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GUIDELINE

EAACI guidelines on the diagnosis of IgE-mediated food allergy

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Abstract

This European Academy of Allergy and Clinical Immunology guideline provides recommendations for diagnosing IgE-mediated food allergy and was developed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Food allergy diagnosis starts with an allergy-focused clinical history followed by tests to determine IgE sensitization, such as serum allergen-specific IgE (sIgE) and skin prick test (SPT), and the basophil activation test (BAT), if available. Evidence for IgE sensitization should be sought for any suspected foods. The diagnosis of allergy to some foods, such as peanut and cashew nut, is well supported by SPT and serum sIgE, whereas there are less data and the performance of these tests is poorer for other foods, such as

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wheat and soya. The measurement of sIgE to allergen components such as Ara h 2 from peanut, Cor a 14 from hazelnut and Ana o 3 from cashew can be useful to further support the diagnosis, especially in pollen-sensitized individuals. BAT to peanut and sesame can be used additionally. The reference standard for food allergy diagnosis is the oral food challenge (OFC). OFC should be performed in equivocal cases. For practical reasons, open challenges are suitable in most cases. Reassessment of food allergic children with allergy tests and/or OFCs periodically over time will enable reintroduction of food into the diet in the case of spontaneous acquisition of oral tolerance.

KEYWORDS
basophil activation test, diagnosis, food allergy, oral food challenges, skin prick test, specific IgE

1 | INTRODUCTION

Food allergy constitutes a major public health issue with increasing prevalence having been documented in the past few decades.[1] It affects about 3–10% of children and up to 10% of adults.[2–4] Data from Australia reported 10% prevalence of food allergy in infants.[5] A UK study reported a prevalence for food allergy of 7.1% at age 3 years in breast-fed infants.[6] In a recent systematic review, the self-reported physician-diagnosed lifetime prevalence of any food allergy was 9.3% for children and 5.0% for adults, respectively.[7] Other studies have reported a higher prevalence of self-reported food allergy compared to clinician-diagnosed food allergy which is higher than that of challenge-proven food allergy. Food allergy can have negative consequences on the health, mental state and well-being of affected patients and their families.[2,3] Precise diagnosis and patient-tailored management of food allergy are of major importance, both in guiding allergen avoidance and emergency treatment, and in avoiding unnecessary dietary restrictions.

Food allergy is an adverse reaction to food that is mediated by the immune system. Johansson et al.[8] integrated food allergy as part of a wider group of clinical entities designated as 'food hypersensitivity', which includes any adverse reaction to food. If such adverse reaction is immune mediated, it is a food allergy; if it is not immune mediated, it is designated a food intolerance.

Food allergy can be classified into IgE-mediated, non-IgE mediated and mixed IgE and non-IgE mediated, depending on the involvement of IgE in its pathogenesis.[8] Specifically, it can be classified depending on whether the underlying mechanism is type I hypersensitivity (IgE-mediated), type III or type IV hypersensitivity (non-IgE-mediated) or a combination of IgE and cellular mechanisms (mixed IgE and non-IgE mediated), respectively.

As part of the differential diagnosis of IgE-mediated food allergy, one can consider food allergies which are non-IgE mediated or are mixed IgE and non-IgE mediated (Table 1). There are other causes of adverse reactions to foods that do not have an immunologic mechanism and need to be considered as part of differential diagnosis of IgE-mediated food allergy.[8] Such clinical entities may be metabolic, pharmacologic or toxic in origin or have a different underlying mechanism (Table 2).

The European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy Guidelines focus solely on IgE-mediated food allergy, as defined by:

1. Typical symptoms (Table 3) that usually develop within 2 h of exposure to the allergen and are reproducible upon re-exposure, and
2. Evidence of IgE sensitization and/or effector cell response to the culprit allergen.

This EAACI Food Allergy Guideline builds on a previous iteration published in 2014[9] and on the immunotherapy for IgE-mediated food allergy guidelines published in 2018.[10] The updated EAACI Food Allergy Guideline is formed of two parts: this first part which aims to provide a state-of-the-art document to guide the healthcare

TABLE 1 Examples of non-IgE and mixed IgE and non-IgE mediated food allergies.

Non-IgE mediated food allergy	Mixed IgE and non-IgE mediated food allergy
• Contact dermatitis	• Exacerbation of atopic eczema[a]
• Food protein-induced enterocolitis syndrome (FPIES)	• Eosinophilic oesophagitis
• Food protein-induced allergic proctitis and proctocolitis	• Eosinophilic gastritis/enteritis
• Food protein-induced enteropathy	• Exacerbation of asthma[a]
• Dermatitis herpetiformis	
• Heiner syndrome	
• Coeliac disease (may also be considered an auto-immune condition)	

[a]Following exposure (namely on contact with the skin or by inhalation) to the culprit food allergen.

TABLE 2 Differential diagnoses of IgE-mediated food allergy.

Mechanism	Clinical entities
Metabolic	• Lactose intolerance • Galactosemia • Intolerance to FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols)
Pharmacologic	• High histamine-containing foods (e.g. aged cheese, fermented meat fish and sauerkraut) • Histamine-releasing foods (e.g. strawberry, papaya, wine, kiwi and pineapple) • Tyramine (aged cheese, pickled fish) • Caffeine • Theobromine (chocolate) • Phenylethylamine (chocolate) • α-solanine (potatoes) • TRPV1 and TRPA1 agonists (spices, capsaicin, allicin in garlic and onion, ginger, wasabi, horseradish, pepper) • Monosodium glutamate (MSG) • Alcohol • Serotonin (tomato, banana) • Tryptamine (tomato, plum)
Toxic	• Infectious gastritis/enteritis • Histamine intoxication (e.g. Scombroid poisoning, poisoning from other types of fish or cheese)
Other	• Infectious/post-infectious acute urticaria • Bacterial/ yeast / fungal overgrowth • Pancreatic insufficiency • Gustatory rhinitis • Frey syndrome or auriculotemporal syndrome • Stress/anxiety • Psychogenic reactions (factitious illness, food phobias/aversions) • Irritable bowel syndrome (IBS) • Gastroesophageal reflux • Peptic ulcer and other dyspeptic disorders • Anatomical disorders (e.g. hiatal hernia, pyloric stenosis, Hirschsprung disease and tracheoesophageal fistula) • Carcinoid syndrome

professionals to diagnose IgE-mediated food allergy in patients of all ages and a second part which will focus on clinical management of IgE-mediated food allergy.

2 | METHODS

2.1 | Scope of guidelines

The EAACI Food Allergy Guideline focuses on IgE-mediated food allergy and is aimed at health care professionals specialized in Allergy and Clinical Immunology or a related specialty and generalists who assess and manage patients with suspected food allergy in their daily practice.

