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A Retrospective Clinical Audit of the ImmunoCAP ISAC 112 for Multiplex Allergen Testing

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Keywords
ImmunoCAP ISAC · Complex allergy · Skin prick test · Oral food challenge · Multiplex allergen testing

Abstract
Introduction: Complex cases of multiple allergies can be particularly difficult to diagnose using standard methods such as skin prick tests and assessment of a patient's allergic history. Multiplex allergy testing may improve outcomes for allergy patients by avoiding misdiagnosis and providing reassurance. The ImmunoCAP Immuno Solid-Phase Allergen Chip (ISAC) 112 is a CE-marked, molecular, multiplex, allergy test that can test for IgE antibodies to 112 components from 51 allergen sources. However, its clinical utility is unknown and is difficult to estimate due to the complexity of the diagnostic pathway in which it is used. ***Objective:*** To assess how the ImmunoCAP ISAC 112 is currently being used in UK practice. The patient populations in which it may have the most benefit were examined, and the sequence of other tests implemented alongside ISAC was determined. ***Methods:*** A retrospective audit of 100 patient cases from 2 UK tertiary allergy clinics was performed. Fifty paediatric and fifty adult cases were selected for audit. The indications for ordering an ISAC test, the other tests used alongside ISAC, and changes in management actioned by the ISAC test were investigated. ***Results:*** 73.6% of paediatric and 78% of adult patients referred for an ISAC test were suspected to have multiple sensitizations. The sequence of testing varied greatly between cases, but 70% of adult and 98% of paediatric patients had at least one other investigation prior to an ISAC test. In most cases, ISAC testing confirmed clinical suspicion. ***Conclusions:*** A prospective research study is necessary to further investigate the clinical utility and cost-effectiveness of the ISAC. A UK national registry would be of great benefit but will require a large resource base.

Introduction

Allergy can be difficult to diagnose using standard techniques such as oral food challenges (OFCs), skin prick tests (SPTs), and assessment of a patient's history of

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symptoms. This is particularly true in people with multiple allergies or who experience severe reactions such as anaphylaxis, which are becoming more common [1].

Multiplex allergen testing allows clinicians to test a person for multiple allergies at once. This could help clinicians diagnose complex or otherwise difficult to diagnose allergies by determining a person's sensitization "profile," rather than testing for individual sensitivities one at a time.

The ImmunoCAP Immuno Solid-Phase Allergen Chip (ISAC) 112 is a CE-marked, molecular, multiplex, allergy test that can test for IgE antibodies to 112 components from 51 allergen sources. It uses a miniaturized platform of allergen components immobilized on a slide and requires a single 30-μL sample of serum, plasma, or capillary blood to be taken from a patient. The test is semi-quantitative and takes around 4 h to give a result. The ISAC test is currently used by a small number of tertiary allergy specialists to investigate complex allergy patients on an ad hoc basis. Its routine use has yet to be defined.

In May 2016, the National Institute for Health and Care Excellence (NICE)'s Diagnostics Assessment Programme (DAP) published diagnostics guidance on 2 multiplex allergen testing platforms, including the ISAC [2]. The assessment consisted of a systematic review of the evidence on test performance, clinical-effectiveness data, and standard clinical assessments. The NICE subsequently concluded that there was currently insufficient evidence to recommend the routine adoption of either test.

There are numerous gaps in the evidence base. Studies lack detail, leading to a high or unclear level of bias [3]. In particular, the current published evidence on the clinical utility, cost-effectiveness, and current use of the ISAC is limited. Information on the current use of the platform is particularly important. This is due to the complex nature of the allergy diagnosis pathway and the ISAC's potential place in that pathway, which has a great impact on the utility of the diagnostic test.

A robust economic evaluation of the ISAC was not possible at the time of NICE's review [2]. All available economic data were taken from abstracts, and therefore, little or no methodological detail was available. Several studies have established Markov models and have found that ISAC increased quality-adjusted life years (QALYs) versus OFCs and SPTs [3–10]. Another study of Finnish children attributed a cost saving of 480 euros per patient using ISAC due to findings that 63% of the children were on unnecessarily restricted diets [11, 12].

Westwood et al. [3] built a concept model to assess the cost-effectiveness of ISAC. However, the model required several unavailable parameters such as the proportion of people who have other investigations prior to, or alongside, ISAC testing and the diagnostic accuracy of those tests (including ISAC).

