



# ImmunoCAP

Is the use of ImmunoCAP ISAC and ImmunoCAP Components recommended for allergy testing?



## Background

In 2016 NICE produced “ImmunoCAP ISAC 112 for multiplex allergen testing” which reported:

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 an allergy that is difficult to diagnose, when used with standard clinical assessment.

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

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



## Summary of the evidence

Eight systematic reviews were identified and published since NICE guidance. In the assessment of Bird Fancier’s lung, the diagnostic accuracy of ImmunoCAP tests lacked precision. [1] For *Anisakis simplex* spp. sensitisation rates the test lacked specificity and may overestimate seroprevalence. [2] For food allergy there was a lack of evidence and inconsistencies in the evidence due to differing cut-off value used. [3] For the diagnosis of chronic pulmonary aspergillosis ELISA proved to have greater diagnostic accuracy (ImmunoCAP was used in five of the included studies) and is recommended as the test of choice in clinical practice. [4] A further review of food allergies recommended that more research is needed to address the accuracy and clinical benefits of microarray-based technology. Particularly consistency and reproducibility, and the lack of sensitivity and specificity compared with other approaches. [6] In the diagnosis of occupational asthma [5] specific IgE test performance was satisfactory for a wide range of allergens, and ELISA does not lead to a substantial loss of test performance. In conditions such as nut allergies where the sequelae are serious and life-threatening the tests lack sufficient sensitivity to base recommendations on. [7, 8]



## Conclusions

There has been a significant number of reviews since the 2016 NICE guidance. Many tests display good precision, however, they report different levels of IgE antibodies, have different cut-off values and have different specificities. None of the reviews reports sufficient test accuracy to change the 2016 NICE guidance.

## Recommendation

There is insufficient evidence to recommend the routine adoption of multiplex allergen testing, ImmunoCAP ISAC 112 or Microtest, to diagnose allergy and predict the risk of an allergic reaction.

Due to its inadequate sensitivity some individuals with allergies will test negative (false negatives), this is particularly concerning in those with life threatening allergies (e.g. nut allergies). In those without the disease the tests lack specificity. Some individuals will test positive but won’t have allergies (false positives), which could create significant interruptions to their lifestyle when they are not warranted.