2.2 | Expert group and stakeholder involvement

The EAACI Food Allergy Guideline was commissioned by EAACI and led by the steering committee chaired by Alexandra F. Santos and formed by Alexandra F. Santos, Isabel Skypala, George Du Toit and Carmen Riggioni. An expert group was formed to advise on the elaboration of the guidelines and formulation of the recommendations, listed as authors herein. The expert group included authors of the last EAACI Food Allergy Guidelines, current board members of the relevant EAACI sections and interest groups, additional experts from countries outside Europe such as the United States, Canada, Brazil, South Africa, Hong Kong, Singapore and Australia, to ensure global relevance of the guidelines, and from key areas such as psychology and nursing, and junior members. Patient representatives were represented as well, namely from the European Federation of Allergy and Airways Diseases (EFA) and the EAACI Patient Organisations' Committee (POC), and provided input throughout the process from inception to publication and will also be involved in future dissemination of the guideline.

2.3 | Systematic review of the evidence and formulation of recommendations

The present food allergy guideline's module on diagnosis was informed by a systematic review of the literature and multiple

TABLE 3 Examples of symptoms of IgE-mediated food allergy.

Organ or system	Symptoms and signs
Skin	Urticaria Angio-oedema Pruritus Flushing Erythema in the predilection sites of eczema Ear or palm itching
Gastro-intestinal	Oral/pharyngeal pruritus Oral/pharyngeal swelling Vomiting Nausea Abdominal cramps Diarrhoea Abdominal pain
Ocular	Conjunctival erythema Pruritus Lacrimation
Respiratory	Rhinitis (rhinorrhoea, sneezing, nasal obstruction, pruritus) Hoarseness Stridor/laryngeal oedema Cough Dyspnoea Chest tightness Wheezing Cyanosis
Cardiovascular	Pallor Cold sweats Heart palpitations Pre-syncope / Syncope Tachycardia Hypotension Shock
Neurological	Anxiety 'Feeling of impending doom' Change in behaviour Irritability Apathy Lethargy Seizures Syncope/Loss of consciousness
Other	Uterine contractions resulting in abdominal pain and bleeding Shivering

meta-analyses on the accuracy of tests to support the diagnosis of IgE-mediated food allergy.[11,12] For other sections of the guideline, in the absence of evidence, an expert consensus-based approach was used. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach[13] was adopted, similar to other EAACI guidelines.[14] The expert group met periodically over a 2-year period to appraise the results of the systematic review and to discuss the recommendations that were drafted in advance of video meetings. Following detailed discussion, the recommendations were voted on electronically in real time using the Zoom voting platform (https://zoom.us/) managed by an independent member of the EAACI headquarters team. A minimum of 80% of votes in favour of the recommendations was required for the recommendations to be approved.

2.4 | Peer-review and public consultation

This guideline have been reviewed by the expert group that formed the EAACI task force and by the EAACI Executive Committee. The guideline was also submitted to public consultation through display on the EAACI website for 2 weeks, and all feedback was carefully considered by the steering committee and incorporated, to the greatest extent possible, in the final version, which was reviewed and approved by all listed authors.

2.5 | Conflicts of interest management

The EAACI Food Allergy Guidelines were commissioned and funded by EAACI to support the effort towards the systematic review of the

literature and meta-analyses. All members of the steering committee and of the expert group worked voluntarily without compensation and filled in a declaration of conflicts ahead of the start of the project, which were reviewed by EAACI.

3 | GUIDELINE RECOMMENDATIONS

Table 4 lists the recommendations formulated and approved by the EAACI Food Allergy Guidelines steering committee and expert group based on the systematic review and meta-analyses done specifically for the guidelines[11,12] and expert opinion, as appropriate. The following sections elaborate on the recommendations and the principles underlying them.

3.1 | Allergy-focused clinical history

> Recommendation 1: In patients with suspected IgE-mediated food allergy, a detailed allergy-focused clinical history is recommended as the first step of the diagnostic work-up (low certainty of evidence, expert opinion).

Reason for recommendation: An allergy-focused diet and clinical history is the first step on the food allergy diagnostic pathway.[15] Key areas are listed in Table 5.[9,16,17] One study determined the minimal information to be collected as part of the history and estimated that the diagnostic accuracy of the clinical history was 91.7% in terms of area under the ROC curve.[18] Another study validated a diet and clinical history questionnaire, against open and blinded oral food challenges for the diagnosis of pollen-food syndrome in adults, which had a specificity 86% of and sensitivity of 94%.

Strength of recommendation: There is little evidence addressing the value of the clinical history to reach an accurate food allergy diagnosis. However, the expert panel considered the clinical history to be fundamental to the diagnosis of food allergy. Specifically, it provides the pre-test probability of disease that is critically needed to properly select and interpret subsequent diagnostic tests. The expert panel considered the clinical history an essential and critical element to reach an accurate diagnosis of food allergy, and a strong recommendation was made.

Practical implications: The clinical history allows the identification of the possible mechanism of food allergy (i.e. IgE or non-IgE-mediated) and the foods/allergens to be tested. It also guides the interpretation of the test results. IgE-mediated reactions to foods can manifest with symptoms and signs involving one or more of the following systems: skin, gastro-intestinal, respiratory, cardiovascular and/or neurological (Table 3). A greater percentage of children with IgE-mediated food allergy will report skin symptoms, whereas adults are most likely to experience oro-pharyngeal symptoms.[19] IgE-mediated reactions generally occur within 2 h of consumption of the trigger food, although there are some exceptions. For example, symptoms due to a co-factor-induced food allergy, or anaphylaxis to mammalian meat due to IgE antibodies to the oligosaccharide

TABLE 4 Recommendations about the diagnosis of IgE-mediated food allergy.

Topic	Recommendations	Certainty of evidence	Strength of recommendation
Clinical history	1. In patients with suspected IgE-mediated food allergy, a detailed allergy-focused clinical history is recommended as the first step in the diagnostic work-up for food allergy	Low	Strong
Diagnostic tests	2. In patients with a history of suspected IgE-mediated food allergy, skin prick test and/or measurement of serum specific IgE are recommended as first-line test to support diagnosis	High	Strong
	3. In patients with a history of suspected IgE-mediated allergy to peanut, hazelnut or cashew nut, specific IgE to Ara h 2, Cor a 14 or Ana o 3, respectively, are recommended, where available, in addition to skin prick test and/or IgE to extracts, to further support diagnosis	High	Strong
	4. In patients with an equivocal diagnosis of IgE-mediated allergy to peanut or sesame, BAT to peanut or sesame, respectively, are suggested, where available, to further support diagnosis	High	Conditional
	5. In patients with suspected IgE-mediated food allergy, the isolated use of IgG and IgG subclass tests and the other tests listed on Table S2 is recommended against to support the diagnosis of IgE-mediated food allergy	Very low	Strong
	6. Reassessment of food allergic children, at regular intervals, depending on age, food and patient's history, is suggested for possible development of spontaneous tolerance	Moderate	Conditional
Oral food challenge	7. A supervised oral food challenge (OFC) is recommended as the reference diagnostic procedure to confirm or exclude food allergy.	High	Strong
	8. Double-blind placebo-controlled food challenges (DBPCFC) are suggested if an open OFC outcome is indeterminate and in research studies	Low	Conditional

TABLE 5 Key questions for an allergy-focused history.

