A systematic review of allergen cross-reactivity: Translating basic concepts into clinical relevance

Ekansh Sharma, Joana Vitte

Review article

A systematic review of allergen cross-reactivity: Translating basic concepts into clinical relevance

Ekansh Sharma, BE, MSc,[a] and Joana Vitte, MD, PhD[b,c,d] *Uppsala, Sweden; and Marseille, Montpellier, and Reims, France*

Access to the molecular culprits of allergic reactions allows for the leveraging of molecular allergology as a new precision medicine approach—one built on interdisciplinary, basic, and clinical knowledge. Molecular allergology relies on the use of allergen molecules as *in vitro* tools for the diagnosis and management of allergic patients. It complements the conventional approach based on skin and *in vitro* allergen extract testing. Major applications of molecular allergology comprise accurate identification of the offending allergen thanks to discrimination between genuine sensitization and allergen cross-reactivity, evaluation of potential severity, patient-tailored choice of the adequate allergen immunotherapy, and prediction of its expected efficacy and safety. Allergen cross-reactivity, defined as the recognition of 2 or more allergen molecules by antibodies or T cells of the same specificity, frequently interferes with allergen extract testing. At the mechanistic level, allergen cross-reactivity depends on the allergen, the host's immune response, and the context of their interaction. The multiplicity of allergen molecules and families adds further difficulty. Understanding allergen cross-reactivity at the immunologic level and translating it into a daily tool for the management of allergic patients is further complicated by the ever-increasing number of characterized allergenic molecules, the lack of dedicated resources, and the need for a personalized, patient-centered approach. Conversely, knowledge sharing paves the way for improved clinical use, innovative diagnostic tools, and further interdisciplinary research. Here, we aimed to provide a comprehensive and unbiased state-of-the art systematic review on allergen cross-reactivity. To optimize learning, we enhanced the review with basic, translational, and clinical definitions, clinical vignettes, and an overview of online allergen databases. (J Allergy Clin Immunol Global 2024;3:100230.)

Key words: *Allergen, cross-reactivity, immunoglobulin E, molecular allergology, precision medicine, translational medicine*

Allergy and hypersensitivity are widespread conditions caused by abnormal or excessive immune responses to real or perceived offenders. The identification and classification of pathophysiologic mechanisms (endotypes) underlying the clinical expression (phenotypes) and the response to treatment (theratype) of allergic patients have progressed since the early 20th century.[1] A key point in allergy diagnosis is proper identification of the offending allergen, supported by 2 diagnostic pillars: a convincing clinical history (anamnesis) and a demonstrated immune response specifically targeting the culprit allergen (sensitization). The conventional approach for collecting proof of sensitization consists of skin or blood testing with extracts of the suspected allergen.[2] Since the turn of the 21st century, allergen molecules have become available for *in vitro* allergy investigation in addition to allergen whole extracts.[3] As an example, the diagnosis of allergic rhinitis to birch pollen is established if symptoms of allergic rhinitis occur during birch pollen season and there is either skin test *(in vivo)* positivity or serum *(in vitro)* specific IgE to birch pollen extract. Further testing with birch pollen allergen molecules seeks confirmation for genuine sensitization to birch pollen (cross-reactivity to another pollen could be the real cause) and establishes the patient's personalized sensitization profile.

Allergen testing at the molecular level, known as component-resolved diagnosis, molecular-based allergy diagnosis, and molecular allergology, improved diagnostic and prognostic accuracy, therapeutic stratification, and follow-up offered to allergic patients.[4] This was achieved thanks to interdisciplinary basic, translational, and clinical research bridging biochemistry, immunology, cell biology, microbiology, botany, aerobiology, agricultural science, physics, and bioinformatics, with final validation through clinical research in allergology leading to novel tools available for the clinical laboratory.[5] As of February 14, 2024, a total of 1108 allergen molecules (hereafter molecular allergens [MA]) have been registered by the International Union of Immunologic Society (IUIS)/World Health Organization (WHO) Allergen Nomenclature Subcommittee.[6] Other MA have been described but have not been submitted for registration with IUIS/WHO. Conversely, fewer than 200 MA are available for patient investigation via singleplex (1 MA assayed in 1 test) or multiplex (dozens or hundreds of MA assessed in 1 test) formats.[4]

From [a]Thermo Fisher Scientific, Uppsala; [b]Aix-Marseille University, MEPHI, IHU Méditerranée Infection, Marseille; [c]the Desbrest Institute of Epidemiology and Public Health (IDESP), University of Montpellier, INSERM, Montpellier; and [d]University of Reims Champagne-Ardenne, INSERM UMR-S 1250 P3CELL and University Hospital of Reims, Immunology Laboratory, Reims.

Both authors contributed equally to this article, and both should be considered first author.

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Corresponding author: Joana Vitte, MD, PhD, Laboratoire d'Immunologie, Pôle de Biologie et Pathologie, CHU de Reims, Rue du Général Koenig, 51092 Reims Cedex, France. E-mail: joana.vitte@inserm.fr.

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Abbreviations used
AIT: Allergen immunotherapy
α-Gal: Galactose-1,3-α-galactose
BAT: Basophil activation test
CCD: Plant cross-reactive carbohydrate determinants
GRP: Gibberellin-regulated proteins
HDM: House dust mite
IUIS: International Union of Immunologic Societies
IVD: *In vitro* diagnosis
LTP: Lipid transfer protein
MA: Molecular allergens
PR-10: Pathogenesis-related family 10
WHO: World Health Organization

Using MA requires knowledge of their clinically relevant physicochemical, taxonomic, environmental, and immunologic properties.[5,7,8] Extending this reasoning to hundreds of molecules requires a systematic approach. MA are classified as biochemical families; cross-reactivity is assessed mainly on the basis of primary to quaternary structure, and assumptions are validated by clinical data and laboratory investigations. Clinical observations may prompt investigation of apparent cross-reactivity among unrelated allergenic sources, such as kiwifruit and molds,[9] or soy and cow's milk.[10] MA are progressively incorporated into daily practice, resulting in personalized or precision medicine for the diagnostic, prognostic, and therapeutic evaluation and follow-up of allergic diseases.[3,4]

This review provides an interdisciplinary update focused on MA cross-reactivity within IgE-mediated allergy.[1,11] Briefly, IgE-mediated allergy corresponds to Gell and Coombs type I, or immediate hypersensitivity elicited by multivalent allergen-induced aggregation of IgE bound to mast cells or basophils, complemented by later discoveries on the central role of IL-4 and of the type 2 immune reaction comprising a continuum of innate players (eg, innate lymphoid cells 2, aka ILC2) and adaptive players (eg, T_H2 cells and IgE-switched antibody-producing plasma cells).[1]

We first introduce the basic biochemical and immunologic concepts, with examples of their translation into clinical relevance and *in vitro* investigation of allergen cross-reactivity. Then we present and discuss a systematic review of the basic and translational progress in allergen cross-reactivity over the last 5 years.

BASIC CONCEPTS UNDERLYING ALLERGEN CROSS-REACTIVITY

Concepts of molecular allergology are conveyed through a vocabulary bridging immunology, biochemistry, and allergology (Table I).[1,3,5,11-18] Addressing MA implies the existence of an adaptive immune reaction.[3,11] Consequently, allergen cross-reactivity does not apply outside allergen-specific humoral or cellular immune responses. Fig 1 shows allergen-specific immune responses within the broader spectrum of immunologic and non-immunologic hypersensitivity reactions.[11-13,19-22]

Allergen cross-reactivity is defined as the recognition of 2 or more allergens by antibodies or T cells of the same specificity, initially raised against one of the cross-reactive allergens.[3,10] Allergen cross-reactivity is the result of structural similarity of exposed surface areas forming the allergen epitopes. While the recognition takes place at the epitope level, cross-reactivity can be observed with allergen sources (eg, some birch-allergic subjects also experience allergic reactions on ingestion of raw apples), allergen extracts (positive skin prick tests and/or detectable serum IgE to both birch pollen extract and apple extract), and MA (eg, birch and apple pathogenesis-related 10 [PR-10] proteins Bet v 1 and Mal d 1).

