes in specific immunotherapy prescriptions. Eighty-five people with respiratory allergy, who would not have had specific immunotherapy based on a standard diagnostic work-up (skin prick test or single specific-IgE test), were given a new prescription for specific immunotherapy after testing with ImmunoCAP ISAC 103. The existing specific immunotherapy prescription was also changed in a further 3 people with respiratory allergy, after ImmunoCAP ISAC 103 testing. No details of the specific immunotherapy prescriptions or any subsequent clinical outcomes were reported.

Evidence on management using ImmunoCAP ISAC

Discontinuation of restrictive diets

4.22 Two studies investigated using ImmunoCAP ISAC to guide discontinuation of restrictive diets in children with food allergies (Hermansson et al. 2014; Noimark et al. 2014). Both studies were only

reported as conference abstracts and so gave only limited study details and results.

4.23 Hermansson et al. (2014) used a database to identify 199 schoolchildren in Harkatie, Finland, having special diets in school catering. The details of this study are confidential at the time of writing this document. No information on clinical outcomes after changes to dietary management was reported.

4.24 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 testing with or without single specific-IgE testing, and an unspecified version of ImmunoCAP ISAC. The authors reported that ImmunoCAP ISAC testing helped with potential food reintroductions (peanut n=4; soy n=2; wheat n=4), in addition to those indicated by single specific-IgE testing alone; the numbers of potential reintroductions based on standard diagnostic work-up (skin prick testing with or without single specific-IgE testing) were not reported. No details were given on which single specific-IgE tests or skin prick tests were done or which ISAC components were assessed. The number of food reintroductions that happened after testing, or clinical outcomes after any changes to dietary management were not reported.

Value of additional information

4.25 Luengo et al. (2010) did ImmunoCAP ISAC 103 testing in 55 people who had well-characterised, poly-sensitisation (as assessed by skin prick test and single specific-IgE tests) with various allergies; no details were given on which ImmunoCAP ISAC components were assessed or how these were interpreted. Participating clinicians judged that ImmunoCAP ISAC 103 gave useful new information for managing the condition in 50 (91%) participants. The added value was the ability of ImmunoCAP ISAC to differentiate between protein homologues and so help in differentiating allergens that were cross-immunoreactive from those responsible for sensitisation. The clinicians considered that it would have been useful to do ImmunoCAP ISAC 103 testing before skin prick testing in 34 (62%) patients, because several protein homologues can be

investigated at once using ImmunoCAP ISAC.

Changes in specific immunotherapy prescriptions

4.26 Sastre et al. (2012) investigated 141 people with respiratory allergy (with or without associated food allergy) in 1 allergy outpatient clinic in Spain. Clinicians first assessed the indications for giving patients specific immunotherapy (Olea e, Platanus a, Cupressus a, grass mix, Cynodon d, Phragmites c, Artemisia v, Salsola k and Plantago l) based on clinical history and skin prick test, blind to the results of ImmunoCAP 96 testing (Ole e 1, Cup s 1, Cry j 1, Pla a 1, Pla a 2, Phl p 1, Phl p 5, Phl p 4, Phl p 6, rPhl p 11, Phl p 12, Cyn d 1, Sal k 1, Aln g 1, Bet v 1, Cor a 1.0101, Amb a 1, Art v1, Art v 3 and Par j 2). Clinicians then re-assessed specific immunotherapy indications based on standard diagnostic work-up and ImmunoCAP ISAC 96 results. There were disagreements between the prescription based on standard diagnostic work-up and that based on all information, including ImmunoCAP ISAC, for 79 (54%) of study participants. No details were reported on which specific immunotherapy prescriptions were actually used, or any subsequent clinical outcomes.