Recent assessments of the performance of ISAC in UK practice found that ISAC had a lower rate of detection than single specific-IgE testing (singleplex component-resolved laboratory tests, such as ImmunoCAP Allergen Components) in patients with nut allergies but had a higher detection rate in patients with oral allergy syndrome [13]. Determining where ISAC is best used in the pathway is still a priority to ensure that it is cost effective.

A study was commissioned by the NICE to investigate the feasibility of performing research investigating the clinical utility of ISAC testing in the UK [14]. They concluded that a multi-centre prospective cohort design would yield evidence on

- the uses of ISAC
- the indications for ISAC testing
- the frequency at which such testing would lead to a definitive diagnosis or change in management

Methods and Aims

A retrospective audit of the use of the ImmunoCAP ISAC 112 in 2 NHS tertiary allergy clinics was performed. The Paediatric Allergy Department at King's College Hospital performed 146 ISAC tests between September 24, 2015, and December 18, 2017. Fifty patients were randomly selected for audit. A total of 53 ISAC tests were performed on the 50 patients (age range: 7 months to 16 years old). Cases were roughly evenly spread across this age range.

Fifty adult cases were selected from the Sandwell and West Birmingham Hospitals Adult Allergy Clinic between July 3, 2013, and December 15, 2017. The age range of these patients was 18–66 years.

As data were collected retrospectively, the information that was available varied between the 2 clinics. Data were extracted from clinical notes and letters. The aim of the audit was to understand ISAC's place in the diagnostic pathway in NHS practice and how its use was affecting clinical management of patients.

The following information was extracted from clinical notes and letters:

1. The indications for ordering an ISAC test. This was recorded either as part of the ordering process or taken from the patient clinic letter as part of the ordering process and is an indication of the clinical suspicion based on the patient's history.
2. The other tests that were performed prior to or alongside the ISAC test, such as SPTs, OFCs, and Single Sp IgE tests.
3. The result of the ISAC test, given as a list of allergens that the ISAC test showed a positive result for (i.e., egg, nuts, and grass).
4. Changes made in patient management after receiving the ISAC result.

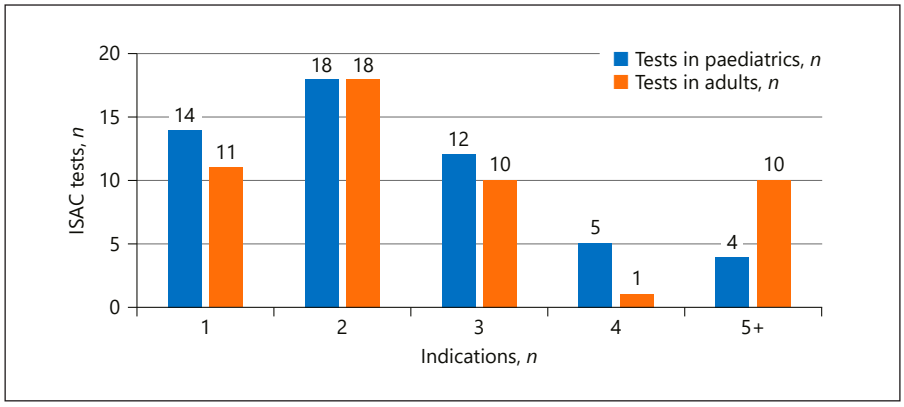

Fig. 1. Number of allergic indications for ordering ISAC tests. ISAC, Immuno Solid-Phase Allergen Chip.

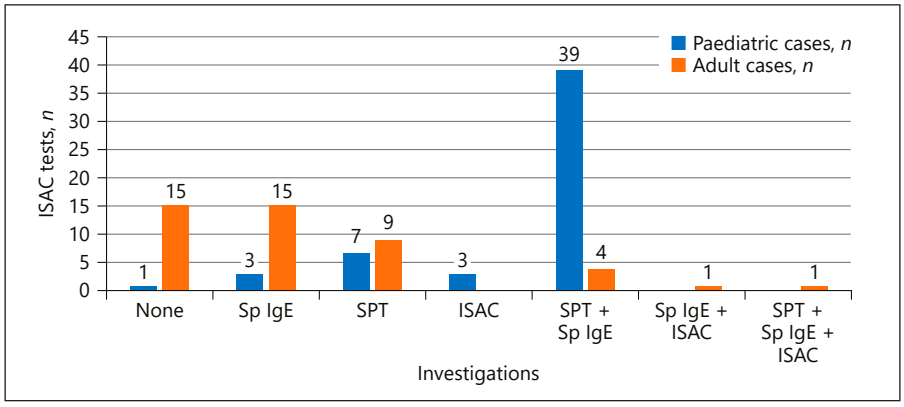

Fig. 2. Investigations performed prior to ordering an ISAC test. ISAC, Immuno Solid-Phase Allergen Chip; SPT, skin prick test.

