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REVIEW

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Chinese expert consensus on allergen component resolved diagnosis

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Abstract

Background: Allergen component resolved diagnosis (CRD) is a method for identifying specific protein molecules that cause hypersensitivity. Unlike traditional methods that use crude allergen extracts containing multiple component species, CRD focuses on individual allergen protein molecules for more precise diagnosis. The World Allergy Organization (WAO) recommends CRD as a supplement to clinical history and allergen extract testing, and in some cases, it can replace crude extract tests.

Methods: CRD involves the use of natural or recombinant proteins to detect specific IgE antibodies directed at individual allergenic components. This method allows for a more detailed analysis of a patient's allergic response compared to the use of whole allergen extracts. The Allergy Prevention and Control Specialty Committee of the Chinese Preventive Medicine Association, in collaboration with multidisciplinary experts, developed an expert consensus that incorporates the consensus of the European Academy of Allergy and Clinical Immunology (EAACI), WAO, and important domestic literature on CRD in recent years.

Results: The consensus aims to standardize the algorithm of allergen diagnosis and provides a reference for clinical practice. It also offers guidance for clinicians on the common protein families identified by CRD, the scenarios where CRD is applicable, and the significance of detecting common allergen components.

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Conclusions: Despite its potential, CRD is not widely used in clinical practice in China due to the lack of allergen component reagents and a general unawareness among clinicians about CRD's application and interpretation of test results. The expert consensus developed by the Chinese Preventive Medicine Association aims to address this gap and enhance the clinical application of CRD in China.

KEYWORDS
allergen, China, component resolved diagnosis, consensus, IgE

The prevalence of allergic diseases in China has been increasing annually, posing significant challenges to public health and the healthcare system. In the accurate diagnosis and treatment of allergic diseases, allergen component resolved diagnosis (CRD)[1] has gained attention as an advanced and precise diagnostic method. However, in the current clinical practice in China, this technology faces a series of issues and challenges.

Firstly, the clinical application of allergen component reagents is restricted in China due to the lack of high-quality reagents, resulting in limited effectiveness of allergen component resolved diagnosis (CRD) on a broad scale. Additionally, there is insufficient understanding among clinical practitioners regarding the application of CRD and the interpretation of test results, hindering the widespread adoption and implementation of this technology in China. Furthermore, the standardization and normalization of allergy testing need improvement, potentially leading to poor comparability of test results and affecting the accuracy of allergic disease diagnosis.

To address this current situation, we are fortunate to find valuable insights from the western countries' experience. European and American countries have made significant progress in allergen CRD,[2,3] successfully applying high-quality reagents and improving comparability of test results through standardized and normalized allergy testing procedures. Moreover, Europe has enhanced understanding through the training and education of clinical practitioners, promoting a deeper understanding of the application of CRD and the interpretation of test results.

Therefore, the Allergy Prevention and Control Specialty Committee of the Chinese Preventive Medicine Association organized experts from allergology, pediatrics, otolaryngology, respiratory, dermatology, clinical laboratory, and other multidisciplinary experts to jointly draft this expert consensus. The development of this expert consensus aims to establish a benchmark for allergen component diagnosis in China by drawing on the successful practices in Europe. By delving into European experiences, we will strive to formulate standards and guidelines applicable to China, facilitating the widespread application of allergen component resolved diagnosis (CRD) and thereby improving the accuracy and effectiveness of allergic disease diagnosis and treatment in China. This consensus seeks to build a communication bridge between China and Europe in the field of allergen component diagnosis, fostering global research and efforts in the prevention and treatment of allergic diseases.

Key message

a. Importance of Accurate Allergen Identification: Crucial for diagnosing allergic diseases. Allergen component resolved diagnosis (CRD) identifies specific protein components within crude-extract allergens.
b. Advancement in Diagnosis and Treatment: CRD represents a significant advancement in precise diagnosis and treatment of allergic conditions. Recommended by the World Allergy Organization (WAO) as a supplementary test alongside clinical history and traditional allergen extract tests.
c. Challenges in Adoption of CRD: Limited use in clinical practice in China. Lack of allergen component reagents. Many physicians, especially non-allergists, are unaware of CRD application and interpretation.
d. Development of Expert Consensus: Initiative by the Allergy Prevention and Control Special Committee of the Chinese Preventive Medicine Association. Collaboration with multidisciplinary experts. Referenced guidelines from the European Academy of Allergy and Clinical Immunology (EAACI), WAO, and recent significant domestic literature.
e. Significance of the Report: First comprehensive report on allergen component diagnosis in China. Aims to standardize diagnostic methods for allergens. Serves as a reference for clinical medical workers.

1 | ALLERGEN PROTEIN FAMILIES AND DATABASES

The established allergen component database is identified and maintained by the Allergen Nomenclature Sub-Committee (www.allergen.org) under the International Union of Immunological Societies (IUIS) and World Health Orgnaization (WHO) Allergen Nomenclature Sub-Committee. The naming of allergens and their components consists of the first three to four letters of the “genus” name, the first or first two letters of the “species” name, and the sequence number of identification and purification of the allergen component or the protein family it belongs to.[4]

Taking Der p 1, the first identified component of house dust mite (HDM) as an example, “Der” is the first three letters of the genus name (*Dermatophagoides*), and “p” is the first letter of the species name (*pteronyssinus*). According to different protein structures and biological functions, allergen components can be divided into more than 20 different protein families, including the Cupin, tropomyosins, gliadins (2S albumin), lipocalins, Protein kinases, Pathogenesis-related proteins, Lipid transfer proteins, Profilins, and Calcium-binding proteins. Detailed information on allergen families can be found in the AllFam database (http://pfam.xfam.org/). Different protein families have different characteristics and sensitization, see Table 1 and Supplementary Material (Appendix S1).

2 | ALLERGEN COMPONENT IgE ANTIBODY ASSAYS

Despite the widespread clinical use of commercial allergen component sIgE testing kits in Western countries such as Europe and the United States,[12] options are limited in China, as detailed in Table 2. Currently, only a few allergen component sIgE products are available for clinical use (HDM, mugwort, milk, and egg), significantly hindering the progress of diagnosis and treatment of allergic diseases in China. There is an urgent need to draw upon clinical experiences from Western countries to drive the development of allergen component diagnosis in China and facilitate the promotion of European and American allergen products in the Chinese market. The introduction of foreign imported allergen component sIgE into clinical practice requires approval from the China National Medical Products Administration (NMPA), conducting clinical trials in China, and collaborating with Chinese partners for product promotion. Despite these limitations, Chinese medical research institutions actively collaborate with foreign allergen product companies to obtain more data related to allergen component research, contributing to advancements in allergen component diagnostics.

3 | CLINICAL APPLICATIONS AND DIAGNOSTIC PROCESS OF ALLERGEN COMPONENT DIAGNOSIS

Traditional in vitro allergen diagnosis relies on extracts,[2] but this method has limitations in differentiating cross-reactivity and identifying major allergen components. CRD can identify single allergen component at the protein level, which have a higher accuracy and specificity.[13]

Before opting for CRD, obtaining a detailed patient history is essential. Interpretation of specific IgE (sIgE) results, including CRD, should closely correlate with the patient's clinical symptoms. CRD is not the initial screening step; instead, skin prick tests (SPT) or extract-based sIgE testing is initially performed for patients suspected of IgE-mediated allergic diseases. CRD may be considered when there is a discrepancy between medical history and routine allergen testing results or when further disease evaluation is needed.

In the clinical setting, the application of CRD for allergic diseases follows a systematic process, with the patient's medical history serving as the cornerstone for diagnosis. Generally, the use of CRD should proceed according to the following process:

- For patients with suspected allergic disease, detailed clinical evaluations (personal history, family history, medication history) and physical examinations (skin, nasal mucosa, conjunctiva, pulmonary examination) should be conducted by specialized physicians.
- For patients suspected of IgE-mediated allergic reactions, Skin Prick Tests (SPT) and/or serum-specific IgE (sIgE) tests using allergen extracts are recommended.
  - Consideration of allergen component testing may arise if there are unrelated positive allergens or if the results are not consistent with clinical manifestations.
  - A positive result for an allergen correlated to symptoms after exposure is almost definitively considered as confirmed. However, the prognosis of the disease can also be judged according to the tests of allergen components sIgE. It is also helpful for the subsequent choice of AIT treatment or allergen avoidance.
  - For patients with multiple allergens or complex allergies, allergen component diagnosis can also be considered. CRD plays a crucial role in distinguishing cross-reactions and true allergies.
  - In the case of negative results, allergen provocation or avoidance tests may be considered. Positive provocation test results may suggest AIT, while negative results indicate a low probability of allergy.

CRD can be considered in the following situations:

1. Improving sensitivity and specificity:

Sensitivity Boost: CRD enhances diagnosis sensitivity by detecting allergen components at low concentrations in native extracts that may be challenging for conventional methods. Some allergen components such as Gly m 4 from soy[14] and omega-5-gliadin from wheat proteins[15,16] are at very low concentrations in native extracts and can be difficult to detect using conventional methodologies.