Evidence on assessment of IgE levels before and after specific immunotherapy

4.27 Gay-Crosier et al. (2010) assessed the relationship between change in IgE levels, measured by single specific-IgE testing, and change in IgE levels, measured by an unspecified version of ImmunoCAP ISAC, before and after a 3-year course of specific immunotherapy, and the clinicians' evaluation of the benefit of specific immunotherapy. This study included only 9 participants who had a total of 31 courses of specific immunotherapy (no details of diagnosis were reported). The location of this study is not reported. The median specific-IgE levels, measured by an unknown ImmunoCAP ISAC version, 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 clinicians' judgements of the clinical benefit of specific immunotherapy (Spearman r=0.46; p=0.02). 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

4.28 Two studies, done in Spain, which did not meet the original inclusion criteria for the systematic review, looked at sensitisation rates to various plant food allergens in people with and without previous allergy symptoms. They have been included because they give examples of studies with positive results that do not always link with clinical reactivity

4.29 Pedrosa et al. (2012) assessed 123 children with food allergy, of whom 55 were classified as having peanut allergy and 68 as tolerating peanuts (skin prick test and single specific-IgE test), and used ImmunoCAP ISAC 103 to assess sensitisation to a range of allergenic components. There were no significant differences between children with peanut allergy and those who could tolerate peanuts in the rates of sensitisation to pathogenesis-related protein family PR-10 allergens (Ara h 8, Act d 8, Cor a 1, Gly m 4, 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 (Par j 2, Pru p 3), cross-reactive carbohydrate determinate Ana c 2, or pollens (Ole e 1, Phl p 1).

4.30 The study by Pascal et al. (2015), reported in a pre-publication manuscript at the time of guidance development, included 130 children with plant-food allergy and lipid transfer protein sensitisation. They found that sensitisation to a particular plant-food lipid-transfer protein, identified with ImmunoCAP ISAC 112, was not always associated with clinical symptoms of allergy to that plant food: 69% (40/58) and 63% (17/27) of children who could tolerate peach and walnut were sensitised to Pru p 3 and Jug r 3 respectively; 60% (21/35) of children without seed or nut allergy were sensitised to storage proteins.

Costs and cost effectiveness

4.31 The external assessment group searched for existing studies on the cost effectiveness of ImmunoCAP ISAC and Microtest, in combination with

standard clinical assessment, to help diagnose allergy and predict the grade of allergic reaction. A de novo economic model could not be developed because of the lack of clinical-effectiveness data.

Systematic review of cost-effectiveness evidence

4.32 Nine publications from 4 studies were considered eligible for inclusion in the systematic review. All included studies were only reported as conference abstracts, so the methods and assumptions used were largely unclear. Essential inputs to the models in the studies were based on expert opinion or inaccessible references, or no references were reported.

4.33 Hermansson et al. (2014; 2 publications) considered the cost effectiveness of using ImmunoCAP ISAC with standard diagnostic work-up compared with standard diagnostic work-up alone, for Finnish school children on a restricted diet because of suspected food allergy (community setting). Data from 24 children drawn from a larger database (including a total of 2,317 school children) were analysed. The results showed an unnecessary restricted diet for 63% of the children, resulting in a cost per avoided unnecessary diet of €480 for ImmunoCAP ISAC compared with standard diagnostic work-up alone.

4.34 Another study by Hermansson and colleagues (Hermansson et al. 2012; Hermansson et al. 2013) examined the cost effectiveness of an unknown ImmunoCAP ISAC version 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 showed that ImmunoCAP ISAC testing was least expensive whereas skin prick testing was most expensive for all 3 countries. ImmunoCAP ISAC was also most effective, leading to 3.97 quality-adjusted life years (QALYs) gained, whereas the DBPCFC strategy was least effective (2.54 QALYs). So, ImmunoCAP ISAC dominated both the skin prick test and DBPCFC strategies.

4.35 Glaumann et al. (2013) examined the cost effectiveness of ImmunoCAP ISAC compared with DBPCFC, open (non-blinded) oral food challenge and skin prick test for children with suspected peanut allergy in Sweden. A Markov model with a 5-year time horizon was developed, and included non-allergic and allergic health states, and mild and severe allergic reactions were modelled as events. The results showed that ImmunoCAP ISAC is least expensive whereas skin prick test is most expensive. ImmunoCAP ISAC was also found to be most effective (4.34 QALYs) whereas the oral-food-challenge strategy was considered least effective (2.23 QALYs). So ImmunoCAP ISAC dominated all 3 alternative strategies.

