NICE National Institute for Health and Care Excellence

**DIAGNOSTICS ASSESSMENT PROGRAMME**

**ImmunoCAP ISAC 112 and Microtest for multiplex allergen testing**

**Diagnostics Consultation Document – Comments**

**Diagnostics Advisory Committee date: 10 February 2016**

**THEME: Evidence – Clinical Effectiveness**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 1 | NHS Professional | 4.7 | Paragraph 4.7 states: '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).'<br><br>The purpose of performing a test in a patient with a clinical diagnosis of allergy is to seek some confirmatory evidence in a clinic or laboratory test of reactivity mediated by IgE antibodies, so as to seek to confirm the clinical suspicion that this may be the mechanism responsible for causing symptoms and events. When viewed in this normal, clinical, operational context of running a clinical service for the primary purpose of coming to the right diagnosis in patients, this paragraph is not relevant, as it relates to those parameters that are to do with the clinical management of the patient. As the purpose of doing these tests is to come to the correct diagnosis, studies should not be expected in this field to report on any of the parameters included in the parentheses in this paragraph. | Thank you for your comment which the committee considered.<br><br>Diagnostics assessments are carried out in accordance with the diagnostics assessment programme manual. As described in section 14.2.2 of the diagnostics assessment programme manual, "the benefits from diagnostic testing generally arise from the results of treatment or prevention efforts that take place based on the testing. There may be some direct benefits from the knowledge gained and some direct harm from the testing, but most of the outcomes are indirect and come downstream. In order to assess these outcomes, consideration should be given not only to the diagnostic process itself, but also to treatment and monitoring".<br><br>On this basis, all diagnostics assessments |

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| | | | This NICE assessment should be focused on the diagnostic usefulness of this test, and not on clinical outcomes and parameters that relate to the success of the allergen avoidance, pharmacological and other management advice given.<br><br>The test is a very useful diagnostic test. It is not a therapeutic manoeuvre. By including mention of clinical outcomes, NICE appears as if it is confused about these two distinct aspects of a Physicians activity, or seeks to link them without any appropriate consideration of the management advice offered, and measures of that (eg what allergen avoidance is recommended, what is the efficacy of such avoidance, what medications are advised, what is the adherence to treatment recommended etc, etc). It is easily possible to negate or minimise a benefit to one part by demanding extended evidence relating to the other part. | consider both diagnostic accuracy and clinical outcome data in order to determine the clinical utility of a diagnostic technology, and establish whether a test enables a clinician to arrive at the correct diagnosis.<br><br>The committee noted that the absence of clinical outcome data had precluded the external assessment group from evaluating the cost-effectiveness of the multiplex allergen tests, this is noted in section 5.12 of the guidance document. |
| 2 | NHS Professional | 4.31 | This paragraph states that : '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 long-term clinical- | Thank you for your comment which the committee considered. The committee heard from the external assessment group that a model could not be constructed to evaluate the cost – effectiveness of multiplex testing because |

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| | | | effectiveness data.'<br><br>Given that the purpose of the ISAC test is to confirm the suspect a clinical diagnosis of allergy, make it less likely or qualify the situation further, it is astounding to read that a de novo economic model could not be developed because of the lack of long-term clinical effectiveness data.<br><br>Are we now in a situation where we are able to develop economic models of the effectiveness of testing only if we have long-term clinical effectiveness data surrounding that new test? If so it follows that we have to wait a long period (? 2 years, 3 years, 5 years…? longer) for long-term clinical effectiveness data to accrue before we can think of introducing a new test, if it is to come with NICE approval. Would NICE for example have applied this logic had it been asked to do an evaluation of PET scanning versus high-resolution CT scanning, or whole exome sequencing vs nucleic acid amplification of currently known mutations, or am I mistaken and there is in fact a long tradition and an evidential record of applying this precise logic whenever NICE assesses any new diagnostic methodology? | of the absence of data on clinical outcomes. The committee decided to change section 4.31 of the guidance document to reflect this. This committee consideration is also described in section 5.12 of the guidance document. |

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| 3 | Thermo Fisher Scientific | 1.1-1.4 | *Thermo Fisher Scientific response*:<br>With respect to the data presented in the DAR, Thermo Fisher Scientific agrees with the provisional recommendations summarised in the DCD, which logically follow from the data evaluated.<br><br>To date, the clinical effectiveness due to diagnostic advantage of ImmunoCAP ISAC®sIgE 112 is still premature to evaluate, even if the available results show its potential.<br>NICE defines the clinical utility of diagnostic as "its capacity to rule a diagnosis in or out, and to help make a decision about adopting or rejecting a therapeutic intervention". *De facto*, ImmunoCAP ISAC 112 should at present be intended as an added tool to achieve better diagnostic effectiveness in difficult to diagnose patients, thanks to its ability to facilitate diagnosis compared to standard diagnostic routines. In fact, ImmunoCAP ISAC 112 provides clinicians with supplementary, detailed and specific information on the patient's sensitisation profile, thus helping them in achieving a more precise, refined, and well informed diagnosis. | Thank you for your comment which the committee considered.<br><br>The committee discussed the clinical utility of the sensitisation profile provided by the multiplex allergen tests, and noted that there was uncertainty surrounding the interpretation of results and the clinical significance of sensitisations identified on multiplex testing that do not correlate with a person's symptoms. This committee consideration is described in section 5.8 of the guidance document.<br><br>The framework used by the diagnostics advisory committee to assess diagnostic technologies is outlined in the diagnostics assessment programme manual. |