Age at symptom onset	When did the manifestations start? Infancy, childhood, adolescence or adulthood
Presenting symptoms—type and severity	Symptom type and organ involved (skin, gut, upper and lower airway, neurological, cardiovascular), and whether they were mild, moderate or severe
Speed of symptom onset and duration of symptoms	Were the symptoms immediate, usually within a few minutes and up to 2 h after eating (3–6 h for alpha-gal allergy)? Did the symptoms resolve spontaneously?
Treatment for previous reactions	Was an antihistamine given and effective? Were other medications administered including adrenaline?
Food(s) suspected	Which foods were new to the individual's diet? Have they been eaten previously without a problem? Were they eaten in a different form previously? Are hidden allergens a likely trigger? Foods commonly implicated in IgE-mediated food allergy: cow's milk, egg, wheat, soya, sesame, peanut, tree nuts, fish, shellfish, legumes, fruits and vegetables. Common hidden allergens: celery, mustard, cochineal, lupin, soy, fenugreek, other legumes such as pea/bean/lentil protein, insects/mealworm, pink peppercorns)
Quantity of food	How much of the ingested food provoked symptoms—a mouthful, or up to a whole portion?
Reproducibility of reactions	Does the reaction occur every time the food is eaten, or can it be tolerated in a different form, or a different variety (fruits and vegetables)?
Food processing	Was the food raw, cooked or processed and does tolerance depend on the cooking method?
Route of exposure	Was the suspected food ingested, touched or inhaled? Occupational exposure to the food?
Involvement of co-factors	Did the reaction only occur when the food was eaten within 2 h and was it linked to exercise, alcohol, aspirin or non-steroidal anti-inflammatory drugs, acid suppressant medications, sleep deprivation, stress, cannabis use, hormonal factors?
Setting of the reaction	Where did the reaction occur? At home, school, restaurant, on holiday or in the workplace?
Potential for cross-reactivity	Is the patient sensitized to pollens, latex or house dust mite? If so, what is the potential for a cross-reactive food allergy?
Dietary history	What is the type of feeding (breast and/or formula feeds)? What is the complementary food history (if applicable), typical daily intake and foods habitually consumed without consequence?
Previous/current food elimination	Which foods are being avoided? Has a food allergy been diagnosed before or was an elimination diet undertaken previously? and if so, what was the result?
Other foods being avoided	Which foods are avoided for personal, religious or cultural reasons?
Dietary Adequacy	Is the current diet nutritionally adequate or is it already compromised due to the exclusion of foods for other reasons? Consider the effect of dietary restrictions with regard to age, growth, weight loss (body mass index) and current food intake.
History of concomitant atopic and other diseases	Are atopic dermatitis, seasonal or perennial allergic rhinitis, asthma and urticaria present?
Family history of atopic disease	Do any of their parents and/or siblings have atopic disease?

		Likelihood of allergy from test results		
		Low	Intermediate	High
Likelihood of allergy from clinical history	High	*Possible allergy*	***Probably allergic***	***Likely to be allergic***
	Intermediate	*Possible allergy*	*Possible allergy*	***Probably allergic***
	Low	***Unlikely to be allergic***	*Possible allergy*	*Possible allergy*

FIGURE 1 Integration of pre-test probability estimated from the clinical history (left column) and the post-test probability (*in italics*) that will be used to support or refute the diagnosis of IgE-mediated food allergy (adapted from[69]).

galactose-alpha-1,3-galactose (alpha-gal), may not manifest until 2–6 h after ingestion of the food allergen.[20]

Symptom history should be taken in conjunction with a detailed dietary history.[21] This should include questions on habitual dietary intake (meals, snacks, beverages); breast/bottle feeding, growth and feeding issues in children and eating disorders in older children and adults; body mass index (BMI) and weight loss in adults; and dietary adequacy. An allergy-focused dietary history will also identify over and under nutrition, micronutrient deficiencies, balanced intake of macronutrients and, in infants and young children, concerns about development, feeding skills and aversive feeding patterns.[22]

Other essential components of the clinical history include ascertaining the presence of other allergic co-morbidities, tolerance to co- or cross-reacting foods, possible occupational exposure to allergens, co-factors, family history of allergic disease, concomitant drug allergies, current/previous medications and previous immunizations.

The value of the clinical history is undebatable; however, it can overestimate the presence of food allergy and further testing is required to confirm the diagnosis. A detailed allergy-focused clinical history will allow to estimate the likelihood (pre-test probability) that a patient has an IgE-mediated food allergy and to guide the selection of IgE sensitization tests and their interpretation to determine the post-test probability of IgE-mediated food allergy, which, in turn, is used for clinical decision-making (Figure 1). A history of regular consumption of age-appropriate portions of the food in the relevant type of processing without developing any allergic symptoms rules out food allergy without the need for testing. However, adults may report new-onset reactions to foods they were previously consuming for many years, and co-factors should be considered if foods are reported to provoke symptoms but not every time the food is consumed.

3.2 | Diagnostic tests

Following an allergy-focused history, evidence of allergen-specific IgE should be sought to support the diagnosis of IgE-mediated food allergy. Such evidence may be provided by one or more of the following tests:

- Skin prick test (SPT) using allergen extracts or fresh foods
- Specific IgE to allergen extracts (sIgE)
- Specific IgE to individual allergen components (MA, molecular allergology)
- BAT

Whilst SPT, sIgE and/or have been implemented in many allergy clinic settings, BAT is making the transition to clinical practice and may not be widely available.

Table 6 lists the tests that are recommended to support the diagnosis of IgE-mediated food allergy, based on a systematic review of the published literature.[11] There are other tests that do not gather enough evidence to be recommended for use in routine clinical practice but are promising and deserve further research (Table S1)—for instance, specific IgE to allergen peptides or epitope profiling and the mast cell activation test (MAT).

The allergens to be selected in allergy tests should be directed by the clinical history, and indiscriminate panel testing should be avoided. However, multiple molecular allergen testing can be useful in specific cases—for example, to clarify clinical relevance of immunologic cross-reactivity in cases of multiple plant food allergy or cases of combined pollen and food allergies and to identify possible hidden trigger of recurrent anaphylaxis.

The suspicion of allergy to a specific food may result from a possible reaction reported by the patient or caregiver or from epidemiological evidence of risk for a specific food allergy, especially when there is opportunity for intervention. For example, in high peanut allergy prevalence countries, children who attend an Allergy clinic with severe eczema and reported reactions to egg who have not yet consumed peanut could be tested to peanut so that peanut can be introduced in the diet if the patient is not allergic to prevent the development of peanut allergy.[23,24] However, in other cases where the pre-test probability of peanut allergy is not high, diagnostic

TABLE 6 Recommended tests to support the diagnosis of IgE-mediated allergy.