4.36 Mascialino et al. (2013; 2 publications) and Hermansson et al. (2012) examined the cost effectiveness of an unknown ImmunoCAP ISAC version with skin prick test compared with a skin prick test alone for Spanish people sensitised to pollen in a complex pollen area. The analysis was based on a Markov model with a 9-year time horizon, and an assumption that people on specific immunotherapy continue the treatment for 3 years and stay healthy for the following 6 years, or stop specific immunotherapy and move to symptom-management treatment until year 9. A dataset from 141 people, with allergic rhinoconjunctivitis with or without asthma, sensitised to pollen was analysed. The results showed that adding ImmunoCAP ISAC to a skin prick test reduces specific immunotherapy prescriptions and so results in cost savings compared with skin prick test only (€2,538 compared with €2,608). ImmunoCAP ISAC with a skin prick test was also more effective (7.03 QALYs) compared with skin prick test only (6.88 QALYs). So ImmunoCAP ISAC with skin prick test dominated skin prick test only.

4.37 The study by Rogriguez-Ferran et al. (2011), reported in a conference abstract, was originally excluded from the review because it did not include effectiveness outcomes, but a description is included for completeness. The study considered the costs of skin prick testing, Phadiatop and ImmunoCAP Rapid used for screening for 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

4.38 Because of the lack of data on the clinical consequences of adding multiplex allergen testing to current clinical practice, the external assessment group developed a long-term cost-effectiveness model, explored current and potential diagnostic pathways, and built a concept model structure instead of a de novo economic model.

Current and potential diagnostic pathways

4.39 Current clinical diagnostic pathways for people referred for specialist allergy investigation in secondary or tertiary care settings may include skin prick testing, single specific-IgE testing and an oral-food-challenge test if needed, combined with clinical history. A skin prick test is often the first investigation in allergy diagnostics. Based on consultations with clinical experts, it was assumed that single specific-IgE testing would be done if skin prick test results are not consistent with the clinical history of a patient. Inconsistency can happen 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. An oral-food-challenge test may also be needed to confirm or rule out allergy to a specific food-related allergen or allergens. If a skin prick test is not acceptable or practical (for example, in children with atopic eczema), single specific-IgE testing might be the first-line investigation, using confirmatory oral-food-challenge testing or skin prick testing as needed. It might also be possible to do an oral food challenge based on a skin prick test (and patient history) alone. The exact sequence of testing in clinical practice in secondary or tertiary care settings in the UK is unclear.

4.40 When considering people with difficult-to-diagnose allergic disease who have been referred for assessment in secondary or tertiary care settings, multiplex allergen testing may be chosen as a further diagnostic test (assuming that all the allergens of interest are included). Its role would be to identify the allergens to which a patient is sensitive. The possible advantage of the multiplex testing is that it can test for homologous and cross-sensitive proteins at the same time and so can help the clinician to decide which confirmatory tests are needed. For example, if the test is

negative for particular proteins this might rule out the need for oral food challenge, but it is also possible that a negative test with an unclear clinical history might result in a decision to also do an oral-food-challenge test. In the proposed pathway, it is unclear if single specific-IgE testing will always be done before multiplex allergen testing (if single specific-IgE testing is applicable) or if multiplex allergen testing may also be done instead of single specific-IgE testing. 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, so reducing the need for an oral food challenge.

Concept model structure

4.41 This section describes a model structure that could 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
- standard clinical assessment.

4.42 The health economic model would possibly consist of a decision tree and a state-transition (Markov) model. The decision tree could 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)'. Potential adverse events of testing can be also considered in the decision tree.

4.43 The long-term consequences in costs and QALYs could be estimated using a state-transition cohort model with a lifetime time horizon. The first health state in the state-transition model would be determined by the short-term outcome from the decision tree. The following health states were included in the state-transition model:

- at risk of allergic reaction
- not at risk of allergic reaction or remission
- allergic reaction (experienced during cycle)
- death.

4.44 Different types and severities of allergic reactions could 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 compared with an ingested allergen.

Model inputs

4.45 To inform the decision tree for the diagnostic pathway, data on the following parameters would be needed, but were not available for the assessment:

- proportion of people who have a particular test (that is, a skin prick test, single specific-IgE test, multiplex allergen test with or without oral-food-challenge test) as well as the number of skin prick tests with or without single specific-IgE tests per patient
- accuracy of the diagnostic pathways (that is, proportion of true positives, false positives, false negatives and true negatives as a result of the combined diagnostic performance of skin prick testing, single specific-IgE testing or multiplex allergen testing)
- the treatment decision.