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| | | | References:<br>Glossary of the Medical technologies evaluation programme (NICE)<br>http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-medical-technologies/Medical-technologies-evaluation-programme-process-guide.pdf | |
| 4 | Thermo Fisher Scientific | 2.2 | *Thermo Fisher Scientific response*:<br>As stated in this section, assessing the clinical effectiveness of ImmunoCAP ISAC 112 by evaluating its capability of helping diagnosing allergy and of predicting the risk of an allergic reaction in difficult to diagnose people addresses perfectly the usage domain of this device.<br><br>The evaluation of clinical outcomes, being rather associated to the success of the patients' management, represents another interesting area of investigation, but it lies beyond the scope of the intended usage of ImmunoCAP ISAC 112.<br><br>References:<br>1) NICE Guidelines Manual published in November 2012, | Thank you for your comment which the committee considered.<br><br>As described in section 14.2.2 of the diagnostics assessment programme manual, "the benefits from diagnostic testing generally arise from the results of treatment or prevention efforts that take place based on the testing. There may be some direct benefits from the knowledge gained and some direct harm from the testing, but most of the outcomes are indirect and come downstream. In order to assess these outcomes, consideration should be given not only to the diagnostic |

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| | | | "Although the assessment of test accuracy is an important component of establishing the usefulness of a diagnostic test, the clinical value of a test lies in its usefulness in guiding treatment decisions, and ultimately in improving patient outcomes."<br><br>https://www.nice.org.uk/article/pmg6/chapter/developing-review-questions-and-planning-the-systematic-review#Review-questions-about-diagnosis<br><br>2) The HTA Core Model Handbook for Diagnostic Technologies made by EUNETHTA, with NICE collaboration, has been developed as applications, each application focusing on the assessment of specific types or uses of health technologies. "In diagnostic technologies the test accuracy and beneficial changes in management are considered as outcomes of indirect effectiveness as well. Proven effectiveness and safety of a technology is fundamental, considering further assessment and the potential use of the technology. http://meka.thl.fi/htacore/ViewHandbook.aspx | process itself, but also to treatment and monitoring".<br><br>Diagnostics assessments are carried out in accordance with the diagnostics assessment programme manual. All diagnostics assessments consider both diagnostic accuracy and clinical outcome data in order to determine the clinical utility of a diagnostic technology, and establish whether a test enables a clinician to arrive at the correct diagnosis or clinical decision. |

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| 5 | Thermo Fisher Scientific | 4.7 | *Text in DCD*:<br>"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)."<br><br>*Thermo Fisher Scientific response*:<br>As precisely defined in the DCD, clinical outcomes are intrinsic to patient management, rather than to patient diagnosis. ImmunoCAP ISAC is a device that can aid the clinician in achieving the correct diagnosis in difficult to diagnose patients; therefore, it is not surprising that studies reporting the added value of ImmunoCAP ISAC's usage to standard practice do not present data on patients' clinical outcomes due to patients' management. | Thank you for your comment which the committee considered.<br><br>Diagnostics assessments are carried out in accordance with the diagnostics assessment programme manual. All diagnostics assessments consider both diagnostic accuracy and clinical outcome data in order to determine the clinical utility of a diagnostic technology, and establish whether a test enables a clinician to arrive at the correct diagnosis or clinical decision. |

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| 6 | Microtest Dx | References | For your information there is one recently published paper analysing the correlation and concordance between SPT, ImmunoCAP, Microtest and ISAC for 10 common food and respiratory allergens.<br><br>Clin Exp Immunol. 2015 Oct 5. doi: 10.1111/cei.12721. [Epub ahead of print]<br>Evaluation of a novel automated allergy microarray platform compared with three other allergy test methods.<br>Williams P1, Önell A2, Baldracchini F2, Hui V2, Jolles S1, El-Shanawany T1. | Thank you for your comment which the committee considered.<br><br>The committee considered the recently published study (Williams et al. 2015) provided by the consultee. It heard from the external assessment group that the study reported concordance data only and did not provide sufficient data to permit a comparison of either the diagnostic accuracy or the clinical effectiveness of the technologies. The committee agreed with the external assessment group that, on this basis, the study did not meet the inclusion criteria for the assessment. |