Diagnostic tests	Rationale for using these tests to support the diagnosis of IgE-mediated food allergy
Skin prick test to allergen extracts	Wheal size reflects the amount of mast cell mediators following stimulation with allergen.
Skin prick test to fresh food (prick-to-prick)	Wheal size reflects the amount of mast cell mediators following stimulation with allergen. Use of fresh foods can increase sensitivity of tests as fresh foods contain allergens that may be destroyed or excluded during preparation of allergen extracts (e.g. thermolabile allergens or lipophilic allergens).
Specific IgE to allergen extracts	Concentration of IgE in the serum reflect the amount of circulating IgE antibodies directed to the allergen tested.
Specific IgE to individual allergen components	IgE to specific allergen components shown to be clinically relevant can be more specific than IgE to whole allergen extracts.
Basophil activation test	Proportion of in vitro allergen-activated basophils reflects the amount of mediators released by circulating basophils following stimulation with allergen. This functional test uses patients' own basophils and detects the combined intrinsic cellular response and effect of allergen-IgE binding.

testing should not be employed and prompt peanut introduction is recommended.

At the population level, patients with a larger SPT wheal, higher allergen-specific IgE and higher proportion of activated basophils in the BAT are more likely to be allergic to that specific food.[25] Conversely, a negative SPT and specific IgE usually have high sensitivity and high negative predictive value (NPV) and are therefore useful to exclude food allergy, especially in the absence of a clinical reaction to that food and in the presence of high-quality extracts containing the relevant allergens. However, no test is absolute, and all test results need to be interpreted considering the clinical context. Food allergy should therefore not be ruled out by a negative test when the history is very suggestive of clinical allergy.

High positive predictive value cut-offs have been defined for some foods, in some (but not all) geographical locations, mostly in children with few studies in adults. In the populations and geographical locations where such cut-offs have been validated, sensitization/effector cell response alone (without previous clinical reactions) can support the diagnosis and avoid an oral food challenge (OFC). For instance, in the case of peanut, allergy can be diagnosed in the United Kingdom and United States based on specific IgE to peanut greater or equal to 15 KU/L and/or SPT greater or equal to 8 mm.[25]

If the results of first-line tests (i.e. SPT and sIgE to extracts) are equivocal or contradictory with history, additional tests may need to be performed. For instance, if SPT is equivocal, specific IgE can be tested and vice-versa. For the foods for which specific IgE to allergen components has additional value compared to specific IgE to extracts (e.g. peanut, hazelnut and cashew nut), these components can be used as additional tests to clarify the diagnosis, especially in individuals sensitized to pollen. In the cases that remain equivocal, the BAT (e.g. to peanut or sesame) could be used to support the diagnosis further. Ultimately, the equivocal cases need to be clarified by OFC. Figure 2 illustrates this integrated approach for the use of tests to support the diagnosis of IgE-mediated food allergy in clinical practice.

> Recommendation 2: In patients with a history of suspected IgE-mediated food allergy, skin prick test and/or measurement of serum specific IgE are recommended as first-line tests in the diagnostic work-up for food allergy (high certainty of evidence).

Reason for recommendation: The systematic review of the literature and meta-analyses that informed these guidelines[11] summarizes the evidence available to support the use of these tests for specific food allergies. The diagnostic performance of the various tests is specific to the food being tested, with sensitivity of SPT and specific IgE being generally moderate and high only for cashew nut (both SPT and specific IgE) and shrimp (specific IgE only) and specificity of SPT and specific IgE being also generally moderate and high only for cow's milk (specific IgE only) and cashew nut (SPT only)—see Table 7 for specific cut-offs and their diagnostic performance.

Strength of recommendation: The underpinning systematic review and meta-analysis provides high certainty evidence for the diagnostic value of SPT and specific IgE for the majority of the foods. Although their sensitivity and specificity are generally moderate, SPT and specific IgE are relatively inexpensive and widely available. So, a strong recommendation was made.

Practical implications: SPT and specific IgE to foods such as cashew showed a high sensitivity (>90%), whereas for other foods only one of these tests showed high sensitivity (for instance SPT to raw egg and specific IgE to shrimp) and for foods such as soya and wheat, both SPT and specific IgE had relatively poorer accuracy. However, SPT and specific IgE to extracts can be the starting point for the diagnostic work-up and followed by additional tests for the foods, where these are available and informative. SPT can be performed with the fresh food for increased sensitivity—this is especially important for food allergens that may not be well-represented in the allergen extracts, such as labile allergens from fresh fruits and vegetables and lipophilic allergens from sesame paste (tahini) or certain nuts. Cut-offs with maximal sensitivity can be used to screen for IgE sensitization and cut-offs with maximum specificity can be used to support the confirmation of clinical allergy, particularly in the presence of a suggestive history. The diagnostic accuracy of tests using maximum sensitivity and maximum specificity cut-offs were reported for a variety of foods in the accompanying systematic review and meta-analyses.[11] The utility of SPT and specific IgE testing may be hampered by the quality of allergen extracts available for testing. Variability and the need for standardization of allergen extracts is an important aspect of reliable allergy testing. Some allergen extracts and individual allergen components are susceptible to cross-reactive carbohydrate determinants (CCD) contamination, which can cause falsely elevated IgE levels with no clinical significance. Up to 30% of allergic patients, especially patients sensitized to pollen and also to plant foods such as peanut, are sensitized to CCD.[26–29]

The interpretation of test results is specific to the food, the geographical location and the individual being tested. For instance, the diagnostic performance of tests is allergen-specific and, in the same patient population, optimal cut-offs vary for different foods—for example, in a single US study, 95% PPV cut-offs were 15 KU/L for cow's milk, 7 KU/L for egg, 15 KU/L for peanut and 20 KU/L for fish allergies.[30] Different geographical locations may present typical IgE sensitization patterns—for example, patients living in birch endemic areas are often sensitized to birch pollen and Bet v 1 homologues in plant foods, whereas in areas where birch pollen exposure is minimal, patients are sensitized to other pollens and more commonly sensitized to lipid transfer proteins (LTP) in plant foods.[31] Allergy to plant foods due to sensitization to LTP can present with systemic reactions including anaphylaxis.[32] In the meta-analyses undertaken to support the current guidelines,[11] specific IgE to peanut had higher specificity in studies conducted in Western Europe compared to Northern Europe, where Ara h 2-specific IgE gained higher specificity. This was probably due, at least in part, to the endemic birch pollen sensitization in Northern Europe.