4.46 To inform the long-term state-transition model, the following parameters would be needed (all conditional on the test result) but were not available for the assessment:

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

- probability of dying.

Health-state utilities

4.47 The systematic review of health-state utilities found 14 studies reporting health-state utilities for allergic conditions. 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 collected with the HUI Mark III instrument. Three studies used a direct utility elicitation technique. Ten studies reported on 28 populations: 14 with rhinitis, rhinosinusitis, rhinoconjunctivitis or asthma; 11 with eczema; 2 with food allergy; and 1 with mixed allergies except food allergies.

4.48 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, and no utility values for food allergies 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; Currie et al. 2014) could be used. Stephens et al (2004) used standard gamble to get utility values for atopic eczema in UK children. Only Stephens et al. (2004) reported utilities according to the degree of severity of the allergic conditions. Utility values for complications of allergies, such as anaphylactic shock, could not be found in the literature, apart from the assumption by Armstrong et al. (2013) that the impact of anaphylactic shock on quality of life was equal to 0 utility for a maximum duration of 9 days.

Resource use and costs

4.49 To estimate the costs of the individual tests, a detailed cost calculation was done that considered test costs, capital costs (if applicable), service and maintenance costs, and personnel costs for doing and interpreting the tests. For ImmunoCAP ISAC and Microtest testing, minimum and maximum prices were calculated and then averaged. For ImmunoCAP ISAC testing, the main differences between the minimum and maximum prices were due to the difference in time (5–60 minutes) needed to

interpret the test results. This was the same for Microtest testing, but the range was smaller (5–10 minutes). It was also assumed that the sample for Microtest testing would be sent to Microtest Dx where the test would be done (most conservative scenario), whereas ImmunoCAP ISAC testing would be done at the service provider's laboratory. So for ImmunoCAP ISAC testing, capital costs were included whereas it was assumed that these costs for Microtest testing would be included in the test costs. Capital costs were annuitised using a cost discount rate of 3.5%.

4.50 Additional costs that would be considered in a long-term cost-effectiveness analysis might include the costs of specific immunotherapy, health-state costs for being at risk of allergic reaction, health-state costs for having had an allergic reaction, and health-state costs for adverse events associated with testing. These costs are likely to be very specific for the population to be considered. Different types of specific immunotherapy might also be provided within a specific population. So, the specific type(s) of specific immunotherapy prescribed and the specific immunotherapy duration would be needed to calculate these costs.

Base-case results

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

4.52 The cost analyses were carried out using 2-way threshold analyses for single specific-IgE and oral-food-challenge tests in addition to ImmunoCAP ISAC or Microtest because the proportion of people having these tests was unclear. Specifically, in pairwise comparisons of 2 test strategies, the minimal reduction (that is, the threshold) in proportions of single specific-IgE and oral-food-challenge tests that was needed for the most expensive test strategy to become cheaper than the alternative test strategy was identified, assuming that everything else stayed equal. Here, 100% for both tests was defined as all people have 8 single specific-IgE tests on average and all people having on average 1 oral-food-challenge test. So, for example, if it was assumed that using multiplex allergen testing would result in no single specific-IgE testing

then this would imply a 100% reduction in single specific-IgE testing compared with the standard diagnostic pathway. Given that multiplex allergen testing was more costly than single specific-IgE testing, threshold analysis could then show what percentage reduction in oral-food-challenge tests would be needed to give the multiplex allergen diagnostic pathway the same cost as the standard diagnostic pathway. But if it was assumed that there was no reduction in single specific-IgE testing by using multiplex allergen testing, this would result in a different threshold for the percentage reduction in oral-food-challenge tests needed to give the multiplex allergen pathway the same cost as the standard diagnostic pathway.

4.53 The following assumptions were made in the base case:

- Number of allergens by skin prick test per patient: 8.
- Cost of skin prick test per patient: £62.28.
- Number of allergens by single specific-IgE testing per patient: 8.
- Cost of single specific-IgE test per patient: £136.37.
- Cost of oral-food-challenge test: £570.
- Minimum cost per ImmunoCAP ISAC 112 test: £154.41.
- Maximum cost per ImmunoCAP ISAC 112 test: £284.60.
- Minimum cost per Microtest test: £140.37.
- Maximum cost per Microtest test: £173.33.