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| 7 | Microtest Dx | 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.<br><br>The Committee noted that there was uncertainty around the interpretation of the results and whether sensitisations (or lack of) on multiplex allergen testing that do not correspond to clinical symptoms are actually false positives, and what the significance is of these. The Committee heard that sensitisation does not always correlate with clinical symptoms and that incorrect interpretation may result in an incorrect diagnosis of allergy, leading to unnecessary restriction of diets.<br><br>The Committee concluded that multiplex allergen testing results should only be interpreted by an allergy healthcare professional with appropriate expertise in its correct interpretation.<br><br>Comment: It is unclear for the reader in what way it is more | Thank you for your comment which the committee considered.<br><br>The committee heard from clinical experts that the resulting sensitisation patterns provided by the multiplex allergen tests can be difficult to interpret because of the wide range of allergens included. In some cases it can be difficult to distinguish cross reactivity and genuine clinical sensitisation using the results of the tests in isolation. The committee concluded that sensitisation profiles should always be interpreted in conjunction with details of a person's clinical history. This committee consideration is described in section 5.8 of the guidance document.<br><br>The committee also heard that there is substantial uncertainty surrounding the significance of sensitisations reported on |

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| | | | difficult to in interpret microarray-based test results compared to skin prick test (SPT) since the bold text above is valid also for skin prick testing. (For more details read below)<br><br>SPT tests must always be done in the context of a complete allergy-focused clinical history. SPT sensitization does not always correlate with clinical symptoms and incorrect interpretation may result in an incorrect diagnosis of allergy leading to unnecessary restriction of diets, e.g. due to cross-reactive pollen related allergens in plant foods such as nuts and fruits. This is currently the situation for all types of allergy tests on the market.<br><br>How do clinicians know how to interpret positive SPT without clinical reaction caused e.g. by pollen cross-reactivity when testing for foods from the plant kingdom such as nuts or fruits, or testing for venoms? | multiplex testing which do not correspond with clinical symptoms. This committee consideration is described in section 5.8 of the guidance document. |

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| | | | Is the difficulty of interpreting multiplex test for example mainly due to<br><br>1) the vast number of allergens tested. Eg when > x allergen sources/extracts are tested per patient interpretation becomes complex? or<br><br>2) is it due to the fact that ISAC contains allergen components, which clinical meaning is still not well known? or<br><br>3) due to the fact that ISAC do not contain all allergens of an allergen sources (or do not have the whole allergen extract on the chip for e.g. cashew nut) so that the interpreter have to be aware of lacking components for a certain allergen species? or<br><br>4) due to low sensitivity or specificity compared to skin prick tests/traditional sIgE tests? Or a combination of all the above? | |

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| 8 | Royal College of Physicians | General | The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with experts in immunology and allergy and would like to make the following comments:<br>Our experts note that ISAC and Microtest are innovative and highly complex serological tests for measuring serum specific Immunoglobulin E (IgE) to multiple allergens with a single blood sample. The readouts contain results of whole as well specific components to multiple allergens. Systematic reviews on the use of ISAC generally show lower sensitivity but higher specificity than skin prick testing or immunocap to whole or component allergens. The relevance of many of the components in predicting resolution or allergy severity is not known and therefore the number of questions arising from the results of testing may be greater than those leading up to testing. A positive result indicates allergic sensitisation rather than clinical allergy and there is a danger that patients are advised to avoid foods or other allergens to which they have a positive test but not reactive clinically.<br>Our experts would caution that in the wrong hands the results can be confusing and lead to inappropriate clinical management. Therefore this is a test that should never be | Thank you for your comment which the committee considered.<br><br>The committee heard from clinical experts that the results of multiplex allergen tests could be difficult to interpret and noted concern that people can be inappropriately advised to follow restriction diets if the tests are interpreted by people without the appropriate expertise. The Committee also noted that people could access allergy testing through commercial routes and in some cases, could result in people receiving advice without the support and expertise for correct interpretation of the test results. This committee consideration is noted in section 5.9 of the guidance document. Further, the committee recommended that an allergy healthcare professional with appropriate expertise is needed to ensure the results of multiplex |

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| | | | requested by non-experts and reserved exclusively for tertiary allergy units for limited indications. | allergen tests are interpreted correctly. This statement is included in section 1.4 of the guidance document. |