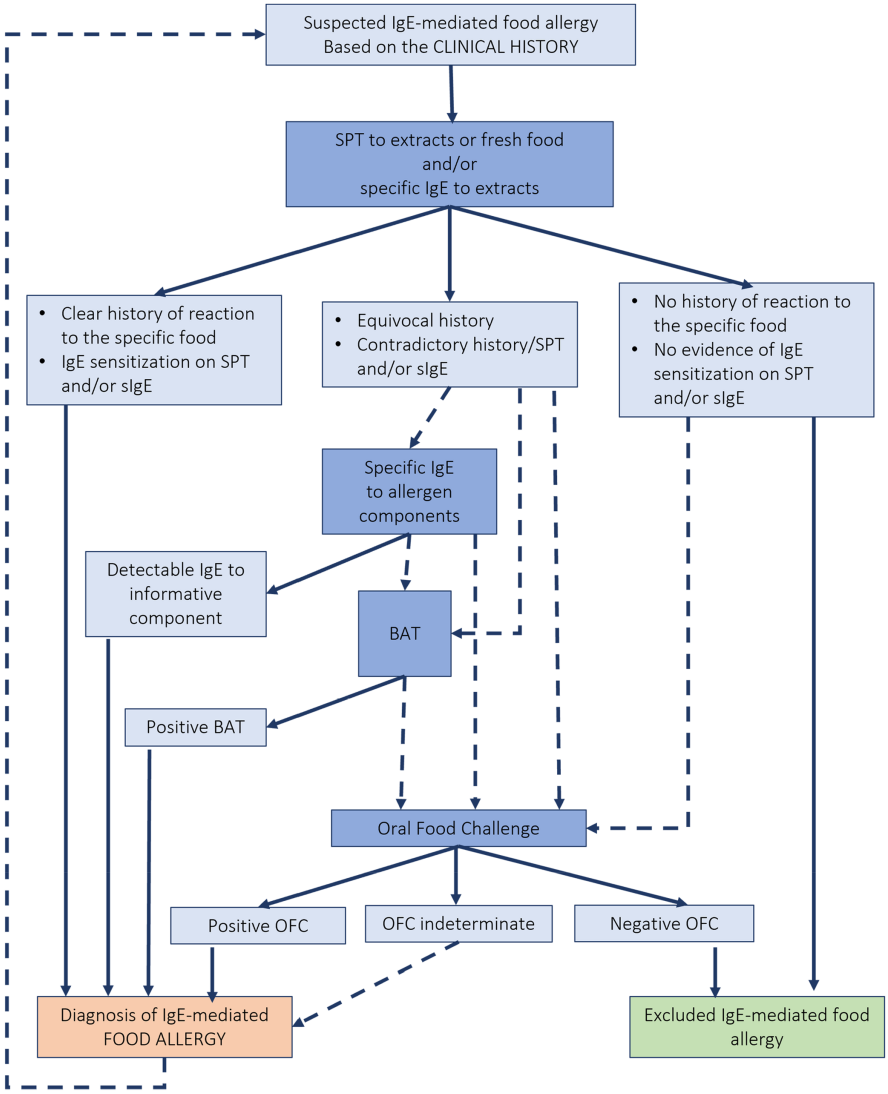

FIGURE 2 Algorithm for the recommended sequence of tests to support the diagnosis of IgE-mediated food allergy. If SPT results are contradictory with the history, specific IgE to allergen extracts can be performed to double-check, and vice-versa. Additional tests may be done, if necessary and if available. The sequence of tests indicates priority for testing and not that all tests need to be performed (thus the dashed lines). The choice of tests depends on the food being tested and the diagnostic performance of specific tests in this context. The long-dashed arrow on the left back to the top represents the periodic reassessment for possible spontaneous resolution of food allergy in children.

Patient-specific factors need to be taken into account when determining the clinical relevance of an SPT or specific IgE result[33]—for example, in young children, lower levels of allergen-specific IgE can have higher probability of clinical allergy.[34] There can also be differences in diagnostic performance of specific tests between age groups. For example, from the meta-analyses conducted for different ages[11] it was evident that peanut-specific IgE had higher specificity in younger children and Ara h 2-specific IgE gained specificity in adults. This is probably due to the higher prevalence of pollen-food syndrome in older individuals. Therefore, the extrapolation of diagnostic cut-offs from published studies into clinical practice needs to be undertaken with caution. Such cut-offs should be used only as guidance to the clinical interpretation of allergy test results and not as clear-cut decision-points.

> Recommendation 3: In patients with a history of suspected IgE-mediated allergy to peanut, hazelnut or cashew nut, specific IgE to Ara h 2, Cor a 14 and Ana o 3, respectively, are recommended, where available, in addition to skin prick test and/or IgE to extracts, to further support a food allergy diagnosis (high certainty of evidence).

Reason for recommendation: Specific IgE to certain allergen components have demonstrated superior specificity compared to specific IgE to allergen extracts, which renders them useful to confirm the diagnosis of food allergy in patients with a suggestive history. This is particularly important when the history is unclear, the results of SPT and/or specific IgE to extracts are not sufficient to support the diagnosis or history and test results are conflicting. Component testing may be particularly helpful in pollen-sensitized patients, where specific IgE to cross-reactive allergens may lead to a false-positive result on specific IgE to the allergen extract, that is to IgE sensitization without clinical relevance.[35] When testing for specific IgE to allergen components, it is useful to simultaneously test for specific IgE to the respective extract to capture sensitization in the broader sense, including minor allergens that may be less common but clinically relevant in some patients. For example, peanut sensitized patients who test negative to Ara h 2-specific IgE may be sensitized to other peanut components and testing to Ara h 2-specific IgE in

TABLE 7 Summary of diagnostic performance of various tests for specific foods based on the results of recent meta-analyses[11].

Diagnostic test	Cow's milk	Egg	Peanut	Hazelnut	Cashew	Sesame	Wheat	Shrimp
Skin prick test								
Cut-offs (mm)	4 (3; 8)	5 (3; 8)	4 (3–8)	5 (3–7)	5 (4–6)	8 (4–10)	3 (3–5)	3 (3–5)
Sensitivity	0.52 (0.24- 0.79)	0.68 (0.37- 0.88)	0.84 (0.69- 0.92)	0.82 (0.68- 0.91)	0.93 (0.89- 0.96)	0.70 (0.55- 0.82)	0.53 (0.23;0.81)	0.62 (0.44 0.77)
Specificity	0.80 (0.65- 0.90)	0.77 (0.64- 0.86)	0.86 (0.79- 0.91)	0.78 (0.44; 0.94)	0.92 (0.82; 0.96)	0.89 (0.76- 0.95)	0.72 (0.57; 0.84)	0.90 (0.31; 0.99)
Specific IgE to allergen extracts								
Cut-offs (KU/L)	3.5 (0.9–10.5)	3.5 (1.7–5.5)	4.3 (0.35–10)	2.34 (0.6–6.3)	1.1 (0.6–3.1)	7.5 (0.9–50)	0.6 (0.35–5.6)	1.2 (0.5–3.1)
Sensitivity	0.82 (0.59; 0.94)	0.85 (0.77; 0.90)	0.81 (0.71- 0.88)	0.79 (0.71- 0.85)	0.94 (0.89- 0.97)	0.70 (0.23- 0.95)	0.72 (0.54; 0.84)	0.96 (0.42; 1.00)
Specificity	0.92 (0.80; 0.97)	0.73 (0.63- 0.80)	0.83 (0.71- 0.90)	0.62 (0.38- 0.81)	0.64 (0.54- 0.74)	0.83 (0.26- 0.99)	0.79 (0.68; 0.86)	0.63 (0.46- 0.78)
Specific IgE to allergen-components								
Cut-offs (KU/L)	Casein 2.6 (1.0–5.3)	Ovomucoid 0.8 (0.35–3.7)	Ara h 2 0.44 (0.3–1.3)	Cor a 14 0.64 (0.35–3.5)	Ana o 3 0.4 (0.2; 0.6)	Ses i 1 2.0 (0.3-4.0)	Omega-5-gliadin 0.3 (0.1–0.6)	Pen a 1 1.1 (0.6; 4.4)
Sensitivity	0.67 (0.53- 0.78)	0.74 (0.54; 0.87)	0.82 (0.77- 0.86)	0.73 (0.53- 0.87)	0.96 (0.91- 0.98)	0.77 (0.64-0.86)	0.79 (0.68- 0.88)	0.62 (0.45- 0.76)
Specificity	0.93 (0.85- 0.97)	0.91 (0.87- 0.93)	0.92 (0.87- 0.95)	0.95 (0.90- 0.98)	0.94 (0.88- 0.97)	0.87 (0.77-0.92)	0.78 (0.66- 0.86)	0.89 (0.75- 0.95)
Basophil activation test								
Cut-offs (%CD63+ Basophils)			5.0 (4.7–7.1)			10.9 (8.2–11. 6)		
Sensitivity			0.84 (0.76- 0.90)			0.89 (0.80- 0.94)		
Specificity			0.90 (0.83- 0.94)			0.93 (0.76- 0.98)		