	Study	PICO	No and type of studies	Outcomes	Conclusions/salient passages
1	<a href="#">Diagnostic Accuracy of Specific IgG Antibodies for Bird Fancier's Lung: A Systematic Review and Meta-Analysis.</a> Ann Transl Med. 2019 Nov;7(22):655. doi: 10.21037/atm.2019.10.65.	P = Patients with suspected BFL I & C = Serologic assays for anti-avian IgG antibodies O = Sensitivity and specificity of serologic assays	9 studies: 6 case controls 2 retrospective cohorts 1 prospective cohort	The pooled sensitivities and specificities of 43.5% (95% confidence interval, 35.3-52.1%) and 100% (95% confidence interval, 0-100%) for ImmunoCAP assays. The overall quality of the collective evidence was low, primarily due to the high risk of bias, indirectness, and imprecision of the included studies.	Conclusion: The Ouchterlony method demonstrated high specificity, the ELISA method showed high sensitivity, and the diagnostic utilities of electrosyneresis and ImmunoCAP assay testing remain unclear.  "Moreover, as the number of publications describing the use of electrosyneresis and ImmunoCAP assays was limited, the assessment of the diagnostic accuracy of these tests lacks precision."
2	<a href="#">Anisakis sensitization in different population groups and public health impact: A systematic review.</a> PLoS One. 2018 Sep 20;13(9):e0203671	P = General population OR occupationally exposed workers I & C = ELISA OR skin prick test OR ImmunoCAP OR Immunoblot OR diagnostic techniques O = hypersensitivity prevalence	41 studies included with a mixture of case-control and cross-sectional studies.	Anisakis sensitization	Pertinent passage: More deeply, Anisakis larvae crude extracts (CE) might contain several cross-reactive allergens with other nematodes [63–65], crustaceans, insects or mites [44, 66, 67], and their use as target antigens in commercial assays, both serological (ImmunoCAP) and clinical ones (SPT), may lead to less specificity and consequent overestimation of seroprevalence.
3	<a href="#">Diagnostic accuracy, risk assessment, and cost-effectiveness of component-resolved diagnostics for food allergy: A systematic review.</a> Allergy. 2018 Aug;73(8):1609-1621.	P = Various allergies in children or adults I & C = molecular-based diagnostic techniques—collectively referred to as component-resolved diagnostics (CRD) O = sensitivity, specificity, PPV and NPV	11 studies: 9 cross-sectional 2 case-control	Mainly sensitivity and specificity	Conclusion: Selected components of cow's milk, hen's egg, peanut, hazelnut, and shrimp allergen showed high specificity, but lower sensitivity. However, few studies exist for each component, and studies vary widely regarding the cutoff values used, making it challenging to synthesize findings across studies. Further research is needed to determine clinically appropriate cutoff values, risk assessment abilities, and cost-effectiveness of CRD approaches.
4	<a href="#">Accuracy of serological tests for diagnosis of chronic pulmonary aspergillosis: A systematic review and meta-analysis.</a> PLoS One. 2020 Mar 17;15(3):e0222738	P = Suspected patients with chronic pulmonary aspergillosis. I & C = ELISA accuracy to reference test (DID and/or CIE) accuracy in CPA diagnosis. O = Test accuracy	14 studies (4 in the meta-analysis) with a mix of case-control and cohort studies	Diagnostic accuracy	Conclusion: Our meta-analysis suggests that the diagnostic accuracy of ELISA is greater than the reference tests (DID and/or CIE) for early CPA detection.  Pertinent passage: Although it is not possible to define the evidence strength, the clinical implications of this study were as follows: precipitin detection is laborious, requiring specialized laboratories and presenting low sensitivity for the diagnosis of CPA; in-house ELISA tests do not present standard concentrations and antigens for comparative studies; commercial ELISA tests show better performance for diagnosing CPA, but additional studies must be conducted to identify the best cut-off value; and the ImmunoCAP and Immulite systems demonstrated the best performances among commercial tests.
5	<a href="#">Performance of specific immunoglobulin E tests for diagnosing occupational asthma: a systematic review and meta-analysis.</a> Occup Environ Med. 2019 Apr;76(4):269-278.	P = Occupational asthma I = Measurement of specific IgE levels C = Inhalation challenge O = Sensitivity and specificity	71 studies were included in the systematic review (53 studies involving HMW allergens and 18 involving LMW allergens), and 62 of these with 2138 test results were	Diagnosis of occupational asthma	Conclusion: sIgE test performance is rather satisfactory for a wide range of HMW allergens with the potential for component-specific approaches, whereas sensitivity for LMW allergens is considerably lower, indicating methodological complications and/or divergent pathomechanisms. A common standard for test validation is needed.  Passage from the main conclusion: "As a recent option, CAP is an appropriate method, and ELISA



## ImmunoCAP



### Evidence: professional bodies

The following societies were mentioned in the work informing NICE's recommendations. We have searched these sites to find any updated guidance on ImmunoCap (2016 onwards):

- American Academy of Allergy, Asthma and Immunology
- European Academy of Allergy and Clinical Immunology
- British Society for Allergy and Clinical Immunology
- American Academy of Dermatology
- British Association of Dermatologists



### Evidence: results

Only one of the organisations had published anything approaching a guideline. The European Academy of Allergy and Clinical Immunology published Molecular Allergology User's Guide in 2016 which includes the following:

#### Common IgE assay systems based on singleplex technology

Many versions of the "classical" IgE assay format have been cleared by governmental regulators over the years. Worldwide, three singleplex autoanalyzers that use the "classical" allergosorbent design dominate the current clinical laboratory market. These are the ImmunoCAP (Thermofisher Scientific/Phadia); Immulite (Siemens Healthcare Diagnostics) and the HyTEC88 (Hycor Biomedical). The latter Hycor assay is being replaced with a new autoanalyzer called the Falcon. In Europe, there are additional assays with the EU mark that use a similar assay design but that are not available worldwide for use in clinical laboratories. The performance characteristics of the three predominant singleplex autoanalyzers have been assessed using masked patient specimens and inter-laboratory proficiency data (13). All three singleplex autoanalyzers use an analogous total IgE calibration curve. They display good precision, reproducibility and they report down to the same 0.1 kUA/L limit of quantitation. Multiple studies have confirmed, however, that they report different levels of IgE antibody for any given specificity, which indicates that they detect different distributions of allergen-specific IgE antibody (13-15). This is most probably due to the use of different allergen containing reagents and possibly a result of slightly different procedures for assay calibration and data computation.