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**THEME: Time to interpret results**

| Comment number | Name and organisation | Section number | Comment | Response |
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| 9 | Thermo Fisher Scientific | 4.49 | *Text in DCD*:<br>"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."<br><br>*Thermo Fisher Scientific response*:<br>We acknowledge the calculation performed using the values listed above is done correctly, but the numerical values for the interpretation of an ImmunoCAP ISAC 112 result report used as input to the model derive from a misunderstanding, and we apologise for this inconvenience.<br><br>In fact, we have investigated minimum and maximum times for interpretation at two immunology centers in the UK that have been using ImmunoCAP ISAC since a few years (the University of Wales, operating since 2009, and the Northern General Hospital, operating since 2011). Both centres have run hundreds of tests *per annum*, to know the actual time they need to interpret an ImmunoCAP ISAC 112 patient report.<br><br>Experts' opinion is in agreement, stating that the maximum | Thank you for your comment which the committee considered.<br><br>The committee heard from clinical experts that results of multiplex testing require interpretation by both laboratory staff and a clinician. Because of the complexity in interpreting the sensitisation profile, clinicians are required to interpret the results in conjunction with a person's clinical history. The committee's considerations of the process for interpreting the results of multiplex allergen testing in clinical practice are described in sections 5.8 and 5.9 of the guidance document.<br><br>Further, the committee heard from the external assessment group that because the model used for the assessment was |

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| | | | time needed to interpret an ISAC result report is 10 minutes, even in complex patients.<br><br>Therefore, we ask here to revise both the calculations with updated numerical values (5-10 minutes), and the conclusions drawn, based on new results. | theoretical and did not include clinical outcome data, narrowing the range of estimates used for the time taken to interpret test results would therefore produce results that are also theoretical. The committee concluded that further analysis of the time taken to interpret results would not impact on the committee's overall conclusion because of the absence of clinical data to inform the model. |
| 10 | Royal College of Physicians | 4.53 | The following assumptions were made in the base case: number of allergens by skin prick test per patient:<br>• cost of skin prick test per patient: £62.28.<br>• number of allergens by single specific IgE testing per patient: 8.<br>• cost of single specific IgE tesper patient: £136.37.<br>• cost of oral-food-challenge test: £570. | Thank you for your comment which the committee considered.<br>The committee heard from the external assessment group that detailed cost calculations were done to estimate the costs of individual tests. This calculation included tests costs, capital costs (if applicable), service and maintenance costs, and personnel costs for doing and interpreting the tests. For the interventions, the time need to interpret |

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| | | | • minimum cost per ImmunoCAP ISAC 112 test: £154.41.<br>• maximum cost per ImmunoCAP ISAC 112 test: £284.60.<br>• minimum cost per Microtest test: £140.37.<br><br>Our experts question whether the economic analyses above have considered and factored in the additional time required to interpret these complex tests. | results for the ImmunoCAP ISAC 112 test ranged from 5 to 60 minutes, and for Microtest from 5 to 10 minutes. This is described in section 4.49 of the guidance document, and the detailed cost calculations can be found in appendix 7 of the diagnostics assessment report. The Committee also noted that the model produced by the external assessment group was a theoretical model only because no clinical outcome data were available. |

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**THEME: Costs**

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| 11 | Thermo Fisher Scientific | 5.11 | *Text in DCD*:<br>"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."<br><br>*Thermo Fisher Scientific response*:<br>Oral food challenges can be considered safe only if performed by experienced medical staff in a hospital setting.<br>A challenge per se lasts between 3 and 5 hours, while the patient is requested to wait two more hours to endure no reactions occur.<br><br>Based on this information, considering that in hospital one hour of medical consultant costs £140 per hour of client contact, we estimate a cost ranging between £420 and £980 for medical consultation only, plus £100 per hour for a qualified nurse.<br><br>Moreover, it has to be considered that only the 1-oral-food-challenge scenario was taken into account in the assessment. Additional costs to the ones pictured above can be expected for | Thank you for your comment which the committee considered.<br><br>The committee heard from clinical experts that in current practice, oral food challenges are typically used to rule-out an allergen where there is doubt about whether there is an allergy, and therefore they are most commonly used for people who are not expected to react. In many units one consultant will oversee multiple patients who are receiving oral food challenges, and further, where a reaction is not expected multiple allergens may be challenged in 1 visit. The committee also heard from a clinical expert that £256 was likely to be the cost recouped by the provider of the oral food challenge test. |

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| | | | multiple testing, as no more than one allergen can be challenged during one day, while ImmunoCAP ISAC 112 is suitable also to address multi-sensitised difficult to diagnose patients that usually would require multiple food challenges.<br><br>References:<br>1) http://www.anaphylaxis.org.uk/knowledgebase/food-challenges-as-a-way-of-testing-for-food-allergies/<br>2) PSSRU Report 2014: http://www.pssru.ac.uk/project-pages/unit-costs/2014/ | |

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**THEME: Standard practice**