Enhanced Specificity: CRD can enhance the specificity of diagnosis, surpassing conventional sIgE testing or SPT using allergen extracts. Studies have shown that the major peanut allergen components Ara h 2 and Ara h 6 are significantly superior to crude extracts based sIgE or SPT in distinguishing peanut allergy.[17]

2. Assessing potential risk in allergic patients:

CRD predicts the risk of anaphylaxis and guides dietary avoidance, providing valuable insights for prevention and treatment.[13]

TABLE 1 Characteristics of different allergen protein family components.

Protein families	Stability	Source and function	Components
Cupin superfamily	Heat and digestion resistant	Important allergens of beans, seeds, and tree nuts	**2S albumins**: Ara h 2 and Ara h 6, Jug r 1, Ses i 1 and Ses i 2 **7S globulins**: Ara h 1, Gly m 5, Jug r 2, Ses i 3 **11S globulins**: Ara h 3, Gly m 6, Ber e 2, Fag e 1
Actin	Heat and digestion labile	Exists in all eukaryotic cells and maintains cell motility, structure, and morphological integrity	Corresponding protein were identified in snow carbs and carpet clam, but not yet nominated
Profilins	Heat and digestion labile, relevant to Pollen Food Allergy Syndrome (PFAS)	Regulation of Actin polymerization, widely exists in flowering plants and food, often causes cross-reaction, and is the most related family to PFAS[5]	**Pollens**: Bet v 2, Cor a 2, Phl p 12, Art v 4, Amb a 8 **Food**: Pru p 4, Mal d 4, Cuc m 2, Pyr p 4, Man i 4, Ara h 5, Gly m 3, Sola l 1, Cor a 2
Non-specific lipid transfer proteins (nsLTP)	Heat and digestion resistant, induce PFAS	The transmembrane transfer of phospholipids and other lipids promotion, plant defense, widely distributed in plants, induce serious allergy symptoms	**Pollens**: Art v 3, Amb a 6, Heb b 12 **Food**: Pru p 3, Mal d 3, Pru av. 3, Cor a 8, Jug r 3, Ara h 9
PR-10 protein	Heat and digestion labile, Bet v 1 cross-reacts with plant foods and can cause PFAS	Plays a role in Phyto steroid vector[6] high sequence homology, and is easy to cross-react between plants	**Pollens**: Bet v 1, Fag s 1, Cor a 1, Aln g 1, Que. a 1 **Food**: Pru p 1, Mal d 1, Pru av. 1, Pyr c 1, Dau c 1, Gly m 4, Ara h 8, Api g 1
Tropomyosin	Heat and digestion resistant	Associated with muscle contractions, cause cross-reactivity between mites, cockroaches, and crustaceans (shrimp, crabs)	**Food**: Pen a 1, Pen m 1,, Bla g 7 **Mates**: Der p 10, Der f 10, Blo t 10 **Parasites**: Cha f 1
Lipocalin	Airborne, easily spread to indoor environment	Small, hydrophobic molecule carriers, exist in mammalian dander, saliva, and urine	**Cow**: Bos d 2 **Dog**: Can f 1, Can f 2, Can f 4, Can f 6 **Cat**: Fel d 1,Fel d 4, Fel d 7 **Rabbit**: Ory c 1, Ory c 2 **Horse**: Equ c 1, Equ c 2
β-Parvalbumins	Heat and digestion resistant	Highly conserved in fish, a major allergen of bony fish and causes cross-reactions between fish	Gad c 1, Gad m 1, Cyp c 1, Cten i 1, Thu a 1, Sal s 1
Serum albumin	Heat liable, show cross-reactivity between animal dander, milk, and meat, induce pork-cat syndrome	Exist in body fluids and solids of mammals, such as cats, dogs, milk, beef, and epithelial cell partial extracts	Bos d 6, Can f 3, Fel d 2, Equ c 3, Gal d 5, Sus s 1, Cav p 4
Cyclophilins	Cyclophilins are a highly conserved family of proteins.	Cyclophilins have been found in a variety of organisms, including mammals, fungi, plants, and microorganisms. Cousing cross-reactive allergic responses[7]	Bet v 7,Asp f 11, Asp f 27, Mal s 6, Rhi o 2, Der p 29
Gibberellins	They are small molecular weight proteins, rich in cysteine, with high thermal stability and resistance to digestive enzymes.	Found in various plants (peach) and can induce IgE-mediated allergic reactions. GRP allergies can manifest with a range of symptoms, from oral allergy syndrome to more severe systemic reactions like anaphylaxis[8]	Pru p 7,Pru m 7,Cit s 7, Pun g 7, Cup s 7
Oligosaccharide galactose-alpha-1,3-galactose	Alpha-gal, a carbohydrate known as galactose-alpha-1,3-galactose. Lead to Alpha-gal Syndrome (AGS).	Found in the tissues of mammals, including beef, pork, lamb, and other red meats. Sensitization to AGS is usually associated with tick bites, especially from the Lone Star tick (Amblyomma americanum)[9–11]	Alpha-gal

TABLE 2 Methodological characteristics and application scenarios for the detection of different allergen fractions.

Analytical instruments	Detection Principle	Sample volume	Testing Number	Advantages	Disadvantages	Applications
Single-weight detection						
ALLEOS[a]	Magnetic particle chemiluminescence	4 μL	One allergen at a time	Increased assay analytical sensitivity and precision. Permits calculation of allergen specific IgE/total IgE-ratio. Minimizes unneeded testing Global availability in many countries	If more allergen components need to be tested, a large sample size may be required, which is not so friendly for pediatric patients. Expensive in case of large-scale screening (i.e., multi-sensitized subjects). Relevant allergens that are not tested may be missed	Identification of specific allergens; Precise treatment and avoidance of allergens; Severe or life threatening anaphylaxis; Treatment monitoring;
ImmunoCAP	Immune fluorescence	40 μL	One allergen at a time			
Multi-component testing						
ALEX2	Solid-phase immunoassay	100 μL	300 allergens/ components at a time	Increased speed of analysis and reduced result turn-around time. Conservation of sample volume facilitating pediatric testing. Reduced cost and technician intervention; Generates a broad sIgE profile with the option of longitudinal predictive and preventive monitoring of patients/people at risk.	Increase patients' medical costs; Interpretation of results requires experienced clinical professionals	Initial comprehensive screening; Evaluation of patients with multiple allergies; Diagnosis and treatment of difficult cases; Establishing a detailed and comprehensive allergy profile;
DX-Blot 45II [b]	Protein microarray (Immunoblotting)	250 μL	9 dust mite allergen components			
ISAC	Immune fluorescence	40 μL	112 allergens at a time (82–84)			
Medall	Immune fluorescence		170 allergens at a time (76)			

[a]HYCOR Biomedical, LLC. Only 9 Der p 1/2/10 (HDM), Gla d 1/2/4 (Egg), Bos d 4/5 (Milk), Art v 1 (Mugwort) were approved by the NMPA.

[b]Hangzhou Zheda Dixun Biological Gene Engineering Co., Ltd. Only 9 components of dust mites allergen (Der p 1/ 2/5/7/10/21/21, Der f 1/2) were approved by the NMPA.

Example: Hazelnut allergens Cor a 9 and Cor a 14 are associated with anaphylaxis.[18] Elevated levels of nGal d 1-specific IgE indicate a longer duration of egg allergy and a delayed onset of tolerance.[19,20]

3. Distinguishing cross-reaction or true allergy:

Cross-reactivity Clarification: CRD differentiates cross-reactivity, categorizing allergen components into families based on characteristics, aiding in the identification of cross-reactivity. Over 700 known allergen components are categorized into a small number of allergen families using CRD,[21] which facilitates the identification of allergen cross-reactivity. Cross-reactivity between allergens can be explained by the same protein family, such as the extensive cross-reactions between pollen and food induced by profilins or polcalcins.[22]

Identify specific allergenic components: CRD can identify specific allergenic components, aiding in precise differentiation. For example, the detection of major allergenic components, such as rSSMA and venom Api m 10, significantly enhances the accuracy in distinguishing between allergies to wasp and honeybee venom.[23]

4. Guiding specific immune therapy:

CRD assists in selecting appropriate Allergen Immunotherapy (AIT) for patients, improving therapy effectiveness by avoiding unnecessary treatments.

