

EDITORIAL

Executive summary of the EAACI guidelines on diagnosis of IgE-mediated food allergy

It has been almost one decade since the first and last EAACI Food Allergy Guidelines were published.¹ These have recently been updated and include two modules, one on diagnosis and another one on management of IgE-mediated food allergy—this editorial focuses on the first module about diagnosis, which is published in this issue of *Allergy*.² The EAACI guidelines on diagnosis of IgE-mediated food allergy have been developed by a large group of multinational and multidisciplinary group of experts. The present editorial provides an overview of the progress made in food allergy diagnostics over the last 10 years and of the new key recommendations for best clinical practice in 2023, and highlights research priorities and upcoming challenges in terms of implementation of the guidelines in clinical practice.

The prevalence of food allergy continues to rise, in both children and adults, impacting communities around the world. The effect on individuals who experience symptoms to foods is never trivial and sometimes the need for excessive exclusion of foods has adverse health, social and psychological consequences for the patient and their family.^{3,4} Infants and young children are particularly vulnerable from a nutritional standpoint and so it is vital to ensure that a robust diagnosis is made in a timely manner to mitigate any effects on growth and avoid the development of aversive eating behaviours.^{5,6} An accurate diagnosis is therefore vital, but results can be difficult to interpret as IgE sensitization does not equate with clinical allergy. Additional diagnostic challenges may arise in older children, adolescents and adults sensitized to aeroallergens, which cross-react with some foods, and the clinician needs to differentiate primary from secondary food allergy. Similar issues can also occur in individuals with atopic dermatitis, or in certain ethnic groups who may have raised total IgE levels and allergen-specific IgE sensitization that is clinically irrelevant. Misdiagnosis can lead to exclusion of a food, and other associated foods. Conversely, potentially severe or even fatal reactions can occur, if the trigger food has been wrongly identified and exposure to the culprit food is not avoided. Similarly, removing a previously tolerated food from the diet due to a positive allergy test can result in clinical food allergic reactions, as IgE sensitization in the absence of continued consumption can lead to development of food allergy.

Since the systematic review of the literature up until October 2012 done to inform the 2014 EAACI Food Allergy Guidelines,⁷ significant advances have revolutionized allergy diagnostics. Not only

our understanding of the use of traditional allergy tests, such as skin prick testing (SPT) and specific IgE has improved, but also advances in the standardization of allergen extracts, innovation with molecular IgE and cellular tests, along with the more widespread availability of multiplex assays have been achieved. Molecular Allergology (MA) has significantly evolved and can enhance the precision of allergy diagnostics. This is especially true for some foods, such as peanut, hazelnut, cashew nut, and sesame.⁸ Molecular IgE tests have increasingly become an integral part of clinical practice in allergy centers worldwide. In addition to IgE binding tests, functional assays have emerged as valuable tools for food allergy diagnosis. Among these, the basophil activation test (BAT) stands out: initially used in the research setting and still with limited availability outside specialized centers, the BAT has been accumulating evidence and gaining popularity as an important test when other allergy tests yield equivocal results.⁹ Taken together, these developments have enhanced accuracy, efficiency, and personalized treatment approaches in food allergy diagnosis.

These advances have become evident in the new systematic review of the literature performed in preparation for update of the EAACI Guidelines on Food Allergy Diagnosis.¹⁰ With broad and open criteria to search for evidence on accuracy of allergy tests to diagnose IgE-mediated food allergy, for any food and any test, we were able to conduct informative meta-analyses on the diagnostic performance of the test-food combination for which there were enough studies. We also conducted meta-analyses looking at diagnostic performance of tests for different age groups and different geographical locations as these factors are known to influence the performance of allergy tests. We built reference tables with cut-offs for tests on which the meta-analyses were based, including optimal cut-offs and maximal sensitivity and specificity cut-offs, as reported by the authors. These cut-offs can be used as a reference to make clinical decisions in patient populations and clinical settings similar to the ones from which these were originated. Highly sensitive tests are useful to exclude food allergy if results are below the cut-offs. Highly specific tests are useful to rule in food allergy if results are above the cut-off. Optimal cut-offs are often used to make decision about whether to challenge patients but should be considered carefully in light of their associate sensitivity and specificity.

The main novelties of the new EAACI Guidelines on Diagnosis of IgE-mediated Food Allergy are four-fold (See [Table 1](#) for key best practice recommendations):

TABLE 1 Key steps in the diagnosis of IgE-mediated food allergy based on the recommendations of the expert panel and respective certainty of evidence and strength of recommendation.