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| 12 | NHS Professional | 4.51 to 4.59 | These paragraphs seem to give the impression that oral food challenge testing may be commonly performed. Whilst this may be the case in paediatric clinics and in a very few specialised adult clinics in the UK, in the majority of adult allergy specialised services food challenge tests are rarely performed due to lack of funding. Great reliance is thus made in such centres on extensive in-vitro testing in order to provide information on these difficult patients. Clinical advice is then given based on such in vitro test results, most often without proceeding to oral challenge testing.<br><br>The relevant question to ask in these difficult patients is thus whether allergy micro-array testing may usefully and economically provide more, and more discriminant information on the sensitisation pattern of individuals in whom food challenge tests are not performed because of lack of funding.<br><br>In such patients, the relevant cost-effectiveness data that should be looked for is the cost-effectiveness of using this laboratory analytical method compared with using other, established laboratory analytical methods in this situation. | Thank you for your comment which the committee considered.<br><br>The committee heard from clinical experts that, although oral food challenge tests were not as widely used in adult practice as in paediatric practice, many adult allergy services are now offering oral food challenge tests.<br><br>The committee noted that the external assessment group had included studies which reported the accuracy of multiplex allergen testing using ImmunoCAP ISAC compared with other in vitro methods. This is described in sections 4.4 and 4.10 to 4.17 of the guidance document. Further, the committee noted that the comparative data provided by these studies was limited and concluded that that more evidence is needed to show if multiplex allergen testing and single specific-IgE testing are comparable. |

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| | | | | These considerations are described in sections 5.5 and 5.6 of the guidance document.<br><br>The committee also considered that the external assessment group had not been able to explore the cost-effectiveness of multiplex allergen testing because of an absence of clinical outcome data. This is noted in section 5.12 of the guidance document. |
| 13 | Thermo Fisher Scientific | 3.7 | *Text in DCD*:<br>"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."<br><br>*Thermo Fisher Scientific response*:<br>We would like to address two pivotal issues: *[the second issue is described in comment number 27]* | Thank you for your comment which the committee considered.<br><br>The committee heard from clinical experts that most oral food challenge tests are performed to rule-out an allergy, and that therefore the majority of tests are not necessarily associated with side-effects. Further, it also heard that when an allergy is ruled-out, food can be reintroduced into a person's diet which |

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| | | | a. Side effects of the comparators selected<br>Eventual side effects of oral food challenges, and the related implications and costs, were not taken into account in the model, which appears as a significant simplification of clinical practice reality.<br><br>References:<br>Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. J Allergy Clin Immunol. 2004 Nov;114(5):1164-8. | may improve their quality of life and reduce anxiety. However, the committee noted that because of the lack of clinical outcome data to inform the model, the external assessment group had developed a conceptual model which aimed to show the data and parameters which would be needed to inform a cost-effectiveness analysis. This is described in section 5.12 of the guidance document. Because the analysis is based on theoretical assumptions only, no conclusions can be drawn on the impact of side effects related to oral food challenge tests on the cost effectiveness of multiplex allergen testing. |

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**THEME: Multiplex testing as a replacement**

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| 14 | Thermo Fisher Scientific | 4.40 | *Thermo Fisher Scientific response*:<br>We agree with what stated in this section, especially with the conclusions drawn about the fact that the adoption of multiplex testing would reduce the need of single specific-IgE tests, by ruling out particular allergens. | Thank you for your comment which the committee considered. |
| 15 | Royal College of Physicians | 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. | Thank you for your comment which the committee considered.<br><br>The committee noted that there was considerable uncertainty around the comparability of single specific-IgE test results and those from multiplex allergen testing and in the cut-off values used for both tests. It concluded that more evidence was needed to show if multiplex allergen testing and single-specific IgE testing are comparable.<br><br>The external assessment group could not develop a de novo economic model but instead developed a conceptual model |

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**Diagnostics Consultation Document – Comments**

**Diagnostics Advisory Committee date: 10 February 2016**

**THEME: Multiplex testing as a replacement**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | Our experts are concerned with inability to determine whether the Microtest/ISAC are equivalent to single specific IgE tests, as the economic analysis was undertaken comparing the two and calculating if one could replace the other. Our experts advise that this contradiction be explained by the appraising committee. | that showed the data and parameters that would be needed to inform a cost effectiveness analysis. The analysis conducted was therefore based on theoretical assumptions and intended to show the potential cost savings that might be achieved by using multiplex allergen testing. The committee discussed the theoretical analysis, but concluded that there was too much uncertainty in the assumptions and data and that more evidence is needed. This is described in section 5.12 of the guidance document. |

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**Diagnostics Advisory Committee date: 10 February 2016**

**THEME: Terminology and classification**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 16 | NHS Professional | 2.4 | The division of hypersensitivity reactions into two simple categories (IgE mediated and non-IgE mediated) seems to slight the very well-established Gell and Coombs classification, one of the very few biological classifications that have stood the test of time. The phraseology of this section (the aforementioned, and 'non-IgE mediated reactions … are mediated by other parts of the immune system) is at present clumsy and unbecoming of a body seeking to claim authority. | Thank you for your comment which the committee considered.<br>The committee heard from clinical experts that there is a move towards classifying reactions as IgE mediated or non-IgE mediated since the publication of the European Academy of Allergy and Clinical Immunology revised nomenclature for allergy. It also heard that this terminology is used in existing guidelines and is used in training for healthcare professionals. |