Sequence identity refers to the percentage of amino acids that show a direct match with the compared sequence during an alignment. It is usually considered that cross-reactivity between 2 proteins is probable if their sequence identity is >70% but is unlikely for values <50%.[10] When an amino acid in the sequence has mutated to a similar residue with preserved physiochemical properties, the process is called conservative substitution, the sequences are termed similar instead of identical, and they are compared by means of sequence similarity.

There are several computational algorithms to determine the percentage of similarity of the sequences of 2 or more molecules, such as FASTA or BLAST.[23] Tools for comparing the sequence and structure of allergens over smaller regions, ideally epitopes, have been proposed, such as the physicochemical property concept underlying the Sequence Database of Allergenic Proteins (SDAP; fermi.utmb.edu) tool available online.[24]

Sequence homology is a concept based on evolutionary biology and outlines the shared ancestry of 2 sequences.[25] A general rule is that 2 sequences are homologous if they share >30% sequence identity.[26] Sequence homology is key in computational analyses of protein sequences and is often used as one of the primary parameters for assessing cross-reactivity between 2 molecules. An *in silico* homology assessment was long considered as unlikely to miss potential cross-reactivity.[27]

Whether clinically relevant (symptomatic) IgE cross-reactivity may occur only for proteins with demonstrable sequence homology or may also happen for unrelated proteins is still debated.[10,27,28] Conversely, clinically relevant cross-reactivity may be lacking despite high sequence identity. As an example, sequence identity suggested cross-reactivity among members of the common olive allergen group 1 (Ole e 1) and homologs from plantain and white goosefoot, but patient MA investigation with plantain Pla l 1 and white goosefoot Che a 1 helped identify distinct patterns of sensitization, with direct consequences for adequate management.[3,29]

Overall, sequence homology supports cross-reactivity through linear epitopes, which are peptide stretches that can be assigned to consecutive amino acids in the primary sequence. They stand in contrast to conformational epitopes, which comprise amino acids from distinct locations in the primary sequence and are a result of protein folding, glycosylation, and/or di-, oligo-, or multimerization.[3] Physical, chemical, or enzymatic processing may affect both linear and conformational epitopes. For example, heating is known to denature heat-labile allergens of the PR-10 family such as apple Mal d 1 and celeriac Api g 1, preventing them from inducing symptoms in cooked food.[3,30] Conversely, processing may also result in neoepitopes—for example, storage protein neoepitopes in roasted peanut.[31] Innovative methods for the analysis of allergens at the epitope level have been proposed with the aim of improving IgE binding prediction.[32,33]

In recent years, ligand binding and the matrix surrounding the allergen have been shown to influence the ability of the latter to induce an adaptive immune response, to affect its polarization toward a type 2 response and ultimately to sensitize the host.

TABLE I. Definitions of clinically relevant concepts in molecular allergology

Term	Definition
Allergy	Hypersensitivity reaction initiated by antigen-specific, adaptive immune response that can be humoral (antibody mediated), cellular (T cell mediated), or both.[1,11]
Allergen	Antigen (molecule) that can cause allergic disease in previously sensitized subjects.[11,12,14,15] This broad definition is sometimes restricted to IgE-mediated allergy, thus considering allergen as antigen capable of binding IgE and inducing IgE-mediated allergic symptoms.[3,12] Terms "molecular allergen" or "allergen molecule" are used to distinguish molecule from extracts or source.[16]
Allergen(ic) source	Allergen-containing product to which subjects are exposed. Food, pollen, animal dander, airborne fungi, and drugs are common examples of allergenic sources.[3,16]
Allergen(ic) extract	Preparation obtained from selected allergen sources with purpose of skin testing, IVD, AIT, or research. Usually available as aqueous, glycerinated, or lyophilized formulations, allergenic extracts are complex mixtures that contain both allergens and nonallergenic substances.[3,16]
Allergenicity	Ability to induce allergic sensitization and allergic reactions in previously sensitized subjects.[3,17]
Allergic sensitization	Development of allergen specific adaptive immune response, which may comprise demonstrable allergen-specific IgE antibodies and/or T cells and is a prerequisite for development of allergy symptoms.[3,5] Within allergology field, "allergic sensitization" or "sensitization" is commonly used to denote buildup or detection of IgE responses to allergens as opposed to IgG or IgA production of similar specificity.[3,12] "Sensitization" also denotes binding of IgE to high-affinity IgE receptor expressed by mast cells and basophils.[3,13]
Component	Single allergen molecule as tool for allergy diagnosis or AIT; early term[18] for "molecular allergen" (see below), mostly replaced by the latter in current guidelines.[3,4]
Component-resolved diagnosis	Early term for allergy diagnosis comprising investigation at MA ("component") level,[18] as opposed to IgE investigations using allergen extracts, now replaced by "molecular allergy diagnostics"[3] or "precision allergy molecular diagnosis applications."[4]
Cross-reactivity	Recognition of epitopes from distinct allergens by same IgE molecule usually occurring with so-called primary sensitizer allergen inducing IgE antibodies able to bind epitopes shared by other, "cross-reactive" allergens.[3]
Epitope	Region of antigen that is recognized by cognate antibody or T-cell receptor. Epitopes can be linear (sequential stretch of 6-10 amino acids) or conformational (3-dimensional structure composed of nonsequential amino acids).[3]
Genuine sensitization	Sensitization that can be attributed to given allergenic source.[3]
Hapten	Small molecules that need to be covalently coupled to carrier protein to become immunogenic.
Hypersensitivity	Objectively reproducible symptoms and signs triggered by exposure to stimulus at dose tolerated by nonaffected subjects.[11] Hypersensitivity may manifest clinically as immediate hypersensitivity (minutes to 4 hours after exposure to eliciting substance) or delayed hypersensitivity (more than 4 hours after exposure to eliciting substance). Immediate hypersensitivity reactions may fall into different mechanistic categories: nonimmunologic, immunologic nonallergic, and allergic (Fig 1).
Immunogenicity	Ability of antigen to induce immune response.
Initiator allergen	Allergen that induces first sensitization response on encounter with corresponding allergenic source.[3]
Major allergen	Allergen that binds to IgE in serum of at least 50% of patients allergic to corresponding allergenic source.[3] In addition to this definition based on IgE prevalence, major allergens often bind large proportion of IgE spectrum directed to given allergen source and are then denoted "dominant allergens."[3]
Marker allergen	Allergen that, if sensitization to it is demonstrated, is diagnostic marker for genuine sensitization and/or for risk of symptom severity.
Minor allergen	Antigen that binds to IgE in serum of less than 50% of patients allergic to corresponding allergenic source.[3]
Molecular fallergen	See *Allergen* and *Component* above.
Panallergen	Protein belonging to family that shares regions of highly conserved sequence and 3-dimensional structure resulting in IgE cross-reactivity.[3]

References 1, 3-5, 11-18.

Examples of ligand effects include the contribution of ligand phytosphingosine to peach allergen Pru p 3–induced sensitization, variations in the IgE-binding ability of the walnut allergen Jug r 3 as a function of ligand-induced conformational changes, and increased allergenicity due to protection by the ligand against protease degradation.[14] The importance of matrix components at the molecular level is illustrated by the lack of allergenicity of the major birch pollen allergen Bet v 1 alone, while the presence of pollen extract, specifically immunostimulatory proteins acting as mimics of the major type 2 cytokine IL-4, results in the induction of sensitization.[34,35] To date, the involvement of ligands and allergen matrix in allergen cross-reactivity has not been described.