4.54 It was assumed that everything, except the number of single specific-IgE tests and the number of oral-food-challenge tests, stayed equal for all test strategies (including the proportion of people having any skin prick test). Skin prick testing is considered a simple, safe and quick test (giving results within 15–20 minutes) that is often used as the first-line investigation in allergy diagnostics. ImmunoCAP ISAC is intended to be used with standard clinical assessment.

4.55 The base-case analysis showed that for ImmunoCAP ISAC and Microtest

to be cost saving compared with the standard clinical assessment, the absolute proportion of oral-food-challenge tests should be reduced by at least 15% and 4% respectively (for example, from 50% to 35% or from 50% to 46% respectively) if there was a 100% reduction in single specific-IgE tests (that is, from 100% to 0%). On the other hand, if there was no reduction in the proportion of single specific-IgE tests (assuming an average of 8 tests per person), the reduction in oral-food-challenge tests should be at least 39% and 28% for ImmunoCAP ISAC and Microtest respectively. Also, 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 was 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 having an average of 8 single specific-IgE tests for ImmunoCAP ISAC should be reduced by at least 44%.

Analysis of alternative scenarios

Scenario analysis 1: Assumption on the number of days that the LuxScan 10K reader is used

4.56 The LuxScan 10K reader (scanner recommended for measuring the fluorescence of ImmunoCAP ISAC) might be used for other purposes, so scenario analysis 1 explored the impact of using the reader 253 days per year. This reduced the cost of ImmunoCAP ISAC testing to £201.91 per patient tested, a decrease of £18. At this reduced cost, for ImmunoCAP ISAC testing to be cost saving compared with standard clinical assessment or Microtest testing, the proportion of single specific-IgE and oral-food-challenge tests would need to be as follows:

Compared with standard clinical assessment:

- The proportion of oral-food-challenge tests should be reduced by at least 11% (for example from 50% to 39%) if there was a 100% reduction in single specific-IgE tests.
- The proportion of oral-food-challenge tests should be reduced by at least 35% if there was no reduction in single specific-IgE tests.

Compared with Microtest testing:

- The proportion of oral-food-challenge tests should be reduced by at least 8% if there was no reduction in the proportion of single specific-IgE tests.
- The proportion of single specific-IgE tests should be reduced by at least 33% if there was no reduction in the proportion of oral-food-challenge tests.

Scenario analysis 2: Assumption that Microtest is run at service provider's laboratory

4.57 Microtest testing might be done at the service provider's laboratory instead of at the Microtest Dx laboratory (as assumed in the base-case analysis) so scenario analysis 2 explored the impact of this. The cost of Microtest testing reduces by £7 to £149.37 per patient tested in this scenario. At this reduced cost, for Microtest to be cost saving compared with standard clinical assessment or ImmunoCAP ISAC, the proportion of single specific-IgE tests and oral-food-challenge tests would need to be as follows:

Compared with standard clinical assessment:

- The proportion of oral-food-challenge tests should be reduced by at least 2%, if there was a 100% reduction in single specific-IgE tests.
- The proportion of oral-food-challenge tests should be reduced by at least 26%, if there was a no reduction in single specific-IgE tests.

Compared with ImmunoCAP ISAC:

- The proportion of oral-food-challenge tests should be reduced by at least 15% if there was no reduction in the proportion of single specific-IgE tests.
- The proportion of single specific-IgE tests should be reduced by at least 39% if there was no reduction in the proportion of oral-food-challenge tests.

Scenario analysis 3: Assumption on the number of allergens tested by single specific-IgE testing varies

4.58 The number of allergens that may be tested by single specific-IgE testing is uncertain, so the third scenario analysis explored the impact of varying the number of allergens tested using single specific-IgE testing (base-case value: 8 allergens tested per person). For testing with ImmunoCAP ISAC or Microtest to be cost saving compared with standard clinical assessment or each other, the proportion of single specific-IgE tests and oral-food-challenge tests would need to be as follows:

Assuming 1 allergen being tested:

- For ImmunoCAP ISAC compared with standard clinical assessment, the proportions of oral-food-challenge tests should be reduced by at least 35% if there was a 100% reduction in single specific-IgE tests.
- For Microtest compared with standard clinical assessment, the proportions of oral-food-challenge tests should be reduced by at least 24% if there was a 100% reduction in single specific-IgE tests.
- 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 was a 100% reduction in single specific-IgE tests.