Example: CRD can predict responses to HDM AIT based on sensitization to specific components Der p 1 and Der p 2.[24]

5. Contributing to Epidemiological Studies:

CRD enhances precision in epidemiological studies, revealing variations in sensitization to allergen components across regions.[25] Multicenter study demonstrated regional variations in the sensitization spectrum of HDM components in northern, central, and southern China.[26] Implementing appropriate allergen component

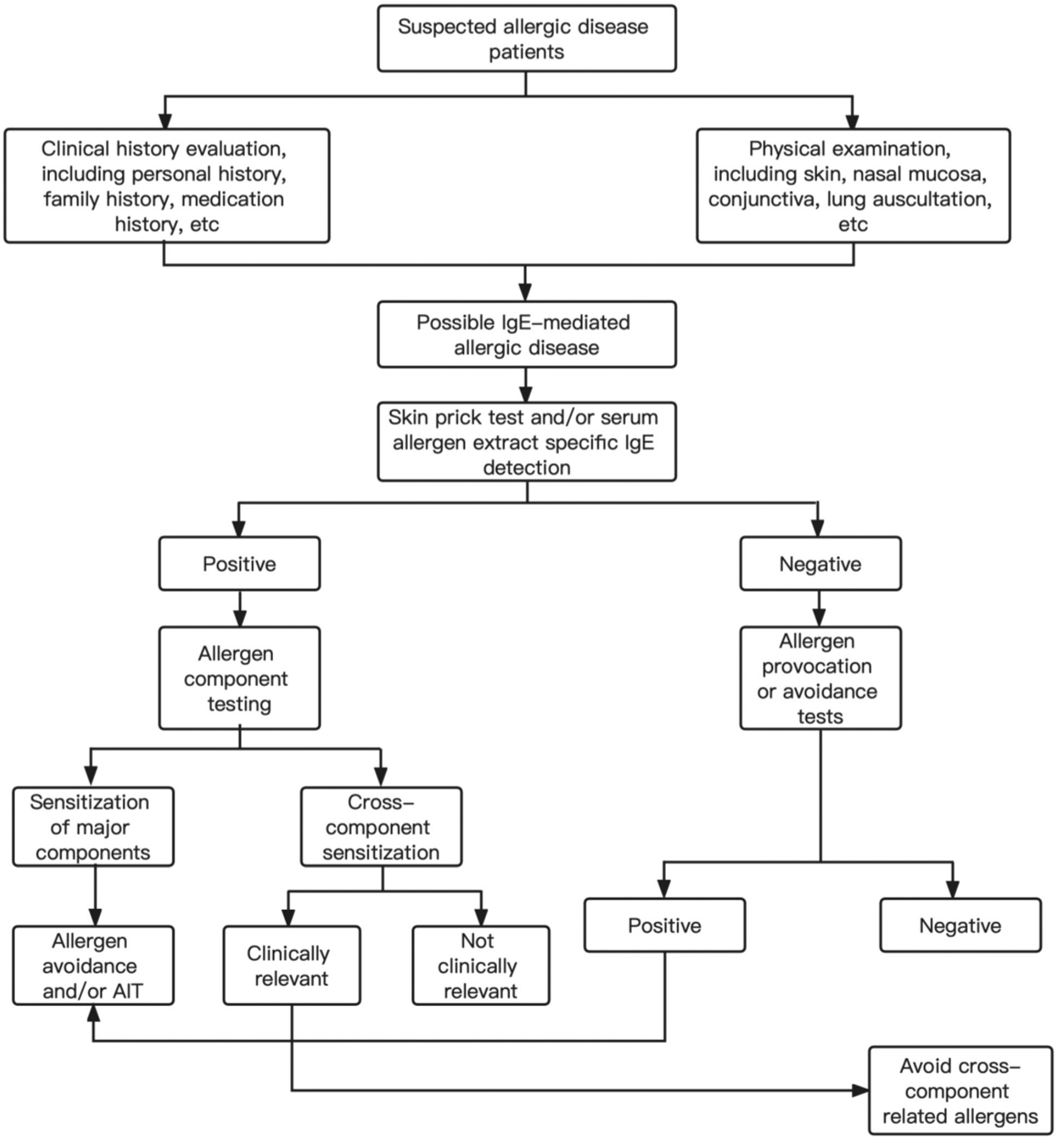

FIGURE 1 Flow chart of clinical application of allergen components diagnosis.

prevention and treatment strategies based on the distribution of distinct species in each region may enhance the efficiency of preventing and treating allergic disease.

The diagnostic flowchart of suspected allergic patients is shown in Figure 1.

6. Digital allergology:

Digital Allergology, as introduced by Matricardi[27] and colleagues, has innovatively propelled the integration of mobile health technology into allergy medicine, improving diagnostic accuracy, elevating the standard of patient care, and enhancing the potential for personalized therapeutic strategies. In China, this approach can be particularly impactful, extending quality care to remote populations and streamlining the management of allergic conditions. Clinical Decision Support Systems (CDSS) are central to this field, offering doctors quick access to organized clinical insights to make informed decisions. Adapting systems like MACVIA's CDSS and @IT-2020 for China focuses on allergen immunotherapy and rhinitis treatment. Widespread adoption requires alignment with local regulations, cultural adaptation, and healthcare infrastructure, including standardized practices and robust data protection. When properly implemented, Digital Allergology can greatly improve the accessibility, efficiency, and effectiveness of allergy care in China, benefiting both patients and healthcare providers.

4 | COMMON ALLERGEN COMPONENTS AND THEIR CLINICAL APPLICATION

Inhalant allergens and food allergens are common allergens. According to the distribution profile, inhalant allergens can be divided into two types: indoor and outdoor. Indoor allergens include HDMs, molds, pet dander and cockroaches, while outdoor allergens include pollen and fungi. Food allergens are mainly high protein content foods such as milk, eggs, seafood and aquatic products, meat, nuts, fruits, and vegetables. The current data of Chinese studies on allergen components were summarized in Supplementary Material (Appendix S2). Based on the existing published research articles on allergen components in China, the difference between the positive rate of components and the European guidelines can be seen in Supplementary Material (Appendix S3).

4.1 | Common inhalation allergens

4.1.1 | Mite allergens

Mites are one of the most common allergens and are widely present in the human living environment.[28] *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are the most predominant mite allergens worldwide[29] and can cause a variety of allergic diseases such as allergic rhinitis (AR), asthma, AD, and other disorders.

The global prevalence of mite sensitization is 1%–2%.[30] A survey study in mainland China demonstrated a large regional variation in sensitization rates to mite among people with suspected allergic symptoms where the average was 33.74% with a high of 40.79% in southern China and a low of 11.21% in northern China.[31] Another study in China also confirmed that HDMs were the main allergen in the southern region using latent class analysis.[32,33] The sensitization rates of HDM in AR patients in central China were about 70%.[34] There are many types of mite component proteins that cause sensitization,[32] with *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* each having nearly 40 allergens. New mite allergens are still being discovered with new methods, especially histological methods, and may facilitate the discovery of more mite allergens.[35] Ji and colleagues revealed two novel allergens Der f 37 and Der f 39 by chromosome-level assembly of HDM genome and transcriptome.[36] The team reported Der f 24 which became the first mite allergen to be included in WHO/IUIS from China.[37] In addition, Li and their investigative team characterized the IgE immune epitope of Der p 39.[38] This study showed that Der p 1, Der p 2, and Der p 23 are the major mite allergens. The sensitization rate of Der p 1 in mite-allergic patients ranged from 70% to 100% whereas Der p 2 appeared to be present at a sensitization rate of 80%–100%; both proteins were found to be present in the fecal pellets of mites. Der p 23, another important mite allergen with a sensitization rate of 74%, is also present on the surface of fecal pellets. These major HDM allergens are associated with respiratory allergy symptoms and the development of asthma; in most cases, mite-specific immunotherapy is recommended.[25,39] Sun and her colleagues[26] conducted an epidemiological study of nine mite allergens and found that Der p 1, Der p 2, and Der f 2 were the major mite allergens in mainland China, and there were significant differences in their distribution across different regions. Yang et al. also found that Der p 1 and Der p 2 were the major components to induce Der p sensitization among AR patients in Central China, the sensitization rate was 71.5% and 64.6%, respectively.[40] The studies of Wang and colleagues found that mite sensitization patterns were related to the type of allergic diseases and that patients with AR combined with asthma had a higher prevalence of the major mite allergens and a greater variety of sensitizing mite allergens.[41] Recent studies have found that Der f 23 is also a major mite allergen with conformational IgE binding epitopes,[42] and more studies are needed in the future to explore its specific functional and clinical significance.

Mite tropomyosins (Der f 10 and Der p 10), which cause cross-sensitization between HDMs and some foods, have a sensitization rate in mite-allergic populations of 5%–18%.[43] Der p 10 and Der f 10 cross-react with promyoglobin from crustaceans (shrimp, crab, lobster, prawns, puffer fish, and crayfish) and mollusks (mussels, oysters, scallops, snails, abalone, squid, cuttlefish, and octopus). Positive IgE to Der f 10/Der p 10 suggests multiple sensitizations or cross-reactivity. There is extensive co-sensitization between distinct species of mites, with up to 70.14% of HDM allergic patients being sensitized to both *Blomia* and *Dermatophagoides*.[44]

When patients exhibit typical symptoms of HDM-related AR and/or asthma, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* testing (IgE or skin test) should be performed; where available, it is recommended to test the important HDM components (including Der p/Der f 1, Der p/Der f 2, Der p 23, and Der p 10). With these testing results, clinicians can consider various treatment regimens including environmental control, mite immunotherapy, or medication. The diagnostic flowchart is shown in Figure 2.