Key recommendations	Certainty of evidence	Strength of recommendation
1. Start with a detailed allergy-focused clinical history	Low	Strong
2. Perform skin prick test and/or specific IgE to allergen extracts (or fresh foods in case of SPT)	High	Strong
3. Use molecular allergology—specific IgE to Ara h 2, Cor a 14, Ana o 3, and Ses i 1, respectively for peanut, hazelnut, cashew nut, allergies, respectively	High	Strong
4. Use BAT to peanut or sesame, if available	High	Conditional
5. Use only recommended tests above	Very low	Strong
6. Reassess over time for possible resolution of food allergy	Moderate	Conditional
7. Oral food challenge is the reference standard test and should be done in the equivocal cases	High	Strong
8. Open oral food challenge are acceptable for most clinical cases and double-blind challenge should be reserved for patients with an inconclusive open challenge or for research	Low	Conditional

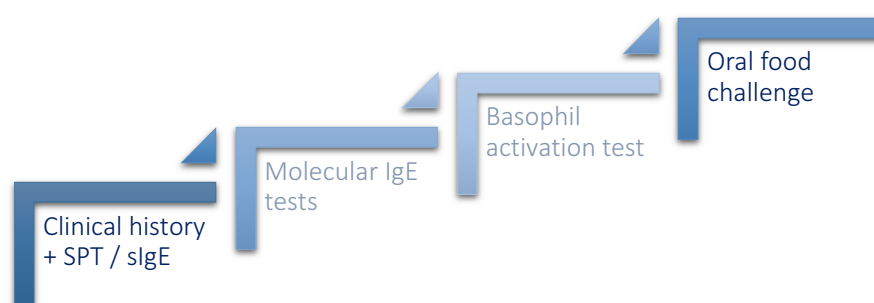


FIGURE 1 Recommended sequence of tests to support the diagnosis of IgE-mediated food allergy. Clinical history and allergen extract IgE evidenced by serology or skin prick test is the basis and oral food challenge the reference standard for diagnosis (represented in darker blue). Molecular IgE tests and the basophil activation test (BAT) are represented in lighter blue and should be used, if available, for investigation of specific food allergies. Molecular IgE tests are recommended for the foods which it provides additional information to tests using allergen extracts, namely peanut, hazelnut, cashew nut. The BAT is recommended for peanut and sesame.

1. Inclusion of molecular IgE testing, in addition to testing for SPT or sIgE to extracts, to support the diagnosis of peanut, hazelnut, cashew nut, allergies;
2. Inclusion of BAT, where available, when other test results are equivocal, to confirm allergy to peanut or sesame;
3. Statement that open oral food challenges (OFC) are appropriate for the majority of cases in clinical practice, leaving double-blind placebo-controlled food challenges (DBPCFC) to specific clinical scenarios, and the research setting;
4. Update of the algorithm proposed for the diagnostic work-up of patients with suspected IgE-mediated food allergy. This process should start with an allergy-focused history followed by investigation of the presence of allergen-specific IgE using SPT and/or specific IgE to allergen extracts (or fresh foods in case of SPT). In cases that cannot be diagnosed with a combination of history and SPT/specific IgE, additional tests may be performed such as molecular IgE tests, for foods that this is informative, and the BAT, where available (Figure 1). The use of this approach aims to reduce the need for undertaking an OFC which is resource-intensive, time-consuming, and not without risk, and to reduce the list for patients waiting for OFC.
5. One of the main barriers to implementation of these guidelines is the heterogeneity of availability of tests in different countries and clinical settings; this is especially true for molecular IgE tests and the BAT. An analysis of the cost-effectiveness of different diagnostic tests is required, balancing diagnostic accuracy and overall impact of a delayed diagnosis or a misdiagnosis for patients, society, and the health care system. Improved understanding of the pathogenesis and endo and phenotypes of food allergy, the roles of food additives and emulsifiers, other environmental factors, microbiome, skin mucosal epithelial barriers, and their diagnostic utility in the context of the epithelial barrier theory are also important.¹¹ Additional research needs in food allergy diagnosis identified by the expert group as having high priority include:
 1. Creation of diagnostic algorithms for primary care based on the clinical history;
 2. Identification of new allergens in foods and assessment of their diagnostic utility;
 3. Collection of additional data on the diagnostic performance of epitope profiling (namely in geographical locations other than the USA, to foods other than peanut and in comparative studies with

existing modalities of testing) and on the BAT, namely to foods other than peanut and sesame;

4. Validation of the utility of the BAT and other biomarkers to predict severity and threshold of allergic reactions;
5. Determination of the diagnostic performance of tests in patient population of different ages, ethnicity, and geographical locations around the globe.

To conclude, an accurate diagnosis of food allergy is essential, particularly in the context of a rising prevalence and rising awareness about atopic diseases, and food allergy specifically. The current EAACI Guidelines on Food Allergy Diagnosis will be followed by EAACI Guidelines on Management of IgE-mediated Food Allergy. We aim to update these guidelines by 2028, or earlier if important evidence emerges. Dissemination and implementation of the updated EAACI Food Allergy Guidelines will be crucial to ensure prompt identification of the disease and optimization of the care of patients living with food allergies.

AUTHOR CONTRIBUTION

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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