Assuming 20 allergens being tested:

- For ImmunoCAP ISAC compared with standard clinical assessment, the proportion of single specific-IgE tests should be reduced by at least 64% assuming no reduction in oral-food-challenge tests.
- For Microtest compared with standard clinical assessment, the proportion of single specific-IgE tests should be reduced by at least 46% assuming no reduction in oral-food-challenge tests.
- For ImmunoCAP ISAC compared with Microtest, the proportion of single specific-IgE tests for ImmunoCAP ISAC should be reduced by at least 18% if there was no reduction in oral-food-challenge tests.

Scenario analysis 4: Assumption on the cost of oral-food-challenge tests

being £256

4.59 The cost of oral-food-challenge in the NHS in England may be lower than that used in the base-case analysis, so scenario analysis 4 explored the impact of using a lower price of £256 instead of £570. At this reduced cost, for testing with ImmunoCAP ISAC or Microtest to be cost saving compared with standard clinical assessment or each other, the proportion of single specific-IgE tests and oral-food-challenge tests would need to be as follows:

ImmunoCAP ISAC testing compared with standard clinical assessment:

- The proportion of oral-food-challenge tests should be reduced by at least 32% if there was a 100% reduction in single specific-IgE tests.
- The proportion of oral-food-challenge tests should be reduced by at least 86% if there was no reduction in single specific-IgE tests.

Microtest testing compared with standard clinical assessment:

- the proportion of oral-food-challenge tests should be reduced by at least 8% if there was a 100% reduction in single specific-IgE tests.
- the proportion of oral-food-challenge tests should be reduced by at least 61% if there was no reduction in single specific-IgE tests.

ImmunoCAP ISAC testing compared with Microtest testing:

- the proportion of oral-food-challenge tests for ImmunoCAP ISAC should be reduced by at least 24% if there was no reduction in single specific-IgE tests
- the proportion of oral-food-challenge tests for ImmunoCAP ISAC should be reduced by at least 46% if there was no reduction in oral-food-challenge tests.

Threshold analyses

4.60 For the situation in which ImmunoCAP ISAC or Microtest are used as replacements for single specific-IgE testing (rather than as an add-on test), a threshold analysis was done to examine the minimum number of allergens tested with single specific-IgE tests so that single specific-IgE

testing is equally or more expensive than multiplex allergen testing, assuming that everything else stays equal. This analysis was also done for skin prick testing. In these analyses, it was assumed that there was no reduction in oral-food-challenge testing with multiplex allergen testing. For standard clinical assessment to be as expensive as the ImmunoCAP ISAC and Microtest pathways, the minimum number of allergens tested using single specific-IgE 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 respectively to be cost saving. For skin prick testing these numbers were 39 and 27 respectively.

5 Considerations

5.1 The diagnostics advisory committee reviewed the evidence available on the clinical and cost effectiveness of using multiplex allergen testing, in combination with standard clinical assessment, to help diagnose allergy and predict the risk of an allergic reaction in people with allergy that is difficult to diagnose.

5.2 The committee considered the evidence on the 2 different technologies, ImmunoCAP ISAC and Microtest. It noted that 20 publications of 15 studies using ImmunoCAP ISAC met the inclusion criteria for the systematic review and of these, 8 reported diagnostic accuracy but none reported clinical outcomes. No evidence was found for Microtest but the committee noted that this was a new technology so evidence may be available in the future. The committee concluded that there was insufficient evidence to determine the clinical and cost effectiveness of Microtest.

5.3 The committee considered the different versions of the ImmunoCAP ISAC. It noted that evidence on all versions of ImmunoCAP ISAC had been included in the systematic review and that 1 of the 15 studies used the most recent version, ImmunoCAP ISAC 112. The committee heard that all versions were considered because the evidence may provide additional information on current versions and that the versions differed in the number of allergen components that can be detected with the test rather than there being technological differences between the versions. The committee concluded that the different versions are technically comparable but noted that there may be differences in the usability and the clinical and cost effectiveness of the different versions because the more recent versions could detect a higher number of allergen components at the same time.