In addition to the aforementioned house dust mites, *Blomia tropicalis* is also a crucial species of mites, particularly in tropical and subtropical regions.[45,46] The study conducted by Rao et al. shows that *Blomia tropicalis* is the dominant species of mites in Haikou, China.[47] A study in Guangzhou showed that 71.54% of serum samples from dust mite allergy patients were sensitized to *Blomia tropicalis*.[44] Currently, there are more than 20 different allergen components of *Blomia tropicalis*. Among them, Blo t 5 and Blo t 21 are considered the main allergens, and these two allergens are closely linked to the onset of asthma.[48] A study in Taiwan indicates that the sensitization rate of Blo t 5 in pediatric asthma patients is as high as 91.8%.[49] However, in the western Chinese city of Chengdu, the sensitization rate of Blo t 5 in patients with allergic rhinitis with or without asthma is only 22%, lower than that of. Blo t 4 (28%).[50]

4.1.2 | Cockroach allergens

Cockroach allergens are classified as derived from German (*Blattella germanica*) or American cockroach (*Periplaneta americana*). A multicenter epidemiological survey of allergens in China showed that cockroaches had a sensitization rate of 24.5% among patients with allergic symptoms, second only to HDMs. The study also revealed that cockroaches had a wide variation in sensitization rates ranging from 5.97% to 29.25% in different regions in China, with the lowest rate found in the northeast and the highest in the southwest.[31] More

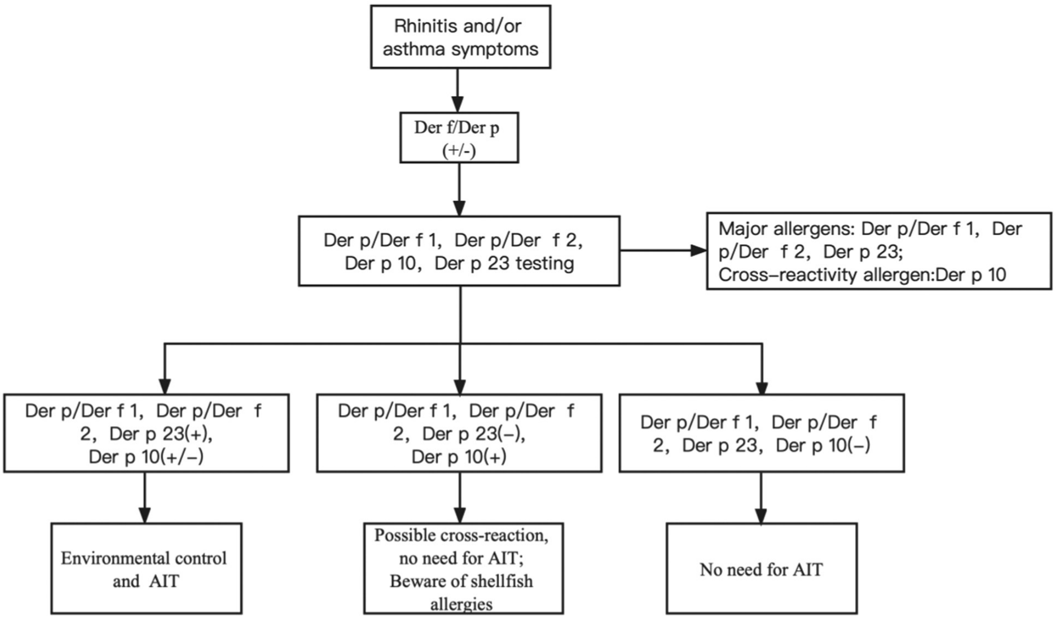

FIGURE 2 Clinical application scenarios of sIgE detection of HDM allergen components.

than 30 different cockroach allergens have been identified, including 11 proteins from the German (*Blattella germanica*: Bla g 1-Bla g 9 and Bla g 11-Bla g 12) and 20 proteins from the American cockroach (*Periplaneta americana*, Per a 1- Per a 20). A recent study showed that most cockroach-allergic patients in Hong Kong were cross-sensitized to other insects and/or shellfish, due to the extensive cross-reactivity of tropomyosin and arginine kinase. In Hong Kong, arginine kinase and tropomyosin were the major cockroach allergens, and their sensitization rates were 64% and 42%, respectively, among cockroach-allergic patients. In particular, Per a 7 (tropomyosin) sensitization was significantly higher in asthmatics. This contrasts with an Austrian cohort in the study that found dissimilar results.

Studies have shown that the cockroach allergens closely related to AR and asthma are Bla g 4, Per a 7, and Bla g 6.[51] Another study showed that the sensitization rate to cockroaches in patients with shrimp allergy was 89.2%, and these patients also had co-sensitization to HDMs, crabs, and moths, and the co-sensitization rates were 88.7%, 85.4%, and 92% respectively.[52] These studies suggest that there are cross-sensitization and multiple sensitizations between cockroaches and various allergens.

4.1.3 | Fungal allergens

Fungi are widely present in indoor and outdoor environments[53] and can cause a variety of allergic diseases,[54] including AR, asthma,[55] and AD.[56,57] The common fungal allergens are Streptomyces (*Alternaria*), *Aspergillus*, and *Cladosporium*.

The exact prevalence of fungal allergy is unknown, and the results vary widely between studies[58]. A survey in China showed a fungal sensitization rate of 3.92%, while there were no significant differences in fungal sensitization rates between regions.[31]

- *Alternaria* allergen source

Alternaria is the most common fungal allergen. It is distributed outdoors and is saprophytic in plants, food, and soil. It can also colonize indoor environments which increases human exposure.[59] *Alternaria* sheds spores from May to November, thus causing allergic symptoms to occur most often in summer and autumn.[60,61] *Alternaria* allergy is closely related to bronchial asthma, AR, hypersensitivity pneumonitis, and allergic bronchopulmonary aspergillosis (ABPA).[62]

Alternaria is currently found to have 12 allergens, namely Alt a 1, Alt a 3–10, and Alt a 12–15. Alt a 1 is the major allergen of Alternaria,[63] and the sensitization rate in patients allergic to Alternaria exceeds 90%.[64]

- Aspergillus fumigatus allergen source

Aspergillus fumigatus sensitization is a risk factor for asthma exacerbation and is associated with bronchodilator exacerbations, frequent hospitalizations, and even death in patients.[65,66] It is estimated that about 28% of asthma patients are sensitized to *Aspergillus fumigatus*.[67] *Aspergillus fumigatus* has 30 allergenic components, namely Asp f 1–19, Asp f 22–24, Asp f 27–29, Asp f 34–39. A study in southern China showed that there was a clear difference between the *Aspergillus fumigatus* component IgE in the serum of patients with *Aspergillus fumigatus* allergic asthma and allergic pulmonary aspergillosis (ABPA). The sensitization rates and IgE levels of Asp f 1, Asp f 2, Asp f 4, and Asp f 6 in ABPA patients were significantly higher than those in fungal allergic asthma.[68] Asp f 1 is the most important allergen of *A. fumigatus*.[69] Similarly, Asp f 2 has been show important with a sensitization rate of 96%,[70,71] and the sensitization rate of Asp f 4 is as high as 92%.[72] Other *Aspergillus fumigatus* sensitized components, such as Asp f 3, Asp f 6, Asp f 8, Asp f 12, Asp f 22, Asp f 27, showed higher similarity with homologous proteins in other fungi so their species specificity is reduced.[73] Two other allergenic proteins (Asp f 9, Asp f 34) have high specificity and demonstrate a high positivity rate is in ABPA patients, suggesting their important clinical significance.[72,74]

4.1.4 | Animal dander allergens

With the growing number of pet owners in China, there has been a corresponding increase in the prevalence of sensitization to animal dander. A 13-year multicenter retrospective study in China found that the sensitization rates to cat and dog increased from 1.33% and 0.83% in 2009 to 15.47% and 10.51% in 2021 respectively.[75] Animal dander is an important source of indoor allergens.[76] Lipocalin constitutes the most important family of animal allergenic proteins.[77] They are synthesized in the salivary glands and dispersed to the environment by saliva and dander. Studies have shown that lipoproteins share a common three-dimensional structure and low sequence identity, and that there is cross-reactivity between allergens belonging to the same lipoprotein family including Horse dander (Equ c 1), Dog dander (Can f 1, Can f 6) and Cat dander (Fel d 4, Fel d 7).[78] Serum albumin is also a highly homologous component of different animal dander, often leading to cross-react between different animal dander allergens. As early as the last century Spitzauer S et al. showed that patients apparently allergic to dog albumin in IgE immunoblotting inhibition studies and histamine release assays develop IgE responses to purified albumin from cats, mice, chickens, and rats,[79] and this result is again supported by our recent study.[80]

Fel d 1 is the major allergen component of cat dander; studies indicate that 60%–90% of cat dander allergic patients are sensitized to Fel d 1. In the diagnosis of cat allergy, Fel d 1-IgE levels are of similar importance to cat extract sIgE. In contrast, Fel d 3 is a minor allergen belonging to the family of cysteine protease inhibitor proteins.

Can f 1 is the most important key component of dog allergens and is superior to dog allergen extracts in assessing the prognosis of dog allergy.[81] Can f 5, a prostatic kallikrein, was isolated from the urine of male dogs, and is also considered to be the major allergenic canine component.

