

# Overview of Component Resolved Diagnostics

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**Abstract** Component-resolved diagnostics (CRD) utilize purified native or recombinant allergens to detect IgE sensitivity to individual allergen molecules and have become of growing importance in clinical investigation of IgE-mediated allergies. This overview updates current developments of CRD, including multiarray test systems. Cross-reactions between allergens of known allergen families (i.e. to Bet v 1 homologues) are emphasised. In pollinosis as well as in allergy to hymenoptera venoms or to food, CRD allows to some extent discrimination between clinically significant and irrelevant sIgE results and the establishing of sensitisation patterns with particular prognostic outcomes (i.e. sensitisations to storage proteins which correlate with clinically severe reactions in peanut allergy). Further promising improvements in diagnostics are expected from additional, not yet commercially available, recombinant allergen diagnostics identifying particular molecules of risk. Overall, CRD may decrease the need for provocation testing and may also improve the specificity of allergen-specific immunotherapy.

**Keywords** Allergy · Alpha-gal · Animal dander · Bet v 1 · Birch · Immunoglobulin E · IgE · Component resolved diagnostics · Cross-reacting carbohydrate determinants · Food allergy · Hymenoptera allergy · In vitro · Lipid transfer protein · Molecular allergy · Multiarray test systems · Pollen-associated food allergy · Pollen allergy · Profilin · Recombinant · Review · Specific immunotherapy · Soy allergy · Storage protein

## Introduction

Until recently, in vitro allergy diagnostics were based on detecting specific IgE (sIgE) to total extracts which contained a series of allergenic and non-allergenic components. Meanwhile, purified native or recombinant allergens, identifying the individual molecules to which patients are sensitised, can be determined by molecular or component-resolved diagnostics (CRD) [1, 2]. An increasing number of allergens, especially from plants (Table 1) [3, 4], have found their way into routine diagnostics in recent years, and individual IgE profiles and allergen patterns allow for closer examinations of cross-reactions, molecules of risk and prognostically significant sensitisations. Overall, it emerges that CRD can improve management of the allergic patient as it allows to some extent discriminating between clinically significant and irrelevant sIgE results and the establishing of sensitisation patterns with particular prognostic outcomes. A further challenge might be the tailoring of specific immunotherapy (SIT) to the molecular sensitisation profiles of individual patients [5]. Here, we present an overview of current developments in IgE diagnostics of frequent allergens. A variety of allergens have already been identified but not yet applied in a CRD approach. Diagnostic tests already commercially available today are characterised by bold type.

## Allergy Laboratory Tests for CRD

Purified (natural/n) or recombinant (r) allergens manufactured by gene technology are employed for sIgE diagnostics. ImmunoCAP™ (Phadia/Thermo Fisher Scientific, Uppsala, Sweden) or Immulite (Siemens Healthcare Diagnostics, Los Angeles, CA, USA) are FDA-approved enzyme-linked immunoassays which give quantitative results of IgE levels in kU/l. Reliable detection of sIgE requires allergen reagents with a

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**Table 1** Frequently sensitizing plant allergen families

| Family                  | Characteristics                                                                                   | Examples of allergens (sIgE already available commercially)                                              |
|-------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Bet v 1 homologue       | Major allergen of birch <i>Betula verrucosa</i> . Similar proteins are termed Bet v 1 homologues. | <b>rApi g 1</b> – Celery<br><b>rAra h 8</b> – Peanut<br><b>rCor a 1</b> – Hazel<br><b>rGly m 4</b> – Soy |
| Lipid transfer proteins | Sensitisations usually in southern Europe, severe reactions, gastrointestinal sensitisation       | <b>rAra h 9</b> – Peanut<br><b>rPru p 3</b> – Peach<br><b>rCor a 8</b> – Hazel                           |
| Profilins               | Little clinical relevance, often responsible for cross-reactions                                  | <b>rBet v 2</b> – Birch<br><b>rPhl p 12</b> – Grass                                                      |
| Storage proteins        | Stable proteins, representing a large proportion of proteins in nuts, seeds, legumes and cereals  | <b>rAra h 2 and 3</b> – Peanut<br><b>rGly m 5 and 6</b> – Soy<br><b>rTri a 19</b> – Wheat                |

(Data from Hoffmann et al. [3] and Hauser et al. [4])

sufficient representation of all relevant allergen components. As this might not be the case in all reagents, some of them are meanwhile enriched with recombinant allergens (also known as spiking) (<http://www.dfu.phadia.com/>). The clinical usefulness of such spiking was shown in children with hazelnut allergy: the negative predictive value of sIgE regarding the outcome of double-blind placebo-controlled food challenge (DBPCFC) was improved by enrichment of test system to hazel with rCor a 1 [6]. Other examples for reagents with enriched recombinant allergen components are nut mix (Cor a 1), latex (Hev b 5) or wasp (Ves v 5) (Phadia/Thermo Fisher Scientific).