5.4 The committee considered the quality and generalisability of the studies using ImmunoCAP ISAC included in the systematic review of clinical effectiveness. The committee noted that generally the evidence was of high or unclear risk of bias because there was insufficient detail in the publications. The committee also heard from a clinical expert that there

were differences in clinical practice for allergy testing in the NHS compared with the rest of Europe, where most of the studies were conducted, and that as a result some of the studies may not be generalisable to clinical practice in England.

5.5 The committee considered the diagnostic accuracy of multiplex allergen testing using ImmunoCAP ISAC. The committee heard from clinical experts that the gold standard for diagnosing allergy was a double-blind, placebo-controlled allergen challenge test. The committee noted that many of the reported diagnostic accuracy studies did not use this as the reference standard, but used a combination of skin prick testing, single specific-IgE tests and challenge testing as the reference standard. The committee also heard from the external assessment group that many of the studies only reported subsets of the allergen components tested, so overall accuracy figures were not reported. The committee noted that there was considerable variation in the reported sensitivity and specificity values of the ImmunoCAP ISAC, and that there was uncertainty in the level of correlation between ImmunoCAP ISAC and single specific-IgE tests in detecting the same allergen. The committee concluded that more evidence is needed on the diagnostic accuracy of ImmunoCAP ISAC and single specific-IgE testing in the same population using an appropriate reference standard.

5.6 The committee considered whether multiplex allergen testing could be used as a replacement for multiple single specific-IgE tests in certain people. It heard from clinical experts that there were some people in whom the number of allergens that needed to be tested was high enough for it to be cheaper to use multiplex allergen testing rather than multiple single specific-IgE tests. It also heard that there was considerable uncertainty around the comparability of single specific-IgE-test results and those from multiplex allergen testing, and that there is uncertainty in the cut-off values used for both tests. The committee concluded that more evidence is needed to show if multiplex allergen testing and single specific-IgE testing are comparable, before multiplex allergen testing could be considered as a replacement test.

5.7 The committee heard from clinical experts that allergy can be difficult to diagnose and manage. The clinical experts advised the committee that

an allergy-focused clinical history is the most important tool in diagnosing allergy and should always be the first step. The committee heard that allergic reactions can vary widely between people and that a person's response to an allergen is not always the same each time, even to the same allergen. It also heard from clinical experts that it can be difficult to identify the causal allergen in some people even after testing and that difficulty in diagnosing allergy is often why allergy is difficult to manage and control. The committee concluded that the benefit of using ImmunoCAP ISAC is most likely to be seen in a tertiary setting in people whose allergy is difficult to diagnose and that in these people, it is likely to be an additional diagnostic tool rather than a replacement for skin prick testing and oral-food-challenge tests. The committee also concluded that more clarity on the context, particularly the sequence of testing and the defined population in which ImmunoCAP ISAC would offer most help in allergy diagnosis, would be useful.

5.8 The committee considered the difficulty in interpreting the results of multiplex allergen testing. The committee heard from clinical experts that correct interpretation of multiplex allergen testing results is difficult and must always be done in the context of a complete allergy-focussed clinical history. The committee heard that multiplex allergen testing results show a pattern of sensitisation. The committee also heard that sensitisations do not always correlate with clinical symptoms and that sensitisations shown on multiplex allergen testing that do not correspond to clinical symptoms could be real sensitisations but of unknown clinical significance. It noted that incorrect interpretation of results may lead to an incorrect diagnosis of allergy, unnecessary restriction of diets, and considerable impact on a person's quality of life. The committee also noted the 2 studies included as examples to show this (see sections 4.29 and 4.30). The committee therefore concluded that multiplex allergen testing results should only be interpreted by an allergy healthcare professional with appropriate expertise in its correct interpretation.