Multiple sensitization to lipid transport proteins (nMus m 1, rEqu c 1, Fel d 4, rCan f 1, 2), kinin release enzyme (rCan f 5), and secretory bead protein (rFel d 1) is associated with severe asthma.[82] In addition, sensitization to the dog dander component Can f 2 and the horse dander component Equ c 1 was more common in children with severe asthma than in children with controlled asthma.[83] In children with cat allergy, IgE antibody levels to Fel d 1 were higher in asthmatics than in patients with rhino-conjunctivitis.[84] In a study of patients with AR due to cat and/or dog allergy, it was found that patients sensitized to Fel d 2 and Can f 3, the secondary allergen components of cat and dog dander, were more likely to be sensitized to other animal dander and were associated with more severe respiratory symptom.[80]

The diagnostic flowcharts of cat/dog/horse dander suspected sensitization are shown in Figures 3-5 respectively.

4.1.5 | Pollen allergen

Tree pollen allergens

Tree pollen allergens are one of the main outdoor inhalation allergens. Common tree pollen allergens include cypress, birch, olive, *Platanus*, *Cryptomeria*, and *Sabina chinensis*. In the large cross-sectional study of AR reported by China, the prevalence of birch sensitization is about 7% to 25%, which is common in patients in central and northern China.[85] Like in Central and Northern European countries Bet v 1 is the key molecule responsible for birch pollen allergy in China, and the positive rate of Bet v 1 in patients with birch pollen allergy is up to 80%.[86,87] Bet v 1 is one of the most common cross-allergic component proteins that cause Pollen Food Allergy Syndrome (PFAS).

Ole e1 is the main allergen component of olive pollen in Mediterranean countries.[88] Although there is little research on olive allergens in China, olive trees are distributed throughout southern China and across the middle and lower portions of the Yangtze River.

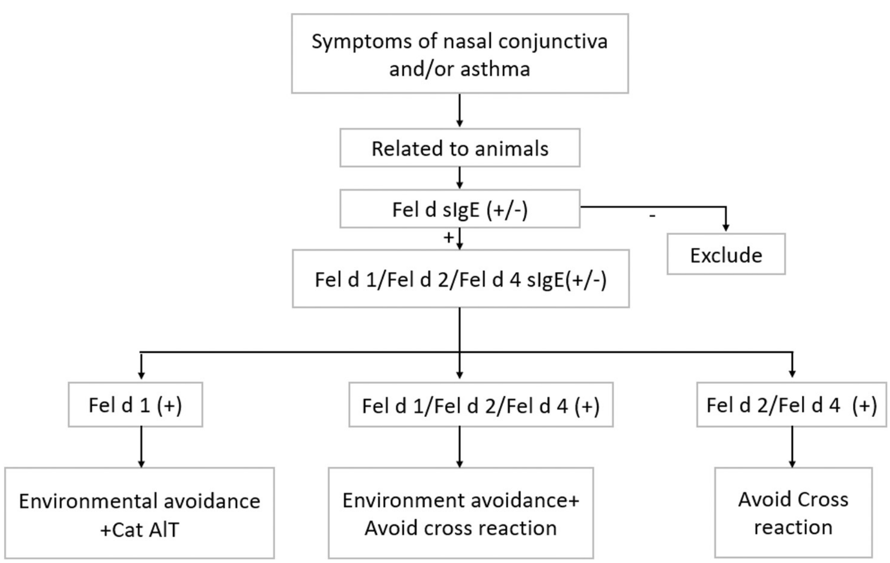

FIGURE 3 Clinical application scenario of sIgE detection of cat allergen components.

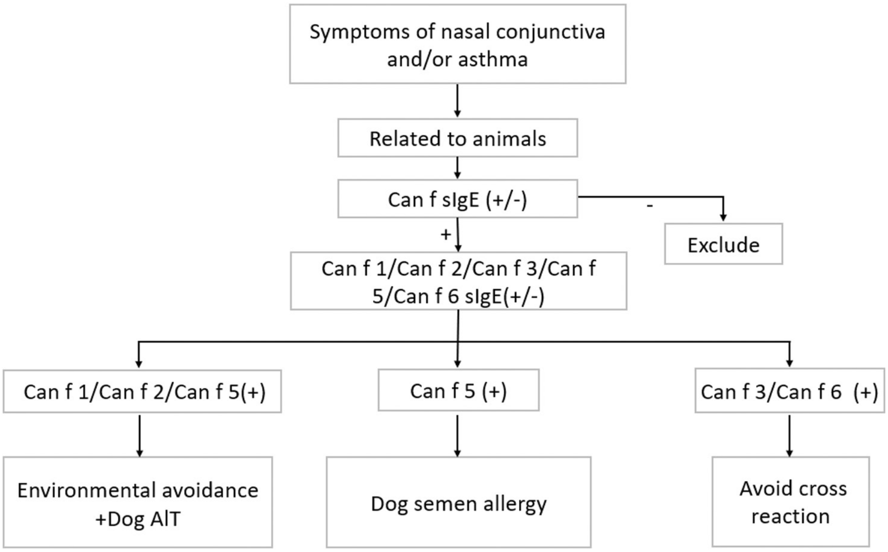

FIGURE 4 Clinical application scenario of sIgE detection of dog allergen components.

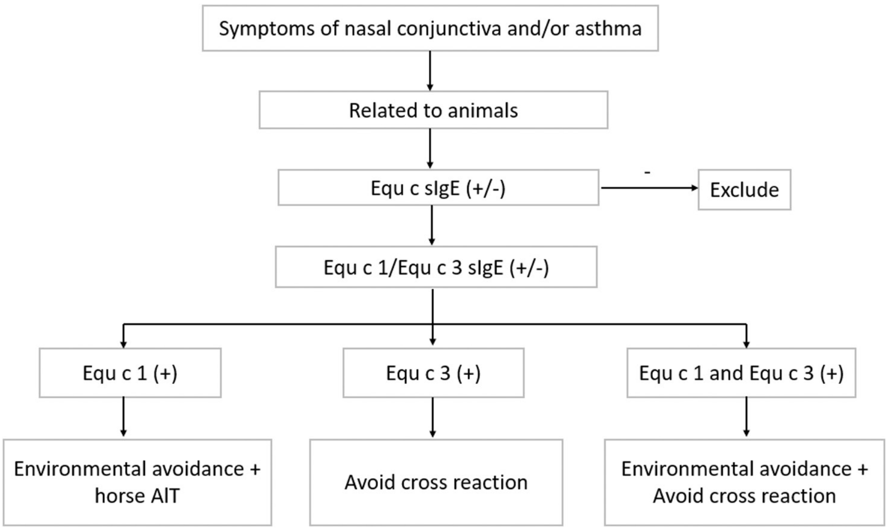

FIGURE 5 Clinical application scenario of sIgE detection of horse allergen components.

Ole e 1, a pollen component of olive tree, is not only cross-sensitized with Ole e-1-like protein family belonging to *Lamilales* trees (Fra e 1 from ash, Lig v 1 from privet, and Syr v 1 from lilac) but also cross-reactive with plantain (Pla l 1), Chenopodium (Che a 1), *Lolium perenne* (Lol p 11), and timothy (Phl p 11).[89,90]

Platanus acerifolia (London plane tree) is a common greening tree in many big cities such as Nanjing and Shanghai in China. The pollen of *Platanus acerifolia* contains more than 20 allergen protein, among which Pla a 1, Pla a 2, and Pla a 3 are the major allergens. It has been reported that there is a cross-reaction between *Platanus acerifolia* and many plant-derived food allergens, which leads to PFAS.[91]

In the Japanese islands, northern China, and the coastal areas of China and Taiwan Province, cedar trees and primarily Japanese cedar, are a primary cause for seasonal rhinitis. Cry j 1 and Cha o 1 are the major allergen components of Japanese cedar and cypress, respectively, which have cross-reaction with other cypress allergens, such as Cup a-1 of *Cupressus arizonica* and Jun a 1 of Mountain cedar.[92,93] The diagnostic flowchart of birch pollen suspected sensitization is shown in Figure 6.