TRANSLATING ALLERGEN CROSS-REACTIVITY INTO CLINICAL RELEVANCE

In terms of clinical relevance, allergen cross-reactivity is usually suspected on allergic reactions to multiple, and sometimes apparently unrelated, allergen sources. A thorough clinical history is needed to reveal culprit allergenic sources before proceeding to *in vivo* or *in vitro* demonstration of sensitization to allergenic extracts and *in vitro* MA testing for sensitization to marker and cross-reactive allergen sensitization (Table I).

A marker allergen is a MA defined by its expression restricted to a species, genus, or family of allergenic sources and its lack of shared epitopes with MA outside the considered allergenic

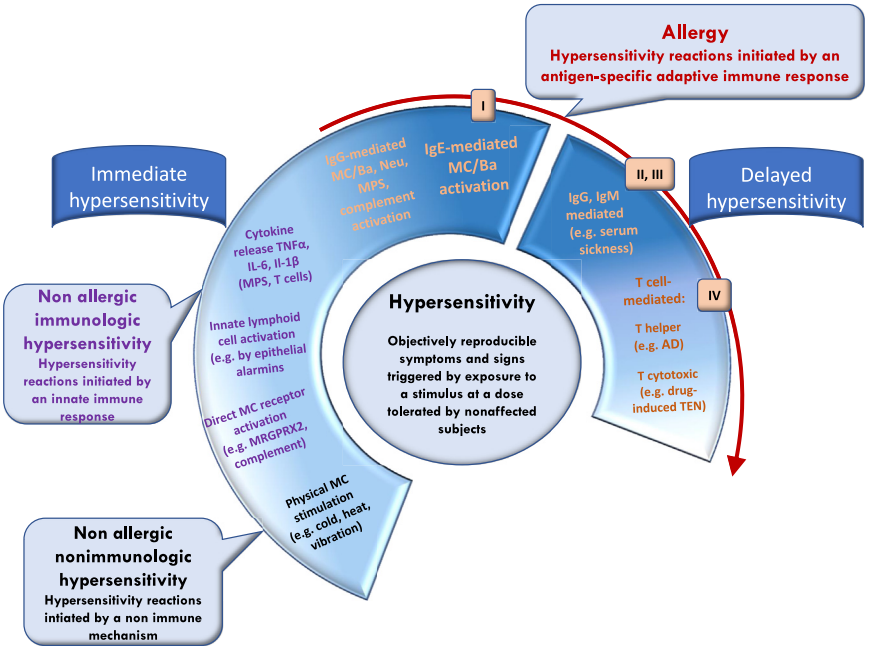

FIG 1. Allergic and nonallergic hypersensitivity reactions. Definitions of hypersensitivity versus allergy and main mechanisms of immediate and delayed hypersensitivity reactions are presented with selected examples. Gell and Coombs classification (type I to IV hypersensitivity) is shown. *AD,* Atopic dermatitis; *Ba,* basophil; *MC,* mast cell; *MPS,* mononuclear phagocyte system (monocyte, macrophage); *Neu,* neutrophil; *TEN,* toxic epidermal necrolysis. References 1, 11-13, 19-22.

sources. Conversely, cross-reactive allergens are defined as MA sharing epitopes and expressed in multiple allergenic sources.

The demonstration of IgE binding to a marker allergen confirms genuine (true) sensitization to the corresponding allergenic source, which is thus identified as the optimal target for allergy management through avoidance or allergen immunotherapy (AIT).

Among marker allergens, most denote genuine sensitization at the taxonomic level of genus or even family, rather than species. As an example, the pectate lyase Cup a 1 from *Hesperocyparis* (formerly known as *Cupressus*) *arizonica* is a marker of genuine sensitization to the tree family Cupressaceae, comprising genera such as *Cupressus* and *Hesperocyparis*.[36] In fact, Cup a 1 is highly cross-reactive with its homologs from *Cupressus sempervirens* and *Juniperus ashei.* Thus, the use of Cup a 1 as a marker of genuine sensitization to Cupressaceae is a trade-off considering (1) its lack of cross-reactivity outside Cupressaceae, (2) its high cross-reactivity with other pectate lyases from Cupressaceae pollen, and (3) the limited availability of other Cupressaceae pectate lyases for diagnosis. Other examples of commonly used marker allergens are honeybee venom phospholipase A2 Api m 1 (marker for *Apis* genus venom), cat dander Fel d 1 (marker for *Felis* genus), and common grass allergen group 1 Phl p 1 (marker for grass pollen).

Allergens initially described as marker allergens may be later reassigned as cross-reactive beyond the genus or family limits. Wasp venom group 5 antigens were considered as specific for *Vespidae* venom, with yellow jacket Ves v 5 and paper wasp Pol d 5 available for *in vitro* diagnosis (IVD), but cross-reactive homologs are now described—for example, Sco m 5 in the venom of the centipede *Scolopendra mutilans* and Tab y 5 in saliva of the horsefly *(Tabanus yao),* among others.[6,37,38]

Depending on the clinical history, some allergens can be used to demonstrate genuine sensitization to very different allergenic sources. IgE to Can f 5 is a marker of genuine sensitization to dog dander in the context of allergy to furry animals, but it can also identify allergy to human seminal fluid.[39] The explanation resides in the cross-reactivity of Can f 5, a prostatic antigen from male dogs, with its human counterpart.

Can f 5, a minor allergen in dog dander-allergic patients, also illustrates that not all marker allergens are also major allergens—that is, inducing sensitization in more than half of patients allergic to the corresponding allergenic source. Conversely, major allergens may not be useful as marker allergens—for example, hazelnut PR-10 Cor a 1.

Demonstrated sensitization to cross-reactive allergens affects patient management because of the risk of clinical relevance (potential reactions to allergenic sources containing homologs of the cross-reactive allergen), the negative effect on AIT efficacy and tolerance, and the potential for molecular spreading.

Cross-reactive allergens may be shared within a small group of allergenic sources; consider, for example, *Hymenoptera* venom dipeptidyl peptidases IV such as honeybee Api m 5 and yellow jacket Ves v 3, or display extensive distribution, such as pollen and plant food PR-10 family, which comprises the aforementioned Bet v 1, Mal d 1, and Api g 1, alongside hazelnut Cor a 1, peach Pru p 1, tomato Sola l 4, and dozens of other homologs.[6]

Such widely distributed cross-reactive allergens are called panallergens. Common examples of panallergen families comprise profilins (pollen, plant food), polcalcins (pollen), cyclophilins (fungi, pollen, plant food), and tropomyosins (from mollusks and arthropods to fish).[3,40] Cross-reactivity may be extensive among members of some panallergen