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**THEME: Restriction diets**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 17 | NHS Professional | 5.9 | You state that 'The Committee also heard from clinical experts that inappropriate use of restriction diets can, in some cases, trigger a real allergy and so should be avoided.' I have not come across this in adult allergy practice and so would be most interested to know the evidence for this, unless you are referring to findings relating to peanut sensitisation in children with eczema published in early 2015. These remarks require qualification, especially if you have found evidence of food having been avoided because of ISAC test results and real allergy resulting as a cause of this food avoidance. | Thank you for your comment which the committee considered.<br>The committee heard from clinical experts that in their clinical experience they had seen cases where inappropriate restriction diets had triggered a real allergy. It noted that the clinical experts were not aware of published data reporting this. The committee decided to change section 5.9 of the guidance document to reflect this. |

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**THEME: Guidelines**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 18 | Royal College of Physicians | 5.9 | The Committee noted there is an absence of guidelines for diagnosing and managing allergy, 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.<br><br>Our experts believe that this statement is incorrect and should be removed as there are at least 10 British Society for Allergy & Clinical Immunology (BSACI) guidelines and 3 NICE guidelines on the diagnosis and management of many different aspects of allergy. | Thank you for your comment which the committee considered.<br>The committee heard from clinical experts that there is currently an absence of guidance on multiplex allergy testing and the interpretation of test results. Further 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 people without appropriate expertise and training. The committee decided to change section 5.9 of the guidance document to reflect this. |

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**THEME: Expertise of the Committee**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 19 | NHS Professional | 5.7 and 5.8 | Paragraph 5.7 states that '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.'<br><br>Paragraph 5.8 states that ' 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 | Thank you for your comment which the committee considered.<br><br>Specialist committee members are recruited in accordance with the process outlined in the diagnostics assessment programme manual. Specialist committee members are recruited for their expertise in the diagnostic technologies under consideration and the care of patients in the pathway in which the results of the test are used. The posts are advertised on the NICE website for at least 5 weeks and applications are reviewed by a panel consisting of the Chair of the diagnostics advisory committee, the programme director and associate director. Their appointment is also reviewed and ratified by the centre director.<br><br>Specialist committee members must meet the requirements of NICE's code of practice for declaring and dealing with |

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**THEME: Expertise of the Committee**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | 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 noted that there was uncertainty around the interpretation of the results and whether sensitisations (or lack of) on multiplex allergen testing that do not correspond to clinical symptoms are actually false positives, and what the significance is of these. The Committee heard that sensitisation does not always correlate with clinical symptoms and that incorrect interpretation may result in an incorrect diagnosis of allergy, leading to 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 4.29–4.30). The Committee concluded that multiplex allergen testing results should only be interpreted by an allergy healthcare professional with appropriate expertise in its correct interpretation.'<br><br>The NICE committee correctly and appropriately expresses the view that judgements about the interpretation and usefulness of Multiplex micro-array assays in allergy need to be made in the light of the patients' detailed histories. It is thus | conflicts of interest. Applicant's with an interest that would not permit them to take part in the committee's decision making is unlikely to be appointed as a specialist committee member. |

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**THEME: Expertise of the Committee**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | most highly regrettable that NICE should have chosen to shoot itself in the foot in performing this evaluation by failing to include in its evaluation panel any Consultant Clinical Immunologist that has experience of running both specialised clinical allergy and specialised laboratory diagnostic allergy services. The evaluation committee seems not to contain any individual with the appropriate level of experience both of diagnosing and managing clinically patients with allergy of all grades of severity and direct experience of use of these microarray assay and all other allergy assays that inform the diagnosis and management of those patients. It is analogous to a number of people trying to complete a jigsaw when each only has a few pieces of the jigsaw in their heads, as opposed to a number of different people completing the jigsaw when all have all the pieces in their heads. This is despite NICE prior to constituting this committee having had an ample number of expressions of interest from individuals falling into the latter category. | |

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**THEME: Wording**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 20 | NHS Professional | 2.1 | The sentence 'The resulting allergen profile may help clinicians to recognise genuine sensitisation, predict the risk of a local or systemic allergic reaction, and identify allergy-triggering components before starting immunotherapy' requires the following insertion …. components in order to be able to give appropriately well-informed advice about allergen avoidance and medical management, which are potentially of critical importance to the patient, and ….before starting immunotherapy. | Thank you for your comment which the committee considered.<br><br>The committee noted that the sensitisation profile provided by the multiplex could be used to help clinicians when providing patients with allergen avoidance advice. The committee decided to add further details to section 2.1 of the guidance document. |
| 21 | Microtest Dx | 4.58 | Assuming 20 allergens being tested:<br><br>□□For ImmunoCAP ISAC compared with standard clinical assessment the proportions of oral-food-challenge tests should be reduced by at least 64% if there was a 100% reduction in single specific-IgE tests.<br><br>□□For Microtest compared with standard clinical assessment the proportions of oral-food-challenge tests should be reduced by at least 46% if there was a 100% reduction in single specific-IgE | Thank you for your comment which the committee considered.<br><br>The committee decided to change section 4.58 of the guidance document to clarify the results of the scenario analysis. |

