NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG24: ImmunoCAP ISAC112 and Microtest for multiplex allergen testing

This guidance was issued in May 2016

The review date for this guidance was May 2019.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Review decision

Transfer the guidance to the 'static guidance list' after a post-publication update to the recommendations to reflect that the Microtest is no longer available to the NHS.

At the Guidance Executive meeting of 5th May 2020, the proposal to transfer the guidance to the static list without consultation was agreed. A list of the options that were considered, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Rationale

The review did not identify any substantial changes to the care pathway, and no data have been published that would have a material impact on the recommendations. The guidance will therefore be placed on the static list, with a static list review initiated if substantial new data, which address the research recommendations, become available. A post publication update to the guidance will be done to reflect that the Microtest is no longer available to the NHS.

3. Implications for other guidance producing programmes

No implications for other guidance producing programmes have been identified.

4. Original objective of guidance

To assess the clinical and cost effectiveness of ImmunoCAP ISAC112 and Microtest for multiplex allergen testing.

5. Current guidance

Adoption recommendations

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.

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 Microtest is a new technology and further research by the company to show its clinical effectiveness is encouraged.

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

Research recommendations

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.

6. New evidence

The search strategy from the original diagnostics assessment report was re-run on Embase, Ovid MEDLINE, PubMed, CDSR, LILACS, NIHR HTA, SCI-EXPANDED, FDA, OpenGrey and IDEAS. References from March 2015 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below.

6.1 Technologies

Since the publication of NICE's diagnostics guidance 24 in May 2016, there have been changes to the ImmunoCAP ISAC 112 test. However, the Microtest appears to be no longer available.

The ImmunoCAP ISAC 112

Thermo Fisher scientific (manufacturer of ImmunoCAP ISAC 112) noted that the name of the technology had changed to ImmunoCAP ISAC$_{E112i,}$ with the six allergens listed below removed since 2011

- Pla a 2 (Plane tree)
- Jug r 2 (Walnut storage protein 7S globulin)
- Api m 1 (Honey bee venom phospholipase A2)
- Api m 4 (Honey bee venom melittin)
- Pol d 5 (Paper wasp venom antigen 5)
- Ves v 5 (Common wasp venom antigen 5)

Six new allergens were added to the panel in 2020

- Gal-alpha-1,3-Gal (Thyroglobulin, bovine)
- Cor a 14 (Hazelnut)
- Ana o 3 (Cashew nut)
- Der p 23 (House dust mite)

- Can f 4 (Dog dander)
- Can f 6 (Dog)

These changes mean that for diagnostic purposes, the ImmunoCAP ISAC panel would now detect reactivity to the newly added allergens and no longer detect reactivity to the removed allergens and components within the multiplex test. However, the removed allergens are available from Thermo Fisher Scientific as specific single IgE tests, for people whose clinical history or skin prick tests indicate possible sensitivity to any of the allergens no longer available on the ImmunoCAP ISAC panel.

The cost of ImmunoCAP ISAC in the original assessment was £219.51 (noted in the Diagnostics Assessment Report). Thermo Fisher Scientific have stated that since the publication of DG24 there have been no changes to the cost of the technology, consumables, maintenance and any other costs associated with the use of the technology.

Microtest

Microtest Matrices Ltd., the manufacturer of Microtest, went into administration in 2018. Records at Companies House show that the company was dissolved on 23rd August 2019. Attempts by NICE to contact representatives of the company were unsuccessful.

Additional technologies

- Macro Array Diagnostics (MADx) Allergy Explorer (ALEX^2) (Vienna, Austria) is a multiplex test, based on proprietary nano-bead technology. The user can select from a combination of up to 120 allergen extracts and 180 molecular allergens to create a bespoke panel for each patient. The company website states that it operates to quality management systems EN ISO 13485 and EN ISO 9001 with defined standards, tested raw materials, components and services. ALEX^2 is CE marked as a medical device under the EU IVD regulations. Information about the CE mark status of ALEX^2 was updated in this document in January 2021.

- Proteometech Inc. PROTIA Allergy-Q (Seoul, Korea) detects up to 134 allergens in a single serum sample, using an immunoblotting technique. The system has an ISO 13485: 2016 certification, but does not appear to be CE marked as a medical device under the EU IVD regulations.

- The FABER screening test (Global Medical Technologies, Manila, Philippines) detects up to 244 allergens, but appears to be delivered as an appointment-

based service in the Philippines, rather than a commercially available product for use in the NHS.