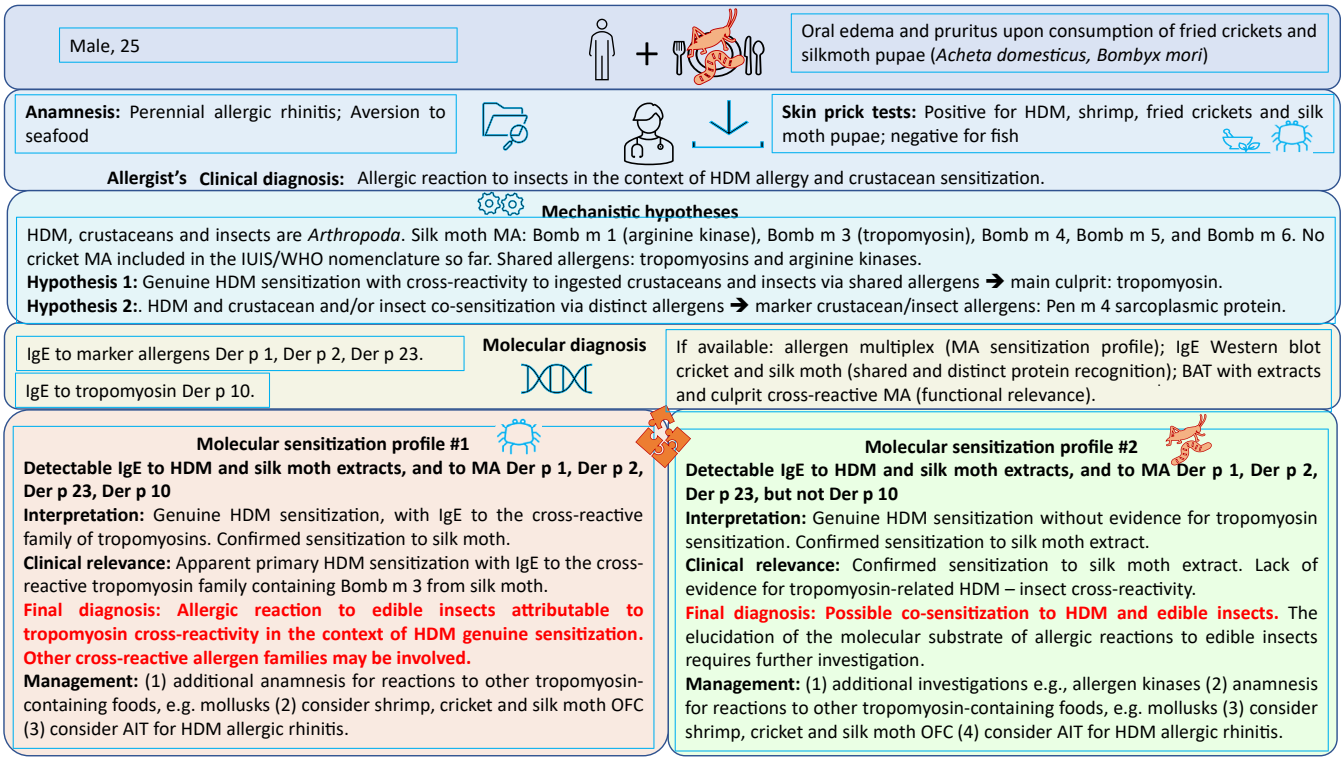

FIG 2. Clinical vignette illustrating HDM, edible insects, and shrimp cross-reactivity. Consider assessing IgE to corresponding allergen extracts for accurate interpretation of IgE to MA. Tropomyosins from arthropods (HDM, insects, and crustaceans), mollusks, and gastropods exhibit extensive cross-reactivity. *OFC,* Oral food challenge. References 3, 41-43.

families. For example, tropomyosin sensitization often results in extended cross-reactivity to inhaled and ingested invertebrate allergenic sources such as house dust mites (HDM), cockroach, or shrimp. The growing consumption of insects as novel foods led to reports of allergic reactions on the first consumption of crickets or mealworms, revealing additional clinical relevance of tropomyosin cross-reactivity. Fig 2 illustrates the MA-assisted investigation of allergic reactions to insects in HDM-allergic subjects, allowing for a personalized diagnosis of cross-reactivity or cosensitization.[3,41-43]

Conversely, members of other panallergen families cross-react with variable intensity, often resulting in a patchy sensitization and clinical reaction profile. An example is the lipid transfer protein (LTP) family, with Pru p 3 from peach efficiently cross-reacting with LTP from other Rosaceae fruit (eg, apple Mal d 3) but less so with wheat grain LTP (Tri a 14) or peanut LTP (Ara h 9).[3,44] In this case, the pattern of sensitization may be related not only to the extent of clinical cross-reactivity but also to the severity of allergic reactions.[45] Of note, the view of complete cross-reactivity among members of the same panallergen family is increasingly challenged, as illustrated by polcalcins.[46] Pollen cross-reactivity may develop among shared allergen families from trees, weeds, and grasses, with clinical implications for the duration and intensity of symptoms, potentially unreliable allergen extract-based skin and blood tests resulting from multiple positive results, and difficult management, especially for the choice of adequate AIT (Fig 3).[3,47-49]

Geographical variation in pollen exposure and subsequent molecular sensitization patterns also guide the work-up of pollen–food cross-reactivity. Identification of the cross-reactive allergen responsible for food plant-induced allergic reactions in the context of pollinosis supports adequate stratification and management, illustrating the clinical relevance of the molecular allergology approach (Fig 4).[3,47,49-53]

Clinically relevant cross-reactivity may happen outside protein families—for example, as a result of unexpected similarity. Soy vicilin Gly m 5 and cow's milk alpha-casein Bos d 9 have been demonstrated to contain similar peptides, which induce cross-reacting IgE responses.[54] Glycosylated side chains are another example of cross-reactivity outside the protein core. Plant cross-reactive carbohydrate determinants (CCD) are highly cross-reactive but have not been associated with definite clinical relevance.[55] Among animal carbohydrates, galactose-1,3-α-galactose (α-Gal) triggers severe IgE-mediated hypersensitivity reactions to red meat, offal, and biologics such as cetuximab.[56] Structural similarity between α-Gal and the blood group antigen B, but not A, results in cross-recognition, the categorization of α-Gal as a "self" antigen, and hence the development of immune tolerance to α-Gal in subjects with B blood groups.[56,57] This illustration of beneficial effects of allergen cross-reactivity is clinically relevant, as subjects with blood group B have a lower risk of allergy to red meat.[58] Finally, another prominent example of allergen cross-reactivity interfering with self/nonself discrimination in the host's immune response is the persistence of T_H2 responses directed against fungal allergens exhibiting cross-reactivity with their human counterparts, such as thioredoxins and manganese superoxide dismutases resulting in persistent atopic dermatitis and the induction of an autoimmune process.[59,60]