5.9 The committee considered current allergy services in the NHS in England. It noted that there was considerable variation in practice, particularly in primary care and in access to allergy specialists. The committee heard clinical experts share their concern that people are on restriction diets unnecessarily because of a lack of education and

training for NHS healthcare professionals in interpreting allergy test results correctly, but also because many people were getting test results through commercial routes and private medical care without support or expertise for correct interpretation of the results. The committee noted that inappropriate allergy testing, particularly using allergy panel tests and multiplex assays, could increase the burden on the NHS because of the high proportion of results that can be incorrectly interpreted by professionals without appropriate expertise and training. It noted that this could lead to long consultations for people who have positive allergy test results to explain the correct interpretation of the results and also, to correct the use of unnecessary restriction diets. The committee also heard from clinical experts that, although there is no published data, in their clinical experience inappropriate use of restriction diets can, in some cases, trigger a real allergy and so should be avoided. The committee noted there is an absence of guidance on multiplex allergen testing and the interpretation of test results, particularly in adults, and concluded that patient and healthcare professional advice is needed on allergy testing to prevent any further increase in the inappropriate use of testing and restriction diets.

5.10 The committee considered the quality control of multiplex allergen testing. The committee heard from experts that there were no reference standards available for component allergens and that getting United Kingdom Accreditation Service (UKAS) accreditation for this test could be difficult. The committee also heard that there are currently no external quality assurance schemes available for multiplex allergy testing. The committee concluded that external quality assurance schemes may need to be considered if multiplex allergy testing were routinely implemented in the future.

5.11 The committee considered the costs included by the external assessment group in the assessment. The committee heard from clinical experts that the cost of £570 for an oral-food-challenge test, which was used in the base-case analyses, was too high and not representative of the cost of oral-food-challenge tests in NHS practice. It heard from the external assessment group that the high cost included the cost of a hospital appointment to implement the food elimination diet before the oral-food-challenge test. The committee heard from clinical experts that

this appointment is not part of the current care pathway. The committee concluded that the cost of £256 used in the scenario analyses, rather than the £570 used in the base-case analyses, is more likely to represent the cost of an oral-food-challenge test in the NHS.

5.12 The committee considered the cost effectiveness of multiplex allergen testing. It noted that because of a lack of clinical data, the external assessment group could not develop a de novo economic model but instead developed a conceptual model that showed the data and parameters that are needed to inform a cost-effectiveness analysis. It also noted that the external assessment group carried out 2-way threshold analyses and scenario analyses based on theoretical assumptions to show the potential cost savings by introducing multiplex allergen testing. The committee concluded that there was too much uncertainty in the potential cost savings to be confident that they would be realised in practice and more evidence is needed.

5.13 The committee discussed the challenges of research into diagnosing allergy. It heard that funding for research into allergy testing is limited and that ideally a study would investigate allergy testing in a large unselected population with allergy. The committee noted that this could be difficult to do because of the heterogeneity and complexity of the population with suspected allergy, but concluded that these difficulties could be minimised if the population and the context in which multiplex allergen testing should be used were clearly defined.

6 Recommendations for further research

6.1 Further research is recommended on using ImmunoCAP ISAC 112 for diagnosing allergy and clinical outcomes associated with using allergy testing for people with allergy that is difficult to diagnose, specifically in people with:

- idiopathic anaphylaxis
- multiple allergies and multiple sensitisations
- plant-derived food allergy
- seafood allergy, but who have a positive history and negative diagnostic test results.

7 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 6 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

8 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Andrew Dillon
Chief Executive
May 2016

9 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland
Chair, diagnostics advisory committee and Professor of Haematology, Barts Health NHS Trust

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Ms Jane Green
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NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Brendan Mullaney
Topic Lead (until January 2016)

Rebecca Albrow

Topic Lead (from February 2016)

Sarah Byron
Technical Adviser

Robert Fernley
Project Manager

10 Sources of evidence considered by the committee

The diagnostics assessment report was prepared by Kleijnen Systematic Reviews Ltd.

- Westwood ME, Ramaekers BLT, Lang SH, et al. 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. October 2015.

Registered stakeholders

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

Companies/sponsors:

- Microtest Dx
- Thermo Fisher Scientific

Other commercial organisations:

- None

Professional/specialist and patient/carer groups:

- British Society for Allergy and Clinical Immunology
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

- The Anaphylaxis Campaign
- UK NEQAS for Immunology, Immunochemistry and Allergy

Research groups:

- None

Associated guideline groups:

- None

Others:

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

Update information

September 2020: we removed Microtest from the recommendations in this guidance because it is no longer available to the NHS. Details are explained in the review decision. Updated information is marked with **[2020]**.

ISBN: 978-1-4731-1858-4