Grass pollen allergens

Worldwide, over 400 million individuals suffer from hay fever and seasonal asthma. The major causative agents of these allergies are pollen-specific proteins called the group-1 grass pollen allergens. Studies indicate that up to 90% of grass pollen-allergic patients are sensitized to group 1.[94,95] The allergen component Phl p 1 from *Phleum pratense* (Timothy grass) is a typical representative of group 1, and it is also an important allergen component that leads to cross-reactivity. No clinical correlation was found in patients sensitized by Timothy grass and Bermuda grass in most parts of China, and component tests showed cross-reaction of glycoprotein determinants or cross-sensitization with minor components of other grass pollens. These patients showed sensitization to nPhl p 4[96] and Phl p 12 and nCyn d 12 (profilin).[97] Only a few patients showed sensitization to grass pollen allergen components with clinical relevance, such as Phl p 1, Phl p 2, Phl p 5, or Phl p 6.[98,99]

Group 5 allergens are considered the second most immunodominant major Poaceae pollen allergens after group 1. Bermuda grass pollen lacks the group 5 allergens and is an important pollen in

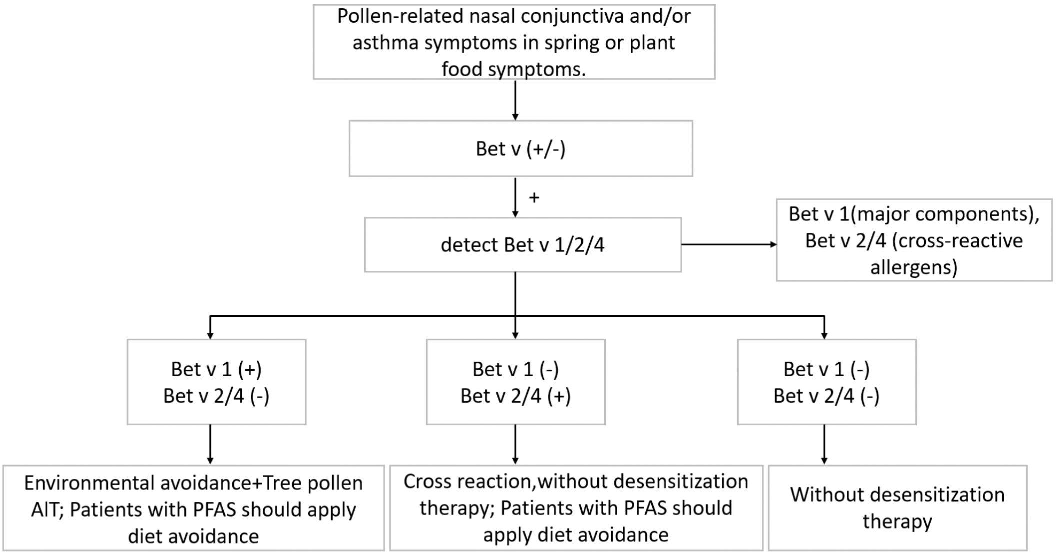

FIGURE 6 Clinical application scenario of sIgE detection of birch allergen components.

China. Among people allergic to grass pollen in temperate regions, the sensitization rate to group 5 allergens is about 65%~85%.[100,101] Phl p 5 is one of the most characteristic group 5 and is considered to be a species-specific component that distinguishes Timothy grass from other members of the precocious grass subfamily. The prevalence of Phl p 5 IgE in northern China is less than 20%.[98]

Other key grass allergens include the Profilins (group 12) and Polcalcins (group 7) which are found in grass, tree, and weed pollen. The members of the Profilin protein family contain: Bet v 2 (birch), Phl p 12 (ladder grass), and Cyn d 12 (Bermuda grass). Polcalcin protein family members include Bet v 4 (birch), Ole e 3 (olive), and Cyn d 7 (Bermuda grass). For each of these two groups, the amino acid sequences are highly conserved and cause extensive cross-reactivity to grass, tree, and weed pollen homologus without showing clinical symptoms. Japanese Hop is said to be one of the main pollen allergens in China. The need for CRD and progress would be important for the Chinese perspective.[102] The diagnostic flowchart of timothy grass pollens suspected sensitization is shown in Figure 7.

Weed pollen allergens

Artemisia (mugwort) pollen is one of the important allergens causing pollinosis in summer and autumn. In northern China, the sensitization frequency of patients with respiratory allergic diseases to mugwort pollen is as high as 50%.[85] Art v 1 and Art v 7 are the most common allergenic components of Artemisia pollen, followed by Art v 3 and Art v 2. The sensitization rate of Art v 1 in patients with Artemisia pollen allergy in China is about 80%.[103] Art v 2 belongs to glycoproteins of the PR-1 protein family, which can be cross-sensitized with allergens of the homologous family in other plants, such as tomato, potato, rape, wheat, and rice.[104] Art v 3 is a non-specific lipid transfer protein of the PR-14 protein family. This pan-allergen protein often causes pollen food allergy syndrome because of its cross-reaction with diverse plant foods such as peanut (Ara h 9), celery (Api g 2), apple (Mal d 3), and peach (Pru p 3). For example, Art v 3 sensitization in mugwort pollen allergic patients in northern China is high, which is often related to Pru p 3-related peach allergy.[105]

Ragweed is mainly distributed in Europe and America, and it is one of five invasive plants in China.[106] In the United States, more than 90% of ragweed pollen allergic patients are allergic to Amb a 1.[107] It is worth noting that although 36.0% of children sensitized by mugwort pollen in western China showed positive results for ragweed pollen, the sensitization rate to the major ragweed allergen Amb a 1 is 13.9%.[97] In many cases, ragweed is attributed to cross-reaction with Artemisia pollen, since ragweed is less pervasive in the China environment and primarily distributed along traffic routes. Amb a 1 has 44%–58% sequence homology with Cry j 1 from Japanese cedar, Jun a 1 from mountain cedar, Art v 6 from mugwort, Cup a 1 from Cypress, and there is the potential for cross-reaction. Many positive ragweed results obtained by SPT or sIgE tests are caused by cross-reactivity with other pollen homologus since ragweed pollen load levels are generally low in most Chinese areas. The diagnostic flowchart of mugwort pollen suspected sensitization is shown in Figure 8.

4.2 | Food Allergens

In this consensus, we focus on the clinical application of common food allergens in China, such as egg and milk, as well as shrimp and crab allergen components. In Supplementary Material (Appendix S4), we present an exposition on the molecular characteristics of peanut and fruit/vegetable allergens.

4.2.1 | Milk allergen

Cow's milk allergy (CMA) is a common food allergy in infancy and early childhood, and its clinical symptoms can involve multiple

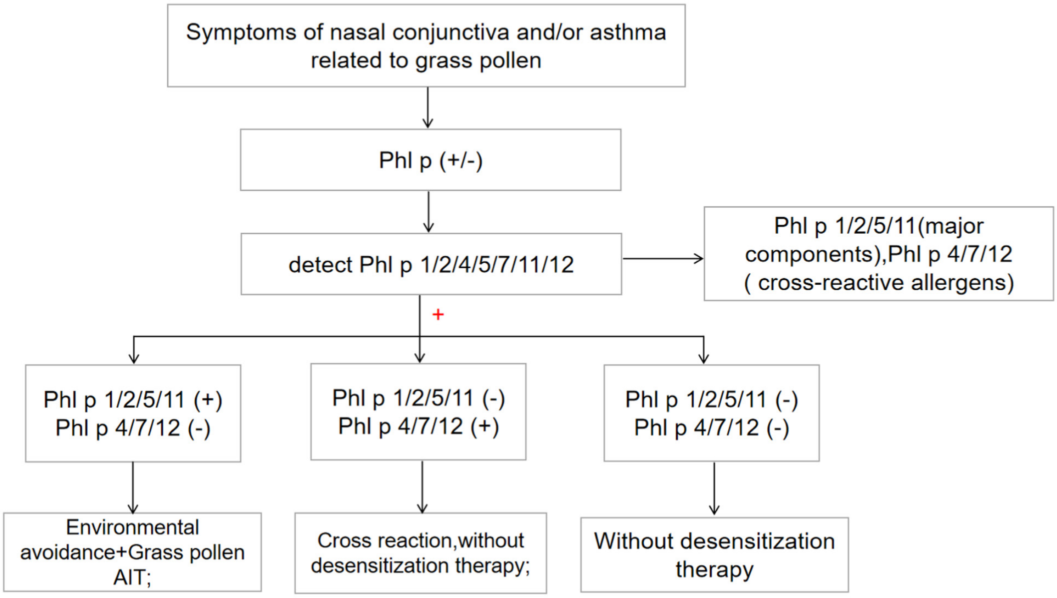

FIGURE 7 Clinical application scenario of sIgE detection of grass allergen components.