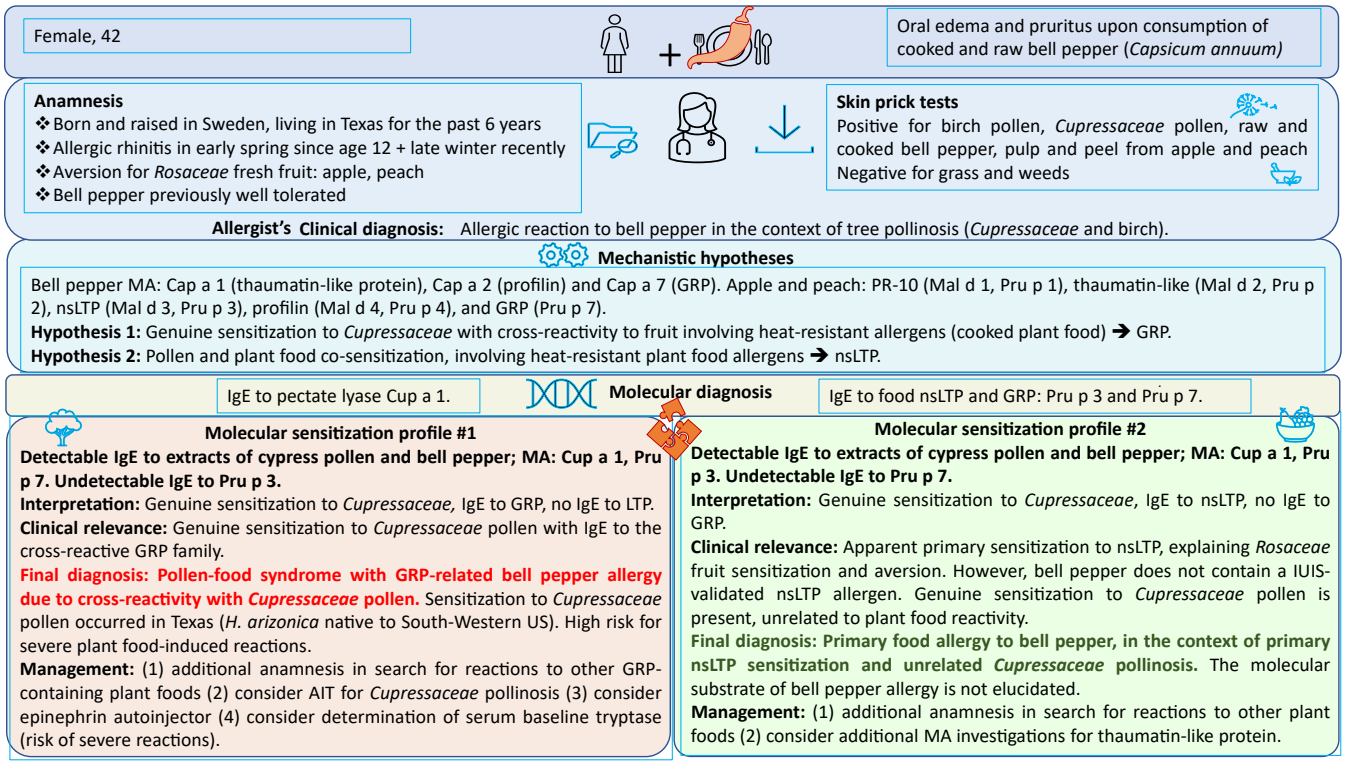

FIG 3. Clinical vignette illustrating pollen and food cross-reactivity. Consider assessing IgE to corresponding allergen extracts for accurate interpretation of IgE to MA. Here, molecular assessment of birch pollen is not useful because it does not contain nsLTP or GRP. Profilin, a plant panallergen family, exhibits extensive pollen–fruit cross-reactivity. Lack of sensitization to grass and weed pollens excludes profilin involvement. PR-10, a cross-reactive family of plant allergens comprising major birch allergen Bet v 1, is heat sensitive. Cupressaceae pollen and bell pepper lack characterized PR-10 homologs. *nsLTP,* Nonspecific LTP. References 3, 47-49.

INVESTIGATION OF ALLERGEN CROSS-REACTIVITY IN THE CLINICAL LABORATORY

Allergen cross-reactivity can be investigated with *in vitro* assays, which are mainly grouped in 3 categories: inhibition immunoassays, MA assays, and functional tests.

Inhibition immunoassays address the ability of an allergen extract or MA #1 to inhibit the IgE binding to another allergen extract or MA #2. Briefly, if IgE binding to #2 is decreased after preincubation with #1, cross-reactivity is demonstrated. More potent inhibition denotes a higher degree of cross-reactivity. The inhibition assay is usually performed in a reciprocal format in order to compare the magnitude of inhibition induced by each extract or MA on its counterpart.[3,48] Thus, the extract or MA inducing the most potent inhibition usually points to the primary sensitizer—that is, the one that initiated the IgE production. For example, in a birch pollen–allergic patient reacting on apple ingestion, the primary sensitizer is birch pollen, and it is expected that birch PR-10 Bet v 1 will inhibit more potently IgE binding to apple PR-10 Mal d 1 than Mal d 1 will inhibit IgE binding to Bet v 1. Inhibition immunoassays are unavailable in most clinical laboratories; they are labor-intensive, time-consuming, and nonstandardized.

Functional tests are mainly represented by the basophil activation test (BAT), which consists of assessing the activating effect of an allergen extract or MA on a patient's basophils collected by venipuncture. In case of demonstrated IgE binding to multiple cross-reactive allergens, BAT may provide further information on the ability of each allergen to induce basophil degranulation, which in turn predicts a higher likelihood of clinical relevance. An example of potential BAT application for allergen cross-reactivity assessment is the differential diagnosis of *Hymenoptera* venom allergy in patients sensitized to multiple venoms.[3] BATs are available in specialized clinical laboratories.

Allergen cross-reactivity assessment in the clinical setting relies mostly on *in vitro* assessment of IgE binding to cross-reactive MA.[3,4] On the one hand, using marker allergens as tools for the confirmation of genuine sensitization is rather straightforward and requires a limited number of MA IgE assays. On the other hand, the investigation of a suspected cross-reactive sensitization profile may be challenging as a result of the open question of the number of homologs that need to be assayed. The answer to this question depends on anamnesis, the results of first-line investigations with allergen extracts if available, the risk of severe systemic reactions, whether a specific treatment such as AIT is available, and if so, whether its initiation depends on the molecular sensitization profile.

The actual use of MA in the daily practice of allergists is different from one country to another. Concordant international guidelines are available.[3,4] However, nonmedical issues, such as the availability of MA testing, its price, and the local policy of health care reimbursement, also come into play. Current