- AdvanSure Alloscreen (LG Life Sciences, Seoul, Korea) and xMAP Food Allergen Detection Assay (FADA) are mentioned in the published literature, but do not appear to be commercially available technologies with any web presence.

Additional tests identified through literature searches appear to have similar functions as the tests evaluated in the original assessment, but it is unclear if these tests are CE marked or available to the NHS. The DG24 Specialist Committee Members who advised the External Assessment Centre (EAC) were unaware of any multiplex allergen testing that have become available to the NHS since the publication of DG24.

6.2 Clinical practice

Two DG24 specialist committee members advised that there have been no changes to the diagnostic and care pathways since the publication of the original guidance. Thermo Fisher Scientific did not note any changes to the care pathway either. A specialist committee member highlighted that regarding new or updated guidelines, the European Academy of Allergy & Clinical Immunology had published a handbook on molecular allergy diagnostics (Matricardi et al., 2016).

Since the publication of DG24, NICE clinical guideline on Food allergy in under 19s: assessment and diagnosis (2011) had a minor update in 2018, to include relevant cross references to other NICE guidelines and minor wording updates. NICE's guidelines on Anaphylaxis: assessment and referral after emergency treatment (2011) and Atopic eczema in under 12s: diagnosis and management (2007) have not had any changes since the publication of the NICE diagnostic guidance 24.

6.3 New studies

Five studies in scope of DG24 were identified (1 case-controlled study, 1 cohort study, 1 retrospective observational study and 2 published case reports). The two case reports (Ukleja-Sokolowska et al., 2018a and 2018b) were judged as not usefully informing the evidence gaps to be addressed, hence they were excluded. Summarised below are the three studies with information relevant to the decision problem.

Chelminska et al. (2016) was a case-controlled study conducted in Poland. The study was aimed at differentiating cross-reactions accompanying latex allergy with the use of the ISAC test. The study compared three groups of people: (i) patients with immediate allergic reactions to latex (group A, n=39); (ii) those with allergic diseases not associated with latex (group B, n=41); and (iii) a group of healthy

individuals (group C, n=20). 14 people in group A and 16 people in group B had a history of food hypersensitivity which could result from cross-reactions between latex and fruit or pollens and fruit allergens. All 100 patients received (i) skin prick tests to latex, airborne and food allergens; (ii) specific IgE (sIgE) tests to latex (k82) and food allergens and (iii) the ImmunoCAP ISAC103 test; compared with history taking. The authors reported tabulated individual patient level outcomes (including sensitisation to latex and cross-reactivity between latex-fruits and pollen fruits. None of the people in group C had a positive test result. The authors concluded that although the ISAC103 was limited due to a small panel of 6 latex allergens (Hev b 11, rHev b 1, rHev b 3, rHev b 5, rHev b 6 and rHev b 8), the component-resolved diagnostic (CRD) information it provides would be a useful addition to traditional methods used to differentiate between latex-fruits and pollen-fruits cross-reactions.

Blazowski et al. (2019) was a cohort study of children (n=237) hospitalised due to systemic allergic reaction and food anaphylaxis in Poland. Serum samples collected on the first day of admission were analysed for total IgE and allergen component-specific IgE antibodies using the ImmunoCAP ISAC sIgE 112 test, supplemented by ImmunoCAP sIgE tests for single food allergen components not included in ISAC (for example, Ana o 3 for cashews and Cor a 14 for hazelnuts). Food-induced anaphylaxis was reported across five grades of severity of systemic reactions. The authors found no correlation between the severity of anaphylaxis and concomitant asthma or atopic dermatitis and they concluded that CRD using ISAC 112 allowed the risk of severe food anaphylaxis to be determined at a component level.

Griffiths et al. (2017) was a retrospective observational study of patients attending the National Adult Allergy Service at the University Hospital of Wales (n=118). The patients in this study had continuing diagnostic difficulty even after skin prick tests and ImmunoCAP sIgE tests. All patients were given the ImmunoCAP ISAC test to obtain diagnostic information in complex clinical presentations of symptoms following exposure to multiple allergens or where it was less expensive to perform an ISAC test than multiple single allergen ImmunoCAP tests. The authors concluded that in this population with diagnostic difficulty, the ImmunoCAP sIgE is the preferred single test for allergy to nuts, wheat, other specific foods, and anaphylaxis of any cause. Test diagnostic performance was thought to vary based on geographical location.

Ongoing studies

One of the DG24 specialist committee members advised that they are currently assessing the utility or relevance of ISAC 112 to peanut allergy in adults and children, at Imperial College London. However, data analysis is still ongoing and therefore no more details are available at the moment. The record of this study could not be found.