Results

Indications for Ordering ISAC Tests

There were a wide variety of indications and combinations of indications for ordering ISAC tests. In paediatric patients, atopic comorbidities were the most common indication for performing an ISAC test ($n = 37$). Food allergies were listed 33 times (62%), while eczema ($n = 21$, 40%), rhinoconjunctivitis ($n = 15$, 28%), and asthma ($n = 11$, 21%) were all cited several times each. Eight cases listed anaphylaxis as an indication.

In adult patients, food allergies were given as an indication in most cases ($n = 41$, 82%). In contrast, however, only 6 cases of eczema were noted and none of the adults had asthma. In 18 cases, patients had reactions to food that indicated a possible cross-reactivity with airborne allergens (pollen-food syndrome).

Multiple indications for testing were much more common than single ones. Figure 1 shows the number of indications listed on each ISAC test request in paediatric patients. For both adult and paediatric clinics, 2 indications were the most common. More than one indication for testing was listed in 39 (73.6%) paediatric patients and 39 (78%) adult patients. The greatest number of indications for a single paediatric patient was 6 and 11 for an adult patient. It should be noted than in 6 (12%) adult cases, "multiple foods" were listed as the reason for requesting.

Sequence of Investigations

Forty-nine (98%) paediatric patients had other investigations prior to the ISAC test being requested. In 39 cases, both SPTs and single specific-IgE testing had been performed. In 20 of these 39 cases, the ISAC test was requested at the first appointment, following the other tests. In 3 cases, only a SPT was performed prior to ISAC, and in 7 cases, only single specific-IgE testing was performed prior to ISAC. There were no OFCs performed prior to ISAC in any cases. Three children had an ISAC test performed at a previous appointment. The exact number of SPTs and single specific-IgE tests performed per paediatric patient was not provided. Explanations for the se-

quence of testing were not reported. Figure 2 shows the number of other tests that were performed prior to ISAC testing in the paediatric cohort.

Fifteen adult patients did not have any investigations prior to the ISAC test being requested. Another 15 patients had single specific-IgE testing before ISAC, while 9 had SPTs. Only 4 patients had a combination of SPTs and single specific-IgE testing. In 5 cases, the sequence of testing was not available. No OFCs were performed prior to ISAC. Figure 2 shows the number of other tests that were prior to ISAC testing in the adult cohort.

ISAC Test Result

In 5 paediatric cases, the ISAC test was negative for all allergens. Nineteen cases (36%) returned 3 positive results, and 18 cases (34%) were positive for 2 allergens. Ten cases returned a single positive result, and 1 patient tested positive for 4 separate allergens. It should be noted that in some cases "multiple food allergies" were reported but this was counted as a single allergy.

The time between the patient's first appointment in the paediatric allergy department and their ISAC test being requested was recorded. Just over half (n = 28) of the patients had their ISAC test requested at their first appointment in the clinic, usually after an SPT and single specific-IgE tests. It should be noted, however, that this may not have been their first appointment overall as some children may have been referred from respiratory medicine or other departments. The longest time difference between a patient's first appointment and their ISAC test request was 12 years.

In the adult clinic, the time between the patient's first appointment and their ISAC test being requested was not recorded. However, the number of appointments the patient had prior to their ISAC test being requested was recorded. Forty patients (out of 49, 1 patient's data were missing) had an ISAC test at their first appointment, while only 3 patients had an ISAC test ordered later than their second appointment.

Changes to Patient Management

Management of allergy patient involves individually tailored advice about the avoidance of allergens and symptomatic management of reactions. In some cases, particularly young children, patients are advised to gradually introduce food into the diet to induce tolerance.