Note: Cut-offs indicated were reported in the studies included in the meta-analyses. Numbers between brackets indicate 95% confidence intervals. All ages. Specific IgE was performed with ImmunoCAP and allergen extracts unless otherwise stated. Cow milk is fresh pasteurized, and egg is whole cooked egg.

isolation may lead to misdiagnosis. In Table 7, one key allergen component is represented for each food; however, other allergens can be clinically relevant and informative in specific cases.

Ara h 2 and Ara h 6 from peanut, Cor a 9 and Cor a 14 from hazelnut showed moderate sensitivity (82%, 87%, 81% and 73%), respectively, with only Ana o 3 from cashew nut showing high sensitivity (96%),[11] whereas Ara h 2, Ara h 6, Cor a 14 and Ana o 3 showed high specificity (92%, 94%, 95% and 94%, respectively) with only Cor a 9 showing moderate specificity (89%) in the recent meta-analyses.[11] The diagnostic performance was similar for both Ara h 2 and Ara h 6.[11] A recent UK study suggests that Ara h 2 is dominant compared to Ara h 6 and that testing to Ara h 6 does not add much at the population level; however, cases of peanut allergy in patients monosensitized to Ara h 6 have been reported.[36,37] The performance of Cor a 14 was superior to that of Cor a 9 in the meta-analysis.[11] Therefore, if minimising the number of components to be tested, Ara h 2 from peanut and Cor a 14 from hazelnut are preferred. If uncertainty remains regarding the diagnosis, specific IgE to additional components such as Cor a 9 and Ara h 6, Ara h 1 or Ara h 3 can be helpful. However, in non-birch-endemic regions, such as Spain and Italy, LTP might be a more usual cause of peanut allergy.[31] Ana o 3-specific IgE stood out in cashew nut allergy for having both high sensitivity and high specificity, with extremely low heterogeneity between studies ($I^2 = 0$). For walnut allergy, Jug r 1-specific IgE may be helpful confirming the diagnosis as specificity was very high (99%); however, sensitivity was very low (43%), and thus, it should not be used without walnut-specific IgE.[11]

Strength of recommendation: The underpinning systematic review and meta-analysis provides high certainty evidence for a high specificity for these foods[11] so a strong recommendation is made.

Practical implications: When testing for specific IgE to these extracts (i.e. peanut, hazelnut and cashew nut), it may be useful to simultaneously test for specific IgE to the component (i.e. Ara h 2, Cor a 14 and Ana o 3, respectively) to confirm a diagnosis. A positive specific IgE to the extract will confirm sensitization to another component when the specific IgE to the key component (Ara h 2, Cor a 14 or Ana o 3) is negative.

> Recommendation 4: In patients with an equivocal diagnosis of IgE-mediated allergy to peanut or sesame, BAT to peanut or sesame, respectively, are suggested, where available, to further support a food allergy diagnosis (high certainty of evidence).

Reason for recommendation: In the meta-analyses performed, BAT to peanut and BAT to sesame demonstrated moderate sensitivity (86% and 89%, respectively)[11] and high specificity (90% and 93%, respectively) with low heterogeneity between studies. The systematic review of the literature captured studies about BAT to other foods,[11] but not in sufficient numbers to allow for meta-analyses.

Strength recommendation: BAT to peanut and the BAT to sesame have a very good diagnostic performance.[11] A conditional recommendation is made as, despite its very good diagnostic performance, BAT is more costly than SPT and specific IgE testing and may not be accessible in many clinical settings. For this reason, BAT should be reserved for cases that remain equivocal after SPT and specific IgE testing, to extracts and components, if available.

Practical implications: BAT should be reserved for cases that remain equivocal after SPT and specific IgE testing, to extracts and components, if available. A positive result confirms food allergy diagnosis, especially in patients with a suggestive history.

> Recommendation 5: In patients with suspected IgE-mediated food allergy, the isolated use of IgG and IgG subclass tests and the other tests listed on Table S2 is recommended against in the diagnosis of IgE-mediated food allergy (very low certainty of evidence, expert opinion).

Reason for recommendation: There are numerous tests purported to be of use in the diagnosis of IgE-mediated allergy; however, they lack evidence and rigorous validation to support their use (Table S2).[38–40]

Strength of recommendation: Despite the absence of specific studies addressing the diagnostic utility of these alternative tests (Table S2), the expert panel considered that there is no rationale and there are ethical issues around conducting such studies. Given the risks involved in the use of these tests (see below), a strong recommendation against these tests was made.

Practical implications: Unvalidated tests lack clinical relevance. The use of unvalidated tests is often made without prior clinical assessment and differentiation between IgE-mediated, mixed and non-IgE mediated food allergy or food intolerance.[41,42] The use of such tests carries significant risks, namely unnecessary dietary restriction which may be associated with dietary compromise, increased costs and reduced quality of life (QoL); and conversely, dietary liberation may be associated with potential exposure to culprit allergens.

> Recommendation 6: Reassessment of food allergic children, at regular intervals, depending on age, food and patient's history, is suggested to identify possible development of spontaneous tolerance (moderate certainty of evidence).

Reason for recommendation: Food allergy can resolve spontaneously, particularly in early childhood and for specific foods (e.g. cow's milk, egg, wheat and soya). For example, by school age (5–6 years), about 50–90% of children with cow's milk or egg allergies, 20–30% of children with peanut allergy and 9% with tree nut or sesame seed allergies experience spontaneous resolution of their food allergies; and 45% resolves fish allergy by adolescence.[43–45] The probability of resolution also changes with age (i.e. the older the individual, the lower the chance of resolution) and with the specific patient population (for instance, it may be higher at the general population level than in patients seen in specialist clinics; additionally, reports from clinic cohorts can overestimate persistence as patients who discover they outgrew allergy based on accidental exposure may not return to an allergy clinic for follow-up).