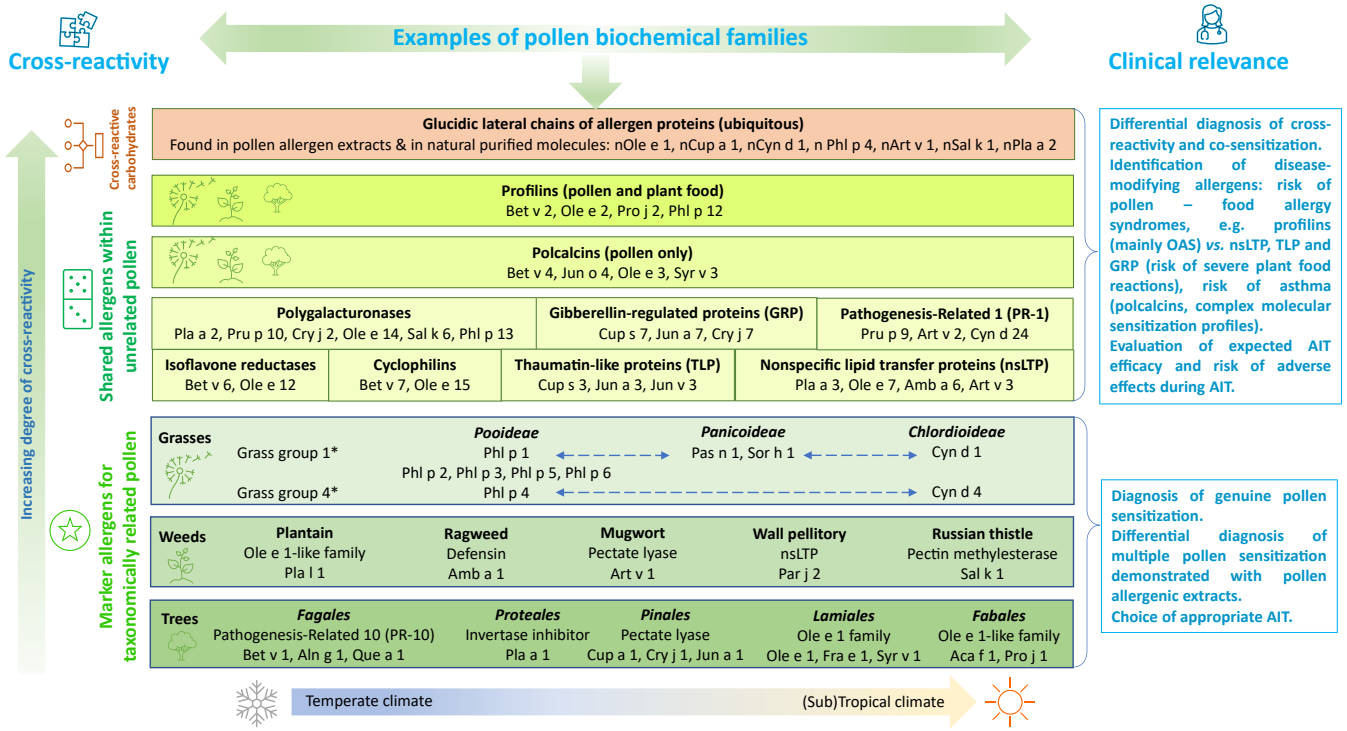

FIG 4. Pollen marker and cross-reactive allergens. Selected examples are shown for marker and cross-reactive pollen allergen families. Genuine sensitization to major taxonomic groups of trees, weeds, and grasses can be identified using marker allergens. Examples include PR-10 allergens from *Fagales* trees (birch Bet v 1, alder Aln g 1, oak Que a 1), invertase inhibitors from *Proteales* (London plane Pla a 1), pectate lyases from *Pinales* (Arizona cypress Cup a 1, Japanese cedar Cry j 1, juniper Jun a 1), Ole e 1–related allergens from *Lamiales* (olive tree Ole e 1, ash tree Fra e 1, lilac Syr v 1), and Ole e 1–like allergens from tropical trees (sweet acacia Aca f 1, *Prosopis juliflora* Pro j 1). Allergen families comprising cross-reactive homologs across unrelated taxonomic groups are denoted as shared allergens. Profilins and polcalcins are ubiquitous in grass, weed, and tree pollen. Profilins, but not polcalcins, are also found in plant foods. Profilins and polcalcins display extensive cross-reactivity (pollen panallergens), while variable cross-reactivity is found with most other families of shared allergens. For example, nsLTP Par j 2 does not cross-react with other pollen nsLTP, while clinically relevant cross-reactivity has been described among other pollen and food nsLTP, such as plane pollen Pla a 3, mugwort pollen Art v 3, and peach (fruit) Pru p 3. Cross-reactivity of olive pollen Ole e 1 with Ole e 1–like allergens is also variable: high cross-reactivity between Ole e 1 and ash tree Fra e 1, moderate cross-reactivity of Ole e 1 with other marker allergens from *Lamiales* order (lilac, privet), and no clinically relevant cross-reactivity with Ole e 1–like allergens from grass or weed pollen. While marker pollen allergens are typically major allergens—that is, sensitization is detected in >50% of allergic patients—shared allergens can present as either major or minor allergens depending on biochemical family and individual exposure. Marker allergens exhibit climate preferences in relationship to plants they are derived from. *IFR,* Isoflavone reductase; *nsLTP,* nonspecific LTP; *PR-1,* pathogenesis-related family 1; *OAS,* oral allergy syndrome; *TLP,* thaumatin-like protein. References 3, 47, 49-53.

recommendations issued by the European Academy of Allergy and Clinical Immunology provide guidance for most of the cases seen in allergy clinics.[3]

A cost-effective approach for pollen allergy was proposed in 2021 combining anamnesis, stepwise investigation, and probabilistic reasoning to limit the use of apparently redundant investigations.[61]

Food allergic, pollen–food allergic, and polysensitized patients may benefit from apparently redundant testing of multiple cross-reactive homologs, as illustrated again by the LTP family. Gibberellin-regulated proteins (GRP), a family of cross-reactive pollen and food allergens eliciting severe systemic reactions, would also benefit from multiple testing; however, peach Pru p 7 is currently the only MA available for clinical laboratory investigation.[48,49,62]

IVD based on IgE binding to MA allows for standardization, quantification, interlaboratory comparison, sample storage, and comparative repeated measurements, explaining the rise of diagnostic and prognostic models based on IgE sensitization to MA.[63,64] Table II provides the definitions of key concepts pertaining to IVD.[65-67]

Interpretation of MA assays is supported by numerous available algorithms, some of them available as international guidelines.[3,4] The interdisciplinary nature of allergen cross-reactivity knowledge and the rapid evolution in the field of molecular allergology are best addressed by online tools, which can be updated and accessed instantly. Multiple online databases are available,[68] supporting personal knowledge and specialist networking among practitioners, laboratory scientists, and clinical scientists (Table III).

TABLE II. Key concepts pertaining to IVD

Term	Definition
Qualitative analysis	Method that indicates presence or absence of analyte without providing precise estimate of its concentration.
Quantitative analysis	Method that can determine precise concentration of analyte, like IgE, as numerical value in appropriate units.
Limit of blank (LoB)	Highest *apparent* concentration of analyte that can be detected when replicates of blank sample containing no analyte are tested.
Limit of detection (LoD)	Lowest concentration of analyte that can be distinguished from LoB while detection is possible.
Limit of quantitation (LoQ)	Lowest concentration at which analyte can be detected and predefined goals for bias and errors are met.
Sensitivity	Ability of IVD test to accurately identify presence of analyte in biological sample (analytical sensitivity) or individual affected by considered disease (clinical sensitivity).
Specificity	Ability of IVD test to accurately identify absence of analyte in biological sample (analytical specificity) or individual free of considered disease (clinical specificity).
True positive	Positive test on sample containing analyte (analytically truly positive) or in individual affected by considered disease (clinically truly positive).
True negative	Negative test on sample that does not contain analyte (analytically truly negative) or in individual free of considered disease (clinically truly negative).
False positive	Positive test on sample that does not contain analyte (analytically falsely positive) or in individual free of considered disease (clinically falsely positive).
False negative	Negative test on sample containing analyte (analytically falsely negative) or in individual affected by considered disease (clinically falsely negative).
Positive predictive value (PPV)	Probability of presence of analyte or disease when test returns positive result; number of true positives out of all positive results.
Negative predictive value (NPV)	Probability of analyte or disease being absent when test returns negative result; number of true-negative results out of all negative results.
Prevalence	Percentage of individuals in specific population having condition of interest.

References 65-67.

SYSTEMATIC REVIEW OF ALLERGEN CROSS-REACTIVITY LITERATURE

A systematic review of allergen cross-reactivity was conducted in accordance with the PRISMA-P guidelines.[69] The protocol can be found in the PROSPERO Registry under the reference CRD42022312363 "Basic concepts and clinical relevance of allergen cross-reactivity: a systematic review" and is summarized as a flowchart in Fig 5. A PubMed search using ((molecular allergen) AND (cross-reactivity)) AND (immunoglobulin E) from January 1, 2018, through January 31, 2022, was matched by 134 articles. Abstracts were manually reviewed for selection of original articles, position papers, consensus publications, guidelines, and official recommendations. Full text of original research articles (n = 108), position papers (n = 1), and consensus publications (n = 1) were retrieved and manually appraised with respect to relevant information on allergen cross-reactivity, resulting in the exclusion of a further 48 publications. The appraisal of full-text publications also led to the identification and manual addition of 17 original articles relevant for the allergen cross-reactivity topic. The final selection comprised 79 relevant publications. Progress in allergen cross-reactivity reported since January 2018 can be categorized in 4 major areas, which we present here, and which are reported in detail in Table E1 in the Online Repository available at www.jaci-global.org.