Actions taken after receiving the ISAC test results in the paediatric cohort are summarized as follows:

- Explanation of symptoms/confirmed diagnosis (n = 22)
- Food challenge/introduction (n = 11)
- Referral for immunotherapy (n = 5)
- Medication changed/added (n = 4)
- Referral to another service (n = 2)
- New diagnosis (n = 2)
- Additional food exclusion (n = 2)

In 11 paediatric cases, there was no information about what happened post-ISAC in the clinical notes. Six patients had 2 outcomes.

A new diagnosis was made in 2 cases. Six patients were referred to another service (5 to immunotherapy, 1 to gastroenterology, and 1 to dermatology) for further management of their symptoms. New medication was prescribed in 2 cases. In 1 patient, a presumed diagnosis of nut allergy was changed to a sesame allergy and pollen allergy was added. In 4 patients, the ISAC facilitated the reintroduction of foods, and in 4 patients, the ISAC test result facilitated the decision to proceed to an OFC. The actions following ISAC testing in adults were not recorded and therefore not available for audit.

Discussion

These data show that the ISAC test is being used in patients with complex allergic disease (>1 allergic comorbidities), both in the paediatric and adult populations. The ISAC test is performed later in the patient pathway in paediatric patients; adult patients were more likely to have had an ISAC test performed at their first visit.

These were retrospective audits conducted using clinical notes and letters alongside data stored by the immunology labs that provided the tests. The sample size was small in both the adult and paediatric cohorts, although this reflects the infrequent use of the technology in the UK. The data that were available were limited but gave some insight into how the ISAC test is being used in tertiary allergy clinics in the UK. Data were not available from other countries where the ISAC is in use, and this was considered outside of the scope of the assessment as per NICE's research recommendations.

The indications for ordering an ISAC test are unique to each case. It is, therefore, difficult to group the patients included in the audit into well-defined populations using the retrospective data available. There are several ways in which allergies can be grouped. For example, atopy can describe diseases such as allergic rhinitis, asthma, and eczema. Anaphylaxis can be idiopathic or can be exercise induced (e.g., in cases of wheat-dependent exercise-induced anaphylaxis). Furthermore, the indications listed

by the auditor are surmised based on a clinician's notes. As it is not possible to verify the quality of the information noted by the clinician or of the auditor's interpretation, conclusions should be drawn with caution. ISAC was used in cases of multiple sensitizations more often than in single ones.

NICE's Diagnostics Advisory Committee heard (DG24, point 5.6) [2] that in some patients, in whom the number of allergens that would need to be tested for was great enough, an ISAC test would be less expensive than performing multiple single specific-IgE tests. Multiplex testing is only semi-quantitative. It is therefore difficult to compare results of single specific-IgE tests and those from multiplex testing. More evidence is needed to show if ISAC can be considered as a replacement test. Our results suggest that it is currently being used most often as an adjunct to both SPTs and single specific-IgE testing and may be used to avoid performing expensive OFCs.

The exact sequence of testing varies. The ISAC test is used at different points in the paediatric and adult patient pathways. In the paediatric allergy clinic, most patients had both the SPT and single specific-IgE testing prior to having an ISAC. No correlation was found between the sequence of testing and the indications for ordering an ISAC test. There were no OFCs performed prior to ISAC in either the adult or paediatric clinic. In 11 paediatric cases, a food challenge or introduction was the next step following ISAC. No information was available on the number of OFCs performed after ISAC in the adult cohort. This may reflect differences in referral patterns of patients to adult and paediatric allergy clinics, or differences in clinical practice. Paediatric allergists are more likely to follow the progression of allergic disease as it develops in their patients, whereas adult allergists tend to offer a "one-stop shop" for the diagnosis and treatment of allergic disease.

In 22 (42%) paediatric cases, the ISAC result confirmed the clinician's suspicions or explained the patient's symptoms. In 28 (56%) of adult cases, the clinician reported that the ISAC result confirmed their clinical suspicion. In all adult cases, the information was focussed on the clinician's thoughts about the ISAC rather than their management of the patient.

A Comparison of ISAC in Paediatric and Adult Allergy Practice

Comparisons between these 2 patient populations should be made with caution. Many of the results are affected by the opinion of the reporting clinicians and by differences in the way data were reported. Nevertheless, some conjectures may be made.