Strength of recommendation: There is no controlled evidence to assess the impact of reassessing patients at different frequencies. The expert panel's opinion though was that reassessment was warranted given the potential for spontaneous tolerance.

Practical implications: It is important to periodically reevaluate children in clinic to assess whether food allergies have resolved. The frequency of reassessment depends on specific food allergies and their natural history (e.g. for food allergies, such as cow's milk or egg, which resolve earlier in life, more frequent reassessment in early childhood is beneficial). Regular assessment of adults with food allergy is less necessary as there is little evidence that the natural history of food allergy changes much in adulthood and the possibility of spontaneous resolution in adulthood is likely to be low. However, new food allergies may develop in adults and older children and need to be investigated. Older adults have not been studied as much as younger adults, but they can still develop food allergy.[2,46] The same tests used to confirm the diagnosis of food allergy can be used to determine the probability of spontaneous resolution and the right time to reintroduce the avoided food to the diet. However, it should be noted that the diagnostic characteristics of the tests are not necessarily the same as for the original diagnosis. Furthermore, attention should be paid to the method used to re-test patients as methods for specific IgE and BAT are not interchangeable and therefore neither are the diagnostic cut-offs.[47–51] Depending on the results of tests and the history of exposure and previous reaction to the specific food, OFC is required to confirm tolerance. This is especially important if there was an allergic reaction in the past, as the risk of a reaction increases even if tests are low.

3.3 | Oral food challenges

> Recommendation 7: A medically supervised oral food challenge (OFC) is recommended to confirm or exclude food allergy in patients with an unclear diagnosis despite IgE sensitization tests (high certainty of evidence).

Reason for recommendation: Although the accuracy of diagnostic tests for some foods, when combined with clinical history, may be sufficient in many cases in clinical practice to provide a robust diagnosis, in others, the reference OFC is needed to make a definitive diagnosis of IgE-mediated food allergy.[9,52,53] Evidence suggests that less than 50% of patients undergoing OFC develop an allergic reaction; thus, OFC is often vital to eliminate unnecessary food avoidance and circumvent potential nutritional deficiencies and/or food aversion.[54–56]

Strength of recommendation: The underpinning systematic review provides high certainty of evidence that IgE sensitization tests do not provide a firm diagnosis in all cases. An OFC is an important part of the diagnostic process and has been demonstrated to improve quality of life.[57,58]

Practical implications: For practical reasons, open OFC is recommended as the routine challenge in the specialist allergy clinical practice. Circumstances where an OFC may be necessary are given in Table 8. Patient selection for challenge is not always dependent on allergy test results.[9,59–61] In some cases, additional factors need to be included in the OFC protocol to reproduce as close as possible real-life conditions—a good example of this is the combination of food and exercise challenge to diagnose food-dependent exercise-induced anaphylaxis. Care must be taken to ensure the challenge is safe; safety criteria include the assessment of the severity of reported reactions, foods involved, allergic co-morbidities, other medical conditions and ability to give consent (Table S3).[52,59,60] Those who are pregnant, have worsening allergic symptoms, an acute infection, or poorly controlled respiratory or cardiovascular conditions, should have their challenge postponed.[9,52,59] An OFC may also be utilized for other purposes, such as education or psychological interventions. An OFC is an important part of the diagnostic

TABLE 8 Indications for oral food challenge.

IgE sensitization, but…	No IgE sensitization, but…
… the food has never been consumed or previously tolerated but avoided for a significant period of time. This might occur for example when an allergy is diagnosed to an allied food group (e.g. peanut allergy diagnosed and also advised to avoid tree nuts), or because allergy tests were positive but without any symptoms to the food tested, or not introduced as a weaning food so far.	… reactions have been attributed to the food.
… the test result is below a validated cut-off point for that food.	… it is necessary to confirm that the allergy is outgrown.
… the history is not consistent with this result, despite a test result above the validated cut-off point.	… the individual and/or parents are highly anxious and/or avoiding multiple foods.
… co-sensitization to house dust mite or pollens may mean that positive tests to some foods (shellfish, fruits, tree nuts or peanuts) are not clinically relevant due to cross-reactivity.	… there is high clinical suspicion.
… the eliciting dose of the allergen needs to be determined. This may be useful when determining therapeutic dosing regimens.	…severe reactions have been reported to the trigger food.
… the development of tolerance is expected due to the natural history of allergy to a specific food.	… a non-IgE-mediated food allergy is suspected.
… the food might be tolerated in an alternative form, for example baked milk or egg, cooked or processed fruits/vegetables/nuts.	

TABLE 9 Gaps in the evidence and research needs in the diagnosis of food allergy.

Gaps in the evidence	Research need	Priority
Diagnostic algorithms for primary care based on the clinical history	Studies evaluating the efficacy of history against allergy tests and food challenge for both children and adults	High
Diagnostic performance of tests to confirm primary and secondary food allergy (i.e. food allergy resulting from sensitization to food allergens and food allergy resulting from cross-reactivity with pollen allergens)	Studies with oral food challenges and outcome defined as pollen food syndrome	Medium
Diagnostic performance of IgG4/IgE ratios and allergen/total IgE ratios for food allergy	Studies comparing allergen-specific IgG4/IgE ratios and allergen/total IgE ratios with the outcome of oral food challenges and determining the added value to existing tests	Medium
Identification of new allergens in foods and assessment of their diagnostic utility	Studies assessing the sensitivity and specificity of new and emerging allergens to support the diagnosis of food allergy	High
Additional data on the diagnostic performance of epitope profiling—for peanut allergy in geographical locations other than the United States; for other foods and determining the added value compared with existing tests	Diagnostic studies comparing IgE binding to allergen peptides with oral food challenges performed in different parts of the world and to foods other than peanut Direct comparison of epitope profiling with existing tests to understand the added value of this test	High
Additional data on the diagnostic performance of the basophil activation test for foods other than peanut and sesame	Diagnostic studies comparing the results of BAT with oral food challenges and other tests for foods other than peanut and sesame	High
Validation of utility of the basophil activation test and other biomarkers to identify allergic patients at risk of severe reactions	Studies comparing various biomarkers (e.g. SPT, specific IgE, BAT and epitope profiling) with the outcome of oral food challenges to various foods	High
Diagnostic accuracy of open OFC versus DBPCFC for individual food allergens	Randomized controlled trialss comparing open versus DBPCFCs for individual food allergens	Medium
Diagnostic performance of tests in different ages, ethnicity and geographical locations	Studies assessing sensitivity and specificity of tests to support diagnosis of IgE-mediated food allergy in specific age groups (very young children, adults, older adults), ethnicities (including diverse and underrepresented groups) and low-income countries	High
Access to specialized care to confirm or refute suspected food allergy	Studies evaluating the efficacy of food allergy diagnosis using telemedicine	Medium

process and has been demonstrated to improve quality of life.[57,58] However, not all those who have a negative challenge will reintroduce the food. Reluctance to do so may be due to psychological or other factors, which re-emphasizes the need to ensure that food exclusion is based on a robust diagnostic pathway[62,63] and to closely monitor whether the food has been reintroduced after a negative food challenge. Key practical aspects to consider when undertaking an OFC are listed in Table S4.