Taxonomic advances

Plant CCD were recognized for the first time as potential allergens with clinical relevance, were included in the IUIS/WHO nomenclature position paper,[55] and were demonstrated to be sufficient for *N*-glycan–supported cross-reactivity among peanut seed storage allergen Ara h 1 variants.[70] Animal CCD galactose-α-1,3-galactose (α-Gal) causing red meat allergy displayed cross-reactivity to human blood group antigen B,[57] while cross-reactive tick–insect proteins carrying α-Gal were identified.[71] A laboratory approach using immunoblot for the investigation of cross-reactivity, individual sensitization patterns, and relationship to meat allergy severity was proposed.[56]

First allergen description in a protein family and its cross-reactivity is an ongoing process, as illustrated by Cic a 1.01 from *Cicer arietinum* (chickpea), a member of the protein family late embryonic abundant protein 4 (aka LEA-4) displaying serum IgE binding not only in *C arietinum* allergic patients but also in peanut-sensitized ones.[72]

Novel members of cross-reactive food allergen families were described within the seed protein families, relevant for legume and nut cross-reactivity, such as vicillins, 2S albumins, and cyclophilins.[73-76] Cross-reactive allergens responsible for latex–food and latex–pollen–food syndromes were identified within the families of latex allergens Hev b 5, cross-reacting with apricot allergen Pru ar 5,[77] and glucanase Hev b 2, cross-reacting with banana Mus a 5 and Japanese cedar pollen allergen CJP38.[78] The GRP family responsible for Cupressaceae pollen–food severe cross-reactivity has been steadily increasing, from the initial peach peamaclein Pru p 7[79] to pollen homologs from cypress Cup s 7, juniper Jun a 7, Japanese cedar Cry j 7, and to fruit homologs from orange Cit s 7, Japanese apricot Pru m 7, pomegranate Pun g 7, bell pepper Cap a 7, and apple applemaclein.[6,47-49,62,80-82]

Another milestone in the elucidation of severe pollen–food cross-reactivity was the identification of the celery root defensin Api g 7 that cross-reacts with pollen defensins such as mugwort Art v 1.[83] Novel members of food panallergens were reported as eggplant profilin Sola m 1,[84] durum wheat LTP Tri tu 14,[85] grass carp beta-parvalbumin Cten i 1,[86] and others.[87]

Novel airborne allergens belonging to the pollen allergen families of polcalcins, defensins, pectate-lyases and

TABLE III. Alphabetical listing of allergen knowledge databases

Database name	Link	Information provided	Managed by	Established	Update cadence/ last update	Relevance
Allerbase	bioinfo.unipune.ac.in/ AllerBase/Home.html	Allergen complemented by sequence, structure, epitopes, and allergenicity tests.	Bioinformatics Centre, Savitribai Phule Pune University, India	2017	Not known	Site provides detailed and comprehensive descriptions with relevant underlined data.
Allerdata	www.allerdata.com	MA and allergenic sources.	French Society of Allergology	2007	Mixed/ unstandardized	Site (which is mostly in French) provides clinical information on allergenic sources and allergens. Interactive tool permits analysis of cross-reactivity among different allergen molecules.
Allergen Encyclopedia	www.thermofisher.com/ phadia/wo/en/resources/ allergen-encyclopedia.html	Allergens that describe epidemiology, living environment, route of exposure, molecular aspects, clinical relevance, and cross-reactivity	Thermo Fisher Scientific	2020	Regular/yearly	Content was included by collaboration among industry and independent leading scientists as well as opinion leaders.
Allergen Online	www.allergenonline.org/	Allergenic safety of proteins present in novel or processed foods	Food Allergy Research and Resource Program (FARRP), University of Nebraska-Lincoln	2005	Yearly/Jan 2022	Site offers alignment of new sequences against databases.
Allergome	www.allergome.org	Identification of allergen and its relationship with other allergens within Allergome	Allergome team	2003	Irregular	Site provides comprehensive allergen sheet with numerous bibliographic sources (eg, structure, function, allergenicity), links to other databases, proteins, sequences, protein families, etc.
AllFam	www.meduniwien.ac.at/ allfam/	Classifying allergens listed by the IUIS/ WHO subcommittee into protein families	Biochemistry and Bioinformatics group, Medical University Vienna	2008	Irregular/2017	Classifying allergens into protein families can help answer questions such as: What makes a protein an allergen? Which allergens are cross-reactive? However, (1) not every member of an allergen-containing protein family is allergenic, and (2) not all allergenic members of a protein family are cross-reactive.
COMPARE	db.comparedatabase.org/	Protein sequences of known allergens accessed via rule-based text-sorting algorithm to identify allergens from publicly posted sequences and literature repositories	Health and Environmental Sciences Institute	2017	Yearly, Feb 2021	All entries are reviewed by independent peer-review panel of public sector allergy experts.
SDAP—Structural Database of Allergenic Proteins	fermi.utmb.edu	Allergenic proteins (IUIS and non-IUIS registered) and computational tools for structural biology	The University of Texas Medical Branch	2001	Regular/2021	Site helps researchers identify sequence and function similarity among allergens and evaluate potential allergenicity of protein; and provides resources on sequence, structure, and epitopes of allergens.
IUIS/WHO Nomenclature Subcommittee	www.allergen.org	MA approved by expert committee	Allergen Nomenclature Subcommittee	1984 (Committee)/ first entry 2003	Regular (per submission)/ 2022	Site provides unique and systematic names to allergens, approved by WHO and IUIS.

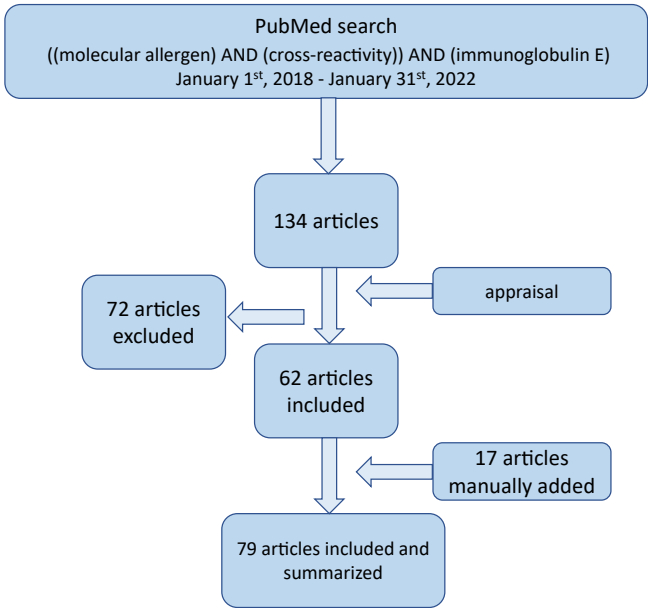

FIG 5. Flowchart of systematic review. A systematic review of allergen cross-reactivity following the PRISMA-P guidelines (Basic concepts and clinical relevance of allergen cross-reactivity: a systematic review, PROSPERO Registry CRD42022312363) identified 134 PubMed articles. The full-text of original articles, position papers, consensus publications, guidelines, and official recommendations was searched for relevant information on allergen cross-reactivity. Exclusion of 72 nonrelevant publications and manual adjunction of 17 relevant original articles resulted in a final set of 79 relevant publications.

polygalacturonases expanded the potential investigation of pollen–pollen cross-reactivity, including the difficult investigation of mugwort pollinosis.[49,50,88-91] Progress was also achieved for indoor airborne allergens, adding novel biochemical and clinical data for HDM,[92-95] molds,[51,96,97] and cat epithelium.[98]

Cross-reactivity of venom allergens injected during *Hymenoptera* (wasps, hornets, and bees) stings with salivary proteins introduced during tick bites was recognized.[71,99] The newly characterized venom allergens phospholipase A2 and vascular endothelial growth factor from the venom of the Mediterranean wasp *Polistes dominula* demonstrated such cross-reactivity.[100]

Novel foods such as *Salvia hispanica* (chia) seed,[101] *Medicago sativa* (alfalfa),[102] and edible cricket *Acheta domesticus*[41] demonstrated IgE cross-reactivity at the molecular level with sesame, hazelnut, or shrimp, suggesting the involvement of novel members of well-known cross-reactive allergen families such as LTP, thaumatin-like protein, PR-10, or tropomyosin.