Many more ISAC tests were ordered without prior investigations in the adult clinic than in the paediatric clinic. This may just be the preference of the clinician. However, from clinical notes, reassuring or convincing the patient is given as a reason for ordering an ISAC test several times in adult allergy and only once in paediatrics (where reassuring the patient's parent was stated). This may suggest that the ISAC is being used for a different purpose in adult allergy than in paediatrics. Clinical experts have previously suggested that ISAC could facilitate a discussion about self-management where results were negative [2]. Furthermore, it appears that many of the patients referred to adult allergy were referred by their GP and clinical notes suggest that patients were often confused by their consultation with their GP.

Both SPTs and single specific-IgE tests were usually performed prior to ISAC testing in the paediatric clinic, while single specific-IgE testing alone was more common in the adult clinic. Again, this may just be the preference of the clinician but could also be due to a difference in the patient pathway and in the way that ISAC is being used.

SPTs were more commonly used in paediatric patients than in adult patients. Skin testing is better tolerated than venesection in young children and offers a faster result, which can inform the advice given in the clinic.

Impact and Future Work

The impact of these audits is limited, and a prospective research study should continue to be a priority. A prospective multi-centre clinical audit could be completed with a relatively small amount of funding and could begin to develop the work detailed in this report. An RCT may be difficult to execute due to the heterogeneity in the clinical pathway.

Any prospective research trial or audit would require standardization as there were several differences between the data available for the 2 audits detailed in this report that made comparisons difficult to draw. Although it is unlikely that practice can be standardized, given the heterogeneity in allergy cases, a standard dataset could be developed. A national ISAC registry and a well-defined population – such as people with food allergies, with the comparator being OFCs – would be valuable in any comparative study. The scope of this research could also be widened by collecting data from other countries where the ISAC is in use. Allergy practice is variable, and a larger sample size will increase the validity of results.

It seems unlikely from our results that ISAC is being used to reduce the number of SPTs and single specific-IgE tests being performed as most ISAC test requests immediately followed the other investigations. Avoiding OFCs may be a more realistic outcome and one that allows for a well-defined population of people, particularly with pollen-food syndrome. These patients, whose reactions to food may indicate a cross-reactivity to inhaled allergens, are a population that could also be included – a population that was sizeable particularly in the adult cohort.

In several cases, ISAC was used to reassure patients. It is vital that patient-centred outcomes are also collected in a prospective study. Furthermore, an economic analysis must consider the potential cost saving to the health and care system of avoiding OFCs and to the patient of avoiding dietary restrictions and food reintroduction programmes.

A prospective study could more accurately (and comparatively) capture metrics such as the time to diagnosis and changes in management. The time to diagnosis requires that patients are followed from their first appointment to at least 1 follow-up appointment after they have begun a management plan (after either ISAC or other investigations) to ensure that their diagnosis is definitive. Changes in management would similarly benefit from this level of follow-up. Furthermore, it is imperative to fully understand the whole pathway, including from where patients are being referred to allergy departments.

The diagnostic accuracy of ISAC remains uncertain. This parameter is of vital importance as it is required to build an economic model of the introduction of the technology. In lieu of a randomized controlled trial, an observational study could potentially aid in understanding the role of ISAC within the diagnostic pathway and what the real comparators to the technology are. Expert elicitation could also be used to estimate a probability distribution for an economic model without the requirement for robust accuracy data, although this approach is imperfect.

Conclusion

The use of ISAC is heterogeneous and dependent on the preferences of the clinician. The number of patients in which ISAC is clinically useful is small. The test is largely used as an adjunct to SPTs and single specific-IgE testing in complex patients with multiple allergies and potential cross-reactions. ISAC testing could be used to avoid OFCs and to reassure patients. More information on resource use and costs of the diagnostic pathway is needed in order to assess the true value of ISAC.

In around half of cases, ISAC confirmed the clinician's suspicions based on clinical history and prior investigations. Various changes to patient management were made in the other half, including changes to medication and referral to other services.

A prospective research study is necessary to further investigate the clinical utility and cost-effectiveness of the ISAC. A UK National Registry would be of great benefit but will require a large resource base. Data from other countries would also strengthen the evidence base.

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Statement of Ethics

The paper is exempt from ethical committee approval as all data were audited retrospectively and no patient identifiable data were included. According to King's College London Research Ethics Committee, audits do not require ethical clearance as long as no patient identifiable data are used or analyzed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jamie Erskine led the development of the design of the protocol, the analysis of the data, and the production of the manuscript. Data collection and audit were performed by Dr. Elspeth Brooker and Dr. Jonathan North. All authors participated in critical review of study methods and read and approved the final manuscript.

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