> Recommendation 8: A double-blind placebo-controlled food challenge (DBPCFC) is suggested if an open OFC outcome is indeterminate and in research studies (low certainty of evidence).

Reason for recommendation: There are three main types of OFC (Table S5), and the choice of challenge should depend on the level of diagnostic accuracy needed, the purpose and the consequences of the result.[9,52] The double-blind, placebo-controlled oral food challenge (DBPCFC) is considered the gold standard test for diagnosing IgE-mediated food allergy, with a negative challenge confirmed by a negative open feeding of an appropriate OFC dose of the food. It is therefore indicated where the result of an open OFC is indeterminate or a definitive diagnosis is needed, for example in research. In infants and young children, open OFC may be acceptable for research purposes.

Strength of recommendation: DBPCFC are time-consuming and resource intensive, requiring the challenge food to be blinded for taste, smell, texture and appearance (consistency, colour and shape).[60,64] When objective outcomes are expected, an open OFC involving the consumption of an age-appropriate serving of food is usually undertaken for practical reasons to make a diagnosis, either on its own or following a negative DBPCFC (Figure S1).[9,60,63] Based on the available evidence, this is a conditional recommendation.

Practical implications: In patients where adverse reactions to foods are likely to be non-immune mediated, reported symptoms are non-specific or difficult to evaluate, in very anxious patients and in research studies, DBPCFC is preferable.[9,60] Challenges may also need to include attention to potential co-factors such as exercise, especially when it is not possible to definitively diagnose co-factor-induced reactions from the history and diagnostic tests.[65,66] Single dose challenges have been used in research studies to date but are not yet established in common clinical practice.[67,68]

TABLE 10 Implementation of the EAACI guidelines on diagnosis of IgE-mediated food allergy.

Area	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
Clinicians suspecting of food allergy	Lack of awareness and knowledge about food allergy	Training of medical students, medical trainees of other specialties about food allergy and supporting specialist training in Allergy	Number of referrals received in specialized clinics in relation to reported prevalence in the country	Cost of specialist appointments and testing
Performing skin prick testing	Appropriate clinical setting with resources to treat allergic reactions; availability of commercial extracts for SPT	Training of healthcare professionals in SPT performance and treatment of allergic reactions	Number of patients tested with skin prick test and number of specialist clinics running that do SPT	Costs of trained staff and clinical space to perform SPT
Testing for allergen-specific IgE	Access[a] to specific IgE tests	Centralize tests in specific laboratories	Number of patients tested with specific IgE	Costs of tests
Testing for allergen components	Access[a] to specific tests[11]	Centralize tests in laboratories Restrict tests to components with documented diagnostic utility	Number of patients tested with allergen components and number of patients undergoing OFC	Costs of tests
Testing for BAT	Access[a] to BAT	Centralize tests in accredited laboratories using standardized methodology Train HCP on the interpretation of result and the evidence supporting BAT	Number of patients tested with BAT and number of patients undergoing OFC	Costs of tests Transportation of samples to lab within 24 h of blood collection
Performing OFC	Facilities and staff trained in treatment of anaphylaxis Capacity of clinical services	Training of HCP on performance of OFC and treatment of anaphylaxis	Number of patients tested on OFC and proportion of referred patients	Costs of OFC Training of HCP Space in clinical services with an appropriate setting

Abbreviations: BAT, basophil activation test; HCP, healthcare professionals; OFC, oral food challenge; SPT, skin prick test.

[a]Access may be limited due to availability of the test, in a specific country or clinical practice, costs of the test (to patients and/or health system), staff, staff expertise and training.

4 | DISCUSSION

4.1 | Summary

Food allergy diagnosis can have a significant impact on the lives of patients and their families. Therefore, an accurate diagnosis of allergy or tolerance is essential for all suspected foods. The diagnostic work-up starts with the clinical history, which is central to the process, and enables the identification of the appropriate allergens for testing and the interpretation of the clinical relevance of the test results. Appropriate tests to support the diagnosis of IgE-mediated food allergy are as follows: SPT, sIgE to extracts, sIgE to allergen components and BAT. SPT and sIgE to allergen extracts are recommended as first-line tests, and sIgE to individual allergen molecules is second-line. If available, BAT can be undertaken in the equivocal cases, should standard allergy tests be insufficient to provide a diagnosis. OFC remain the reference standard and should be reserved for cases that cannot be clarified with SPT, sIgE and/or BAT. For practical reasons, open OFC can be used in most clinical situations and DBPCFC can be used if open OFC are equivocal or for research. Given the natural history of food allergy, children should be re-assessed, and tests repeated to assess for possible resolution and enable reintroduction of the food into the diet.

4.2 | Strengths and limitations

Strengths of the current guidelines are that they are evidence-based following the GRADE methodology and developed by an expert multidisciplinary group and patient representatives, from Europe and other parts of the world. These guidelines were informed by a purposefully performed systematic review of the literature and meta-analyses on the accuracy of tests to support the diagnosis of IgE-mediated food allergy. The absence of a systematic review of the literature to inform the sections about clinical history and about OFC was a limitation. However, it is likely that such systematic review would be quite limited given the small number of studies addressing specific aspects of history taking and of OFC, and ethical limitations of undertaking such studies.

4.3 | Future perspectives

The current Guideline intends to provide guidance for best clinical practice and refer to specific studies included in the systematic review of the literature and meta-analyses that informed the guidelines. However, the quality and design of the included studies needs to be carefully reflected upon when considering extrapolating study findings, namely cut-offs and measures of diagnostic accuracy, to one's own clinical practice. There are also external factors that may hamper the implementation of the guideline's recommendations, such as the lack of resources, both human (e.g. enough specialized allergy clinics or enough staff) and material (e.g. availability of tests in specific countries or access to tests in the health service). Table 9 lists some of the gaps identified in the evidence and how these could be addressed, and Table 10 lists the barriers and facilitators of implementation of the guidelines.

5 | CONCLUSION

The allergy-focused clinical history is a key element in the diagnostic work-up of IgE-mediated food allergy, allowing the estimation of a pre-test probability of food allergy and guiding the choice of allergens to test for. The evidence of IgE sensitization to the suspected allergens can be sought using SPT, sIgE to extracts or individual allergens and/or the BAT, if available. The post-test probability, based on the combination of the history with the results of tests, will determine whether an OFC is required to clarify the allergic status to the suspected food. An OFC is the reference standard, especially for equivocal cases, to confirm the eliciting food and support clinical decision-making. Periodic reassessment of food allergic children using a similar work-up enables reintroduction of food in the case of spontaneous acquisition of oral tolerance and the investigation of new food allergies that may develop over time.

AUTHOR CONTRIBUTIONS

AFS, IS, CR and GR wrote the manuscript based on the online meetings of the expert group. All authors critically reviewed the manuscript and approved its final version.

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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