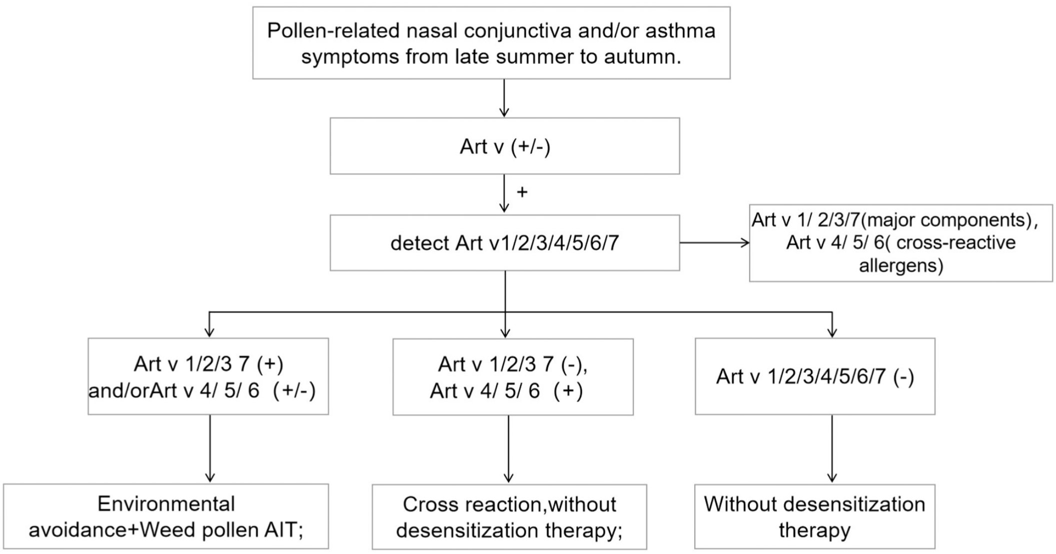

FIGURE 8 Clinical application scenario of sIgE detection of Artemisia allergen components.

systems, with allergic skin reactions being the most common, as well as reactions in the digestive and respiratory tracts. In China, an oral food provocation study showed a prevalence of CMA around 3% in the infant population and a self-reported CMA rate of approximately 2% in children aged 1–7 years in southern China.[108]

The main proteins of milk consist of casein (Bos d 8) (about 80% of the total milk protein) and whey protein (about 20%).[109] Casein comprises four different isoforms: Bos d 9, Bos d 10, Bos d 11, and Bos d 12. The major whey proteins are α-lactalbumin (Bos d 4) and β-lactoglobulin (Bos d 5), while minor allergenic proteins such as bovine serum albumin (Bos d 6), immunoglobulin (Bos d 7), and lactoferrin constitute the remaining allergenic components of milk.[110]

The allergenic spectrum of milk components is not consistent in different regions of China.[111] In Taiwan, the main allergenic component in milk-allergic children is Bos d 4.[112] In southern China, Bos d 4 and Bos d 5 sensitization was predominant in CMA patients[113]; in the north, Bos d 8 sensitization positivity was higher in CMA patients (~42%–56%), while Bos d 4 was lower (~23%).[114]

Casein (Bos d 8) plays a crucial role in the CMA process. Bos d 8 remains stable after heat treatment and remains active after 60 minutes of heating at 95°C,[115] and patients with high Bos d 8-sIgE levels are more likely to have an allergic reaction to baked milk. In addition, high levels of specific IgE to Bos d 8 suggest an increased risk of long-term milk allergy and have been identified as a good indicator to differentiate between transient and persistent CMA.[116] Chinese

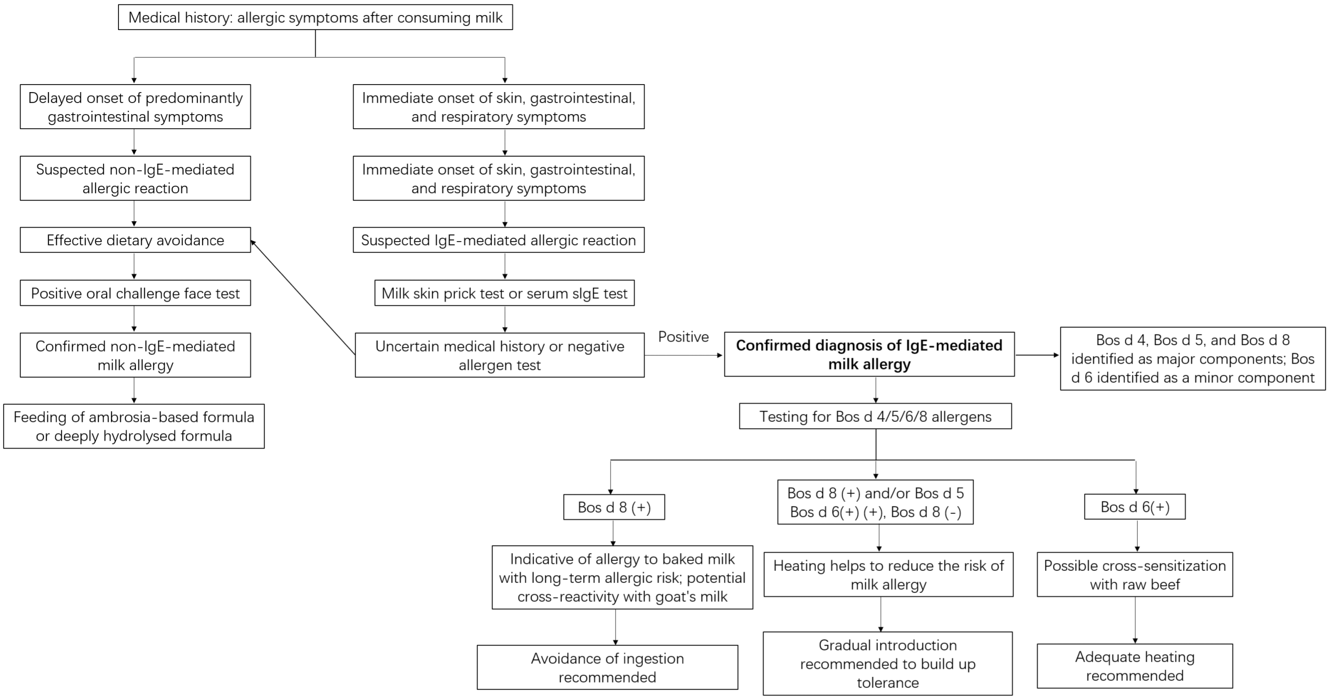

FIGURE 9 Clinical application scenario of sIgE detection of milk allergen components.

scholars testing milk and casein sIgE in distinct types of CMA such as raw cow's milk, cow's milk fermented products, and baked milk have also confirmed significantly higher levels of casein sIgE concentrations in patients allergic to baked milk than other types.[117] In contrast, whey proteins are thermally unstable and the allergenicity of whey proteins can be reduced by heating to disrupt conformational epitopes.[118] It was further found that κ-casein (Bos d 12) showed excellent diagnostic efficacy in differentiating between milk-allergic and non-milk-allergic patients, and that the combination of Bos d 5 and Bos d 12 further enhanced the accuracy of milk allergy diagnosis compared to a single component.[114] In addition, approximately 10% of children with CMA develop an allergic reaction to beef consumption,[119] which may be related to the fact that the main allergens in beef are bovine serum albumin (Bos d 6) and immunoglobulin IgG (Bos d 7). Therefore, the sIgE response to Bos d 6 may be useful in identifying beef-induced allergic reactions during diagnostic testing in children with CMA. The diagnostic flowchart of milk suspected sensitization is shown in Figure 9.

4.2.2 | Egg allergen

Egg allergy (EA) is the second most common cause of food allergy in children. Egg whites contain more allergenic proteins than egg yolks, including ovomucoid (Gal d 1, approx. 11%), ovalbumin (Gal d 2, approx. 54%), ovotransferrin (Gal d 3, approx. 12%) and lysozyme (Gal d 4, approx. 3%).[120] Gal d 2 and Gal d 1 are the main sensitizing proteins in Chinese EA patients, with sensitization rates exceeding 80%,[121] whereas Gal d 4 sensitization is uncommon in EA patients[121] (Table 3).

Ovomucin (Gal d 1), a highly glycosylated protein fraction[122] with heat resistance and protease digestibility stability, is the major allergenic component of eggs. Egg-allergic children with high Gal d 1-sIgE levels tend to have symptoms that persist into adulthood,[20] whereas the IgE-binding epitope of ovalbumin Gal d 2 may be disrupted upon heating,[123] suggesting that children sensitized to Gal d 2 tend to tolerate boiled or cooked eggs.[124] Chicken serum albumin (Gal d 5) in eggs is thought to be a major component associated with avian egg syndrome,[125] in which patients develop respiratory symptoms, such as rhinitis and/or asthma, following exposure to birds and have an allergic reaction to the ingestion of eggs. Therefore, testing for Gal d 5-IgE can assist in the diagnosis of avian egg syndrome.

The diagnosis of egg allergen components helps to determine the allergic phenotype of children with egg allergy. In a Finnish study, Gal d 1-sIgE was used to differentiate allergic patients who could tolerate heated eggs, with values above 3.7 kUA/L being mostly positive for the oral egg provocation test, while 95% of patients tolerating heated eggs when Gal d 1-sIgE was below 0.9 kUA/L,[126] suggesting that the detection of egg components is an important predictor of allergic outcome. The diagnostic flowchart of egg suspected sensitization is shown in Figure 10.

4.2.3 | Crustacean and mollusk allergens

A variety of shellfish, including crustaceans (e.g., crab or shrimp) or mollusks (e.g., clams or scallops), can cause pruritus, gastrointestinal reactions, and oral allergy syndrome.[127] The prevalence of shellfish allergy is about 0.5%–2.5%, and the prevalence is higher in Asian countries where shellfish are habitually consumed. In China, the SPT

TABLE 3 Characteristics of the different components of egg allergens.