Translational and diagnostic advances

Climate and geography-related variability was addressed for more accurate diagnosis. Local characteristics of MA cross-reactivity were reported for HDM in Brazil,[103] China,[104,105] Taiwan,[106] and Algeria.[107] Phospholipase A_1-supported cross-reactivity was studied in the venom of *Hymenoptera* species native to South America and Europe.[108] Cross-reactivity among grass pollen allergens belonging to group 1 was studied in Thailand.[109,110] Novel allergens were characterized in edible *Fabaceae* cultivated in Africa and Asia.[111] Severe clinical presentations of pollen–food cross-reactivity supported by GRP members were reported from France, Japan, Italy, and Spain.[48,112-114]

Clinical relevance was shown for sensitization to birch pollen Bet v 1 as a predictor of asthma development,[115] for variations in hazelnut Cor a 1 potency as a function of conformational variations affecting IgE binding,[116] for cross-reactivity of tropomyosins from HDM and mosquito.[117] Conformational variations altering surface exposed epitopes and IgE binding were demonstrated for beech pollen Fag s 1, similar to its homolog Bet v 1 from birch pollen.[118]

Frequent clinical cross-reactivity among walnut, other tree nuts, and seeds was elucidated and attributed to the walnut vicillin Jug r 6 and its homologs.[119]

Other studies addressed the interindividual variations in clinical expression of sensitization to panallergen families at the epitope level. Species-specific epitopes, which do not induce cross-reactivity, and shared cross-reactive epitopes were identified in mugwort LTP Art v 3, in profilins, and in cyclophilins.[120-122] The latter works illustrate at the submolecular level the marker versus cross-reactive work-up of IgE binding.

Progress in clinical laboratory investigation of cross-reactivity versus cosensitization and genuine sensitization was reported from cohort studies to plant storage proteins,[123-125] *Anisakis simplex*,[126] tree nut allergy,[127] and storage mites versus HDM.[106] Longitudinal evaluation of cross-reactive allergen sensitization was reported for LTP, showing molecular spreading in one third of food-allergic patients and new LTP-related food reactions in 13% of previously sensitized but not allergic ones.[128] Allergen multiplex investigation helped identify cross-reactivity patterns and culprit allergen families, improving diagnostic accuracy and efficiency.[51,102,115,129-131] Cellular tests addressing functional responses (basophil, mast cell, and T-cell activation) were performed in clinical, translational, and research settings for the evaluation of allergen cross-reactivity.[132] Improving the quality of available molecular tools was also addressed with a focus on weed *Parietaria* pollen nonspecific LTP Par j 1 and Par j 2,[52] and IgE binding to plant, venom, and HDM CCD.[133]

Veterinary applications of allergen cross-reactivity were reported, such as fish–chicken cross-reactivity in allergic dogs.[134]

Conceptual advances and new tools for cross-reactivity investigation

Reports on potential cross-reactivity of MA previously considered as unrelated, such as kiwifruit cysteine protease Act d 1 and egg white conalbumin Gal d 3, or walnut 2S albumin and codfish parvalbumin Gad c 1,[115] suggested that insights into the mechanisms of cross-reactivity at the epitope level and the design of epitope-based strategies are translational approaches with promising relevance for clinical application. Conversely, some of these observations may be recognized as artifactual when accurate investigation becomes available, as illustrated by the demonstration that apparent cross-reactivity between structurally unrelated peanut allergens Ara h 1 and Ara h 2 is in fact due to molecular complexes containing both proteins.[28]

Insights into mechanisms of cross-reactivity at the epitope level were reported. In one study, monoclonal IgE binding with high affinity to 3 distinct epitopes of the cat major allergen Fel d 1 was engineered and reversed to the corresponding germline configurations, which bind the same epitopes but with low affinity. At the epitope level, low-affinity IgE binding to the same epitope models cross-reactive IgE binding. The functional assessment of low affinity IgE with BAT confirmed their ability to induce mast cell

degranulation provided they also exhibited high avidity binding.[135] A phage display-based method distinguished wheat allergen epitopes bound by serum IgE of wheat-allergic patients from wheat allergen epitopes bound by serum IgE of wheat-tolerant subjects.[136]

Assessment of crystal structures, epitope grafting, and chimera protein engineering of allergens followed by assessment of IgE binding and functional basophil activation assessment were used to gain further data on the contribution of epitopes to cross-reactivity. Examples include mud crab triose phosphate isomerase Scy p 8 and its crustacean counterparts,[137] olive pollen cyclophilin Ole e 15 and its human counterpart peptidyl-prolyl *cis-trans* isomerase A,[53] dog lipocalin Can f 6,[138,139] strawberry PR-10 Fra a 1.02,[140] and shrimp and other shellfish.[141] The absence of IgE cross-reactivity to epitopes with similar conformation and exposure was also reported in a study addressing HDM allergens Der p 5 and Der p 21.[142]

An approach combining structural and physicochemical characterization and the establishment of murine T-cell clones evidenced the effect of thermal and pH treatment on endolysosomal peptide generation and T-cell cross-reactivity of shrimp tropomyosin Pen m 1 with its homologs Der p 10 from HDM, Bla g 7 from cockroach, and Ani s 3 from the fish parasite *Anisakis simplex*.[143]

Computational approaches for predicting allergenicity and cross-reactivity were increasingly reported,[144,145] with some tools already available on the web.[115,146]

Therapeutic advances

Taken together, clinical evaluation of cross-reactive molecules and individual sensitization patterns affect AIT prescription, efficacy, and monitoring;[3,147] help evaluate novel approaches such as apple oral AIT for birch pollinosis;[148] and extend protection through cross-blocking reactivity.[149]

The study of host immune cross-recognition contributed to further insight into Bet v 1 cross-reactivity at the IgG and IgE level after allergen vaccination or AIT,[150] and B-cell memory at the mucosal allergen exposure sites.[151] Finally, intervention-directed approaches such as identification of apple cultivars with low clinical cross-reactivity could be considered for birch-allergic patients with pollen-related food allergy to apple.[152]

CONCLUSION AND PERSPECTIVES

This systematic review of allergen cross-reactivity research demonstrates a significant shift toward computational tools and increased awareness of the role of host immune responses while pursuing a clear translational goal of clinical applications. Practicing allergists have become familiar with allergen multiplex investigations, so the main clinical question is shifting from molecular elucidation of clinically reported cross-reactions to the prediction of cross-reactions that might occur on encounter with new allergen sources, the search for novel biomarkers, and improved patient management in the context of ongoing pathophysiologic research.[153,154] Artificial intelligence and machine learning algorithms are expected to provide powerful new tools for predictive medicine including allergy and immunology,[155] thus filling the gap of clinically available knowledge on allergen cross-reactivity.

Major efforts have addressed food and airborne allergen cross-reactivity. Yet despite the persistence of unmet needs in drug cross-reactivity, drug allergy was the focus of only 2 publications retrieved with the systematic search—a finding that may help incentivize further research in this area.

Further unmet needs include the commercial availability of MA for IVD, with a stark contrast evident between the large number of demonstrated allergens and the limited number of those available for IVD; automation and improved standardization of allergen multiplex methods that allow personalized profiling at the molecular level; and finally better dissemination of basic and clinical allergen knowledge through the use of databases and online algorithms.

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