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**THEME: Wording**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | tests.<br><br>Comment: Is the numbers correct? According to Figure 14 it looks like "100% reduction" should be "0% reduction" in single specific-IgE tests. | |
| 22 | Thermo Fisher Scientific | 4.4 | *Text in DCD*:<br>"….to predict clinical reactivity as defined by SPT or oral-food-challenge testing."<br><br>*Thermo Fisher Scientific response*:<br>We suggest rephrasing as follows:<br>"….to predict clinical reactivity as defined by clinical history and SPT and/or oral food-challenge" | Thank you for your comment which the committee considered.<br>The committee decided to add further details to section 4.4 of the guidance document. |
| 23 | Thermo Fisher Scientific | 5.5 | *Text in DCD*:<br>"… the gold standard for the diagnosis of allergy was a double-blind placebo-controlled oral challenge test (for food and other allergies)." | Thank you for your comment which the committee considered.<br><br>The committee noted that the gold standard for diagnosing allergy was a double-blind placebo-controlled allergen |

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**THEME: Wording**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | *Thermo Fisher Scientific response*:<br>We suggest rephrasing as follows:<br>"… the gold standard for the diagnosis of food allergy was a double-blind placebo-controlled food challenge test. " | challenge test. The committee decided to change section 5.5 of the guidance document to reflect this. |
| 24 | Thermo Fisher Scientific | 5.8 | *Text in DCD*:<br>"… that do not correspond to clinical symptoms are actually false positives, …"<br><br>*Thermo Fisher Scientific response*:<br>We suggest rephrasing as follows:<br>"… that do not correspond to clinical symptoms are clinically irrelevant sensitisations, …"<br><br>References:<br>Hamilton RJ, and Oppenheimer J. Serological IgE Analyses in the Diagnostic Algorithm for Allergic Disease. J Allergy Clin Immunol Pract 2015;3:833-840. | Thank you for your comment which the committee considered.<br><br>The committee noted that sensitisations on multiplex allergen testing that do not correspond to clinical symptoms are not necessarily false positive sensitisations, rather their clinical relevance may be unknown. The committee decided to change section 5.8 of the guidance document to reflect this. |

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**THEME: Wording**

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**THEME: General**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 25 | Microtest Dx | | We acknowledge the thorough literature search and excellent work done by the NICE assessment group. | Thank you for your comment which the committee considered. |
| 26 | Royal College of Nursing | | No Comments | Thank you for your comment which the committee considered. |
| 27 | Thermo Fisher Scientific | 3.7 | *Text in DCD*:<br>"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."<br><br>*Thermo Fisher Scientific response*:<br>We would like to address two pivotal issues [*the first issue is described above in comment number 13*]:<br><br>b. Legal aspects<br>In the near future, changes in the availability of *in vivo* diagnostic methods are foreseen, due to revisions to the national legislations, and patients will not be offered as | Thank you for your comment which the committee considered.<br>The committee noted that changes to the European in-vitro diagnostic directive are currently in progress, but that the details of the changes are not yet finalised and any changes are unlikely to be implemented immediately for existing tests. |

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**THEME: General**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | many diagnostic alternatives. Therefore, multiplex testing could become a cost-effective solution compared to other laboratory diagnostic methods.<br><br>In the DCD, the legal environment is not contemplated among the comparators' limitations, especially considering that the intended patients are likely to be multi-sensitised, and that the new regulations will limit the amount of test available for SPT and provocations through documentation requirements for each individual allergen and each route of administration of a test solution.<br><br>References:<br>1) http://www.who.int/bulletin/volumes/86/8/08-051078/en/<br><br>2) https://www.nice.org.uk/article/pmg9/chapter/6-the-appraisal-of-the-evidence-and-structured-decision-making<br><br>3) Klimek L, Hammerbacher AS, Hellings PW, Fokkens WJ, Hoffmann HJ, Muraro A, Papadopoulos N. The | |

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**THEME: General**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | influence of European legislation on the use of diagnostic test allergens for nasal allergen provocation in routine care of patients with allergic rhinitis. Rhinology. 2015 Sep;53(3):260-9. doi: 10.4193/Rhin14.316<br><br>4) Klimek L, Werfel T, Vogelberg C, Jung K. Authorised allergen products for intracutaneous testing may no longer be available in Germany: Allergy textbooks have to be re-written. Allergo Journal International. 2015;24(3):84-93. doi:10.1007/s40629-015-0051-7<br><br>5) EU Directive 89/342/EEC, EU Directive 2001/83/EC Article 1 | |
| 28 | NHS professional | General | The Committee Membership lists [redacted] as [redacted] This designation is for [redacted] and so it should perhaps be changed to [redacted]. Do you intend to list the qualifications (degrees) of all Committee members in the final report? | Thank you for your comment.<br><br>Specialist committee members are recruited in accordance with the process outlined in the diagnostics assessment programme manual. Specialist committee members are recruited for their expertise in the diagnostic |