Egg allergen components	Generic protein name	Relative molecular mass(kDa)	Stability	Characteristics
Gal d 1	Ovomucin	28	Heat-stable, resistant to protease digestion	Highly allergenic, a good predictor of persistent egg allergy
Gal d 2	Ovalbumin	45	Heat-labile, susceptible to digestion.	Present in the highest amount, associated with allergic reactions to raw or slightly heated eggs
Gal d 3	Ovotransferrin	76		Role not yet clarified
Gal d 4	Lysozyme	14		Antibacterial activity, role not yet clarified
Gal d 5	Albumin	65–70		Present in egg yolk and chicken meat, associated with bird-egg syndrome

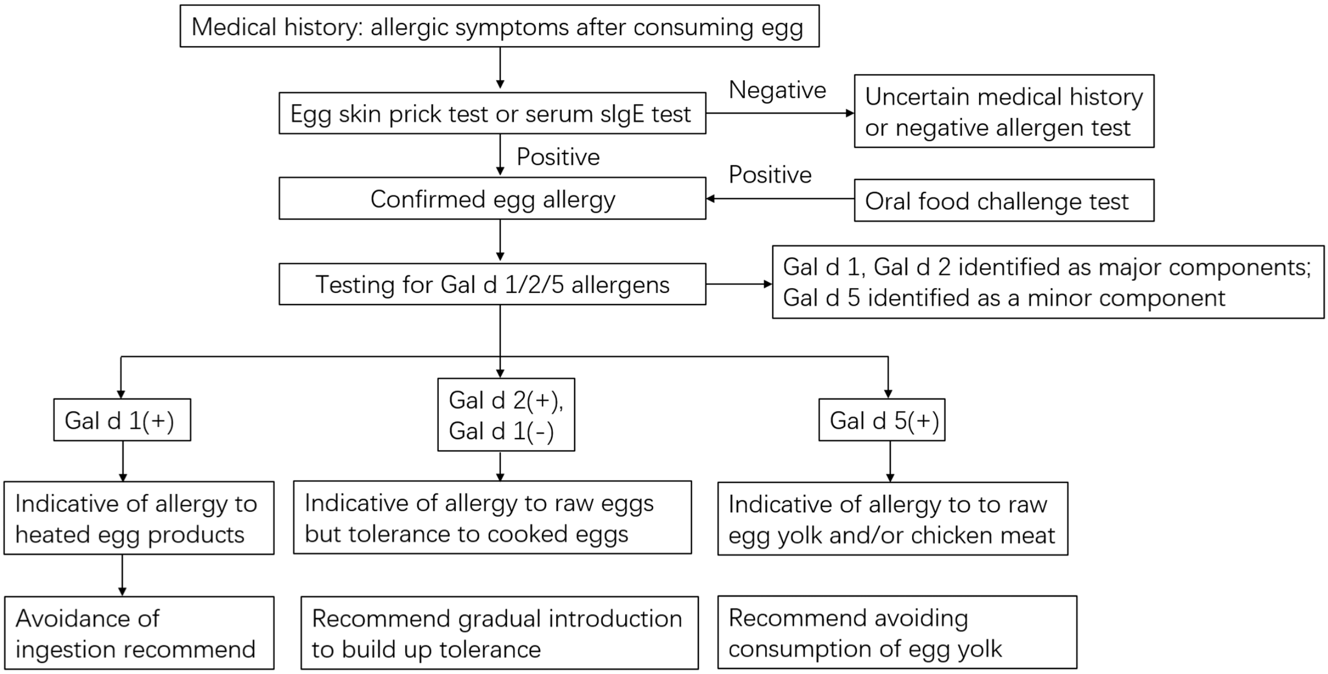

FIGURE 10 Clinical application scenario of sIgE detection of egg allergen components.

positive rate for shrimp and crab is reported in southeast coastal areas (Hong Kong, Guangzhou, Shaoguan) at about Supplementary Material (1%–5%.[128] The self-reported prevalence rate in Taiwan was ~7%.[129]

Tropomyosin (Pen a 1, Pen m 1, Lit v 1, and Tod p 1) is the major allergen of shellfish allergens, belongs to a family of highly conserved structural proteins, is stable to heat, and is resistant to digestion by pepsin.[127] Tropomyosin causes cross-reactivity as an important pan-allergen among invertebrates including crustaceans, arachnids, mites, and mollusks. Up to 90% of patients with shrimp allergy have a positive IgE response to HDM.[130] Other allergens, such as arginine kinase and sarcoplasmic calcium-binding protein, have also been found in crustaceans with a sensitization rate of 10%–15%.[131] The sensitization rate of tropomyosin light chain in shrimp allergic patients exceeds 50%. Tropomyosin, myosin light chain, and sarcoplasmic proteins all have heat-stable properties, while arginine kinase has significantly reduced IgE reactivity after heat and acid treatment.

4.3 | Insect venom allergens

Hypersensitivity to hymenoptera venoms (including bees and wasps) occurs in approximately 9%–29% of the adult population, and systemic sting reactions occur in 0.3%–7.5% of the adult population.[132,133] The rate of sensitization to bee venom is related to the degree of exposure and, therefore, is higher in rural areas than in urban areas, especially among beekeepers and their family members.[134] At present, Api m 1, Api m 2, Api m 3, Api m 5, and Api m 10 have been confirmed as the main allergens. The prospective study reveals that Api 4 sensitization (sIgE > 0.98 kUA/L) serves as a potential predictor of systemic reactions during the initial phase of venom immunotherapy (VIT) and more severe allergic reactions following stings,[135] underscoring the significance of venom allergen component testing in assessing allergic predisposition and informing individualized treatment strategies.

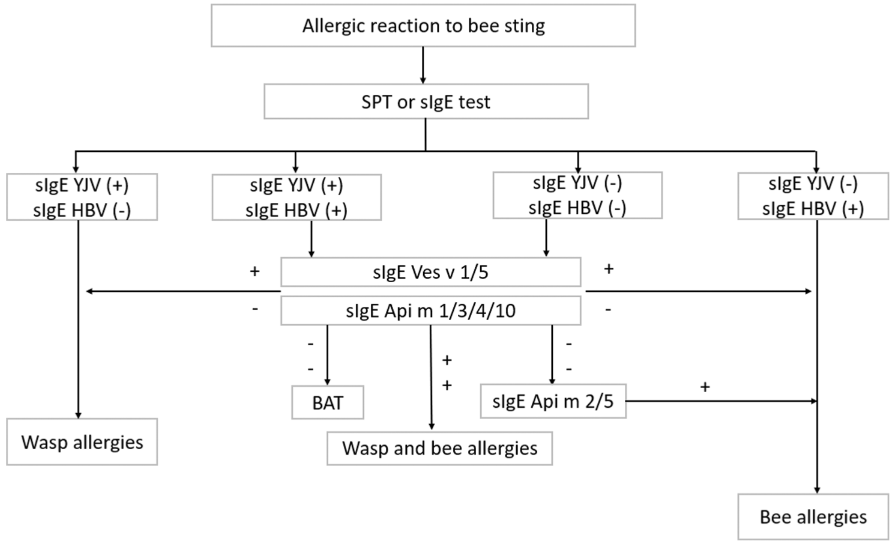

FIGURE 11 Clinical application scenarios of sIgE detection of bee venom allergen. Notes: HBV: honeybee venom, YJV: yellow jacket venom.

In the diagnosis of bee venom allergy, the cross-reaction between allergens needs to be considered, and the cross-reactive carbohydrate determinants (CCDs)in the bee venom extract may be a key factor leading to multiple positive test results, but relying solely on CCD-sIgE detection cannot completely exclude the possibility of sensitization to protein epitopes from various venoms. The joint detection of bee-derived allergens Api m 1, Api m 2, Api m 10, and wasp-derived allergens Ves v 1, Ves v 5, and Pol d 5 can be used to distinguish true sensitization and cross-reactivity. The diagnostic flowchart of bee venom suspected sensitization is shown in Figure 11.

SUMMARY

Accurate detection of allergen components plays a crucial role in the prevention and treatment of allergic diseases. It not only helps in predicting the occurrence and risk of allergic diseases but also aids in identifying cross-reactions, guiding dietary choices, and predicting the effectiveness of AIT. Although there are fewer commercially available allergen component detection reagents used clinically in China compared to Europe and the United States, allergen component test still offers a foundation for the accurate diagnosis, prevention, and treatment of allergic diseases, and holds significant potential for broader applications.

This expert consensus carefully reviews and examines the clinical application guidelines for allergen component sIgE in Europe, understanding the latest perspectives and practices in the diagnosis and treatment of allergic diseases. Simultaneously, it incorporates domestic research findings and patient characteristics in China as the foundation for the guidelines. Taking into account China's allergy epidemiological data, the patterns of allergic diseases, and treatment outcomes, it formulates localized diagnostic guidelines for allergen component sIgE. We plan to regularly update the guidelines to reflect new scientific research and medical advancements, adjusting them promptly to adapt to the continuously evolving field of allergy research. We encourage multidisciplinary professional teams to participate in guideline development, ensuring the involvement of physicians, laboratory technicians, and epidemiology experts, among others, to enhance the comprehensiveness and professionalism of the guidelines. In summary, the development of China's allergen component sIgE diagnostic guidelines is based on respecting and incorporating European experiences while fully considering China's specific conditions, aiming to provide clinical guidance that better meets the needs of local patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

CONSENT FOR PUBLICATION

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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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