6.4 NICE's research commissioning activities

KITEC EAC (Brooker et al, 2019) was commissioned to address the research recommendation. They audited data from 2 NHS Allergy clinics, [redacted] The audit gives some insight about the use of the ImmunoCAP ISAC in the NHS as an adjunctive or a confirmatory test which is useful in proving reassurance to the patient. The audit results did not provide data on the clinical effectiveness of the technology or data to inform the economic model. The audit was limited to two centres, hence its findings may have limited generalisability to the wider NHS.

7. Summary of new evidence and implications for review

This review focused solely on the ImmunoCAP test because the Microtest which was also assessed in the original guidance, is no longer available. Five published studies were identified which were in scope of the decision problem but only 3 of these studies were thought to provide relevant information. The three studies provided similar, limited, diagnostic outcomes as reported in the original DG24 evidence base (including additional diagnostic information for cross-reactions, component trigger of anaphylaxis and detection rates for different allergies), but did not provide any data on clinical outcomes subsequent to changes in treatment or management of allergies. The new studies did not report outcomes for any of the specific populations noted in the research recommendations.

Although some new evidence has become available for the technology, none of it suggests a material change to the current recommendations would be likely. Also considering that the care pathway has not changed and that there have been no changes to the cost of ImmunoCAP ISAC and other costs associated with the use of the technology, NICE proposed a transfer to the static list. It will be noted on the guidance landing page that the Microtest is no longer available.

8. Implementation

Thermo Fisher Scientific, noted that the ImmunoCAP ISAC 112 is being used in five NHS organisations.

9. Equality issues

No equality issues were raised in the original guidance

Paper sign off: Rebecca Albrow, Associate Director, August 2020

Contributors to this paper:

Technical Lead: Tosin Oladapo

Technical Adviser: Frances Nixon

Project Manager: Donna Barnes

Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

Drug allergy: diagnosis and management (2014) NICE guideline CG183

Anaphylaxis: assessment and referral after emergency treatment (2011) NICE guideline CG134

Food allergy in under 19s: assessment and diagnosis (2011) NICE guideline CG116

Atopic eczema in under 12s: diagnosis and management (2007) NICE guideline 57

Intranasal phototherapy for allergic rhinitis (2018) NICE interventional procedures guidance 616

Omalizumab for treating severe persistent allergic asthma (2013) NICE technology appraisal guidance 278

Referred - QSs and CGs

None

Suspended/terminated

None

Details of new technologies

None of the additional tests identified are commercially available in the NHS.

Registered and unpublished trials

None

References

Blazowski L, Majak P, Kurzawa R, Kuna P. & Jerzynska J. (2019) Food Allergy Endotype With High Risk Of Severe Anaphylaxis In Children-Monosensitization To Cashew 2s Albumin Ana O 3. *Allergy: European Journal of Allergy and Clinical Immunology,* 74, 1945-1955.

Brooker W, Chalkidou A, Erskine J, Keevil, S. & Rodriguez, Y. (2019) Rx167: Immunocap Isac 112 For Multiplex Allergen Testing: Results from a multi-centre retrospective audit.

Chelminska M, Specjalski K., Rozylo, A.,et al. (2016) Differentiating Of Cross-Reactions In Patients With Latex Allergy With The Use Of Isac Test. *Postepy Dermatologii I Alergologii,* 33, 120-127.

Griffiths, R. L. M., El-Shanawany, T., Jolles, S. R. A., et al (2017). Comparison of the performance of skin prick, Immunocap, and ISAC tests in the diagnosis of patients with allergy. *International Archives Of Allergy And Immunology,* 172, 215-223.

Matricardi P. M, Kleine-Tebbe, J, Hoffmann, H. J, et al. 2016. Eaaci Molecular Allergology User's Guide. *Pediatric Allergy And Immunology,* 27, 1-250.

Ukleja-Sokolowska N, Gawronska-Ukleja E, Lis K. et al. (2018a) Anaphylactic reaction in patient allergic to Mango. *Allergy, Asthma, & Clinical Immunology : Official Journal Of The Canadian Society Of Allergy & Clinical Immunology,* 14, 78.

Ukleja-Sokolowska N, Gawronska-Ukleja E, Zbikowska-Gotz M, et al. (2018b) Recurrent Anaphylaxis In Patient Allergic To Eggplant - A Lipid Transfer Protein (Ltp) Syndrome. *Asian Pacific Journal Of Allergy And Immunology,* 36, 109-112.