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**THEME: General**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | | technologies under consideration and the care of patients in the pathway in which the results of the test are used. The posts are advertised on the NICE website for at least 5 weeks and applications are reviewed by a panel consisting of the Chair of the diagnostics advisory committee, the programme director and associate director. Their appointment is also reviewed and ratified by the centre director. The committee membership list includes all members of the committee involved in the development of the diagnostics guidance and their job titles. |

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**THEME: Part 2: Population**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 29 | Thermo Fisher Scientific | 6.1 | *Thermo Fisher Scientific response*:<br>We agree that more investigations are indeed needed to further demonstrate the added value that ImmunoCAP ISAC 112 provides in helping clinicians achieving a correct diagnosis in difficult to diagnose patients.<br>We would recommend including the following items to the proposed recommendations for further research studies especially focusing on:<br>1) "multi-sensitised and multi-allergic patients": as correctly pointed out in section 2.6 of the DCD, the number of multi-allergic patients are increasing in UK as well as in the rest of the world, thereby presenting greater diagnostic challenges where multiplex testing may be a useful facilitating aid for the clinicians;<br>2) "patients with combined food and inhalant allergies", as they do represent one of the most relevant patient groups where ImmunoCAP ISAC 112 would help in achieving a correct diagnosis.<br><br>Despite its intrinsic interest, we think that further research specifically focused on seafood allergy lies beyond the | Thank you for your comment which the committee considered.<br><br>The committee considered the suggested populations and agreed that multi-sensitised and multi-allergic patients were an important group for further research. The committee decided to change section 6.1 of the guidance document. The committee also considered people with combined food and inhalant allergies but concluded that those who are difficult to diagnose are likely to be included in the populations for whom further research is recommended.<br><br>Further the committee noted that the recommendation for further research in people with a seafood allergy is focused on a subgroup who are difficult to diagnose because their clinical history does not correlate with the results of |

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**THEME: Part 2: Population**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | present scope of usage of ImmunoCAP ISAC 112, as patients affected by this allergy are not necessarily difficult to diagnose, multi-sensitised and/or multi-allergic patients.<br>Therefore, we suggest removing this item from the list, in order to avoid creating confusion. | previous allergy testing. |

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**THEME: Part 2: Recommendations**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 30 | Royal College of Physicians | 1.1 to 1.4 | 1.1 There is currently insufficient evidence to recommend the routine adoption of multiplex allergen testing, ImmunoCAP ISAC 112 or Microtest, 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.<br><br>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<br>1.3 Microtest is a new technology and further research by the company to show its clinical effectiveness is encouraged.<br>1.4 An allergy healthcare professional with appropriate expertise is needed to ensure the results of multiplex allergen tests are interpreted correctly.<br><br>Our experts believe the recommendations require considerable clarification. Although it is stated that these tests should not be used routinely, NICE should indicate that tertiary centres can continue to use these tests in certain circumstances. | Thank you for your comment which the committee considered.<br><br>The committee considered that although there were scenarios where multiplex allergen tests could be potentially cost saving, there were uncertainties around the comparability of single specific-IgE test results and those from multiplex allergen testing. This is noted in section 5.6 of the guidance document. Further the committee noted that, because of the lack of clinical data there was too much uncertainty in the clinical effectiveness of using the multiplex allergy tests and consequently, too much uncertainty in the potential cost savings to be confident that the savings would be realised in practice. This committee consideration is described in section 5.12 of the guidance document. Because of the limited diagnostic accuracy data, and absence of clinical effectiveness data the committee |

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**THEME: Part 2: Recommendations**

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | ISAC should only be requested in specific circumstances and if there are explicit questions relating to allergy sensitization requiring testing for multiple allergens simultaneously. In some circumstances it may be less expensive to request an ISAC than many single allergen components and may therefore save NHS funds. ISAC requests should be limited to tertiary allergy centres in the following circumstances:<br>1. When it is less expensive to request an ISAC than testing for multiple single allergens<br>2. In cases of severe refractory atopic dermatitis where allergy to additional allergens is suspected<br>3. In cases of eosinophilic oesophagitis where allergy to multiple food allergens is strongly suspected<br>4. In multisystem allergy where identification of additional allergens is likely to improve patient outcome.<br>5. In idiopathic anaphylaxis in which the clinical history points to a consistent allergic trigger<br>6. When it is vital to confirm exclusion of allergy. | concluded that there was currently insufficient evidence to recommend the routine adoption of multiplex allergen testing and wished to encourage further research in people with allergy that is difficult to diagnose. |

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**THEME: Part 2: Recommendations**

| Comment number | Name and organisation | Section number | Comment | Response |
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