In addition to the individual determination of sIgE, it is now possible to simultaneously determine sIgE towards more than 100 allergen components by use of modern biochip technology, using only a very small quantity of serum (about 30 µl) (i.e. ImmunoCAP™ ISAC sIgE 112, Phadia/Thermo Fisher Scientific; request for FDA approval under way) [7, 8]. This solid phase enzyme-linked immuno assay gives semi-quantitative results (ISAC standardised units/ISU).

When comparing conventional allergy diagnostics (i.e. skin prick test, sIgE to total allergen by Phadia/Thermo Fisher Scientific) and CRD by two different methods (Advia-Centaur™, which has been withdrawn from the market, and the ImmunoCAP ISAC™; Phadia/Thermo Fisher Scientific) in 120 patients with IgE-mediated respiratory symptoms to a panel of allergens, it was shown that CRD modified the conventional diagnosis by detection of a new relevant allergen in 35 of 120 patients (30 %) [9]. However, the analytical sensitivity of the previous editions of the multiarray test system (testing 89 or 105 allergens) was still somewhat lower than the sensitivity of individual allergen diagnostics to recombinant allergens, especially in patients with very low concentrations of IgE antibodies [4, 10]. The use of the multiarray system (now including 112 allergens from pollen, mites,

venom, animal, food and others) seems to be sensible in polysensitised patients [10] and in patients with repeated anaphylaxis of unclear history.

## Inhalative Allergens

### Pollen

Sensitisation to the major birch pollen allergen **Bet v 1** is found in over 90 % of patients with birch pollen allergy [9], and Bet v 1 in combination with natural birch pollen extract should identify allergies from birch with a sensitivity of 99.2 % [11]. Bet v 1 belongs to the family of thermo- and acid-labile pathogenesis-related (PR)-10 proteins [11]. Cross-reactive allergens (Bet v 1 homologues) are found in a series of allergens from pollen, fruits and nuts, as well as in vegetables and legumes (Table 1). When there is a history suggesting birch pollen-associated food allergy, sIgE against **rBet v 1** should be determined [12]. Reactivity to the allergens **rBet v 2** (profilin) and **rBet v 4** (polcalcin), identifies polysensitisation and cross-reactivity and has only little clinical relevance [11].

When testing for the recombinant allergens **rPhl p 1** and **rPhl p 5** natural timothy extract, patients with grass pollen allergy are identified at a sensitivity of 99.3 % [11]. Antibodies against major allergens Phl p 1 and Phl p 5 can be used as a marker of allergy to grass in adult patients, while children may react more frequently to minor allergens [13]. In adults, sIgE against minor allergens **rPhl p 12** (profilin) and **rPhl p 7** (polcalcin) are also positive in about 75 % of patients, but these are considered to be cross-reacting allergens without clinical relevance [11]. Recombinant allergens may offer advantages in predicting the severity of patient's symptoms, as IgE concentrations in *Phleum* allergy assessed

with recombinant allergens were significantly higher in 27 patients with allergic asthma than in 33 patients with allergic rhinitis [14]. When evaluating the sensitisation pattern of 19 weed allergic patients by microarray, all ragweed-allergic individuals were sensitised to Amb a 1, among them 30 % were monosensitised to this major ragweed allergen. Art v 1 and Art v 3 were recognised by 89 % of mugwort pollen-allergic patients [15].

The chance of alleviating symptoms through SIT depends on how much the molecular profile of the SIT preparation matches the patient's sensitisation profile. When testing 176 children with sIgE to *Phleum pratense* for sIgE to molecular allergens rPhl p 1, 2, 4, 5, 6, 7, 11 and 12, the molecular profile of an experimental SIT preparation (containing Phl p 1, 2, 5 and 6) matched that of only 7 (4 %) of 176 children: in 28 % it was underpowered, in 32 % overpowered (with risk of new sensitisations), in 30 % over- and underpowered and 5 % of patients had received SIT to unrelated allergens [16•]. When comparing patients sensitised to minor or major allergen, in a retrospective investigation, sensitisation to major allergens Bet v1 and Phl p 1/5 seemed to be closely correlated with a better subjective effect of SIT [17]. Thus, CRD was suggested to be a tool for better selection of patients for SIT. Also, in a complex pollen area (olive, plane, grass, cypress), molecular diagnosis significantly changed decisions for allergen SIT compared to conventional diagnosis [18].

#### Animal Dander

**Fel d 1**, the major allergen in cat allergy, is produced by the skin and by salivary and lacrimal glands of the cat. Molecular diagnostics seems to be reasonable before SIT [19]. Other sensitisations to cat allergens might appear to lipocalin (**rFel d 4**), to cat albumin (**nFel d 2**), and to the oligosaccharide galactose- $\alpha$ -1,3-galactose ( $\alpha$ -gal) on cat IgA (Fel d 5w) [20]. sIgE to  $\alpha$ -Gal was shown to cause impaired allergy diagnostics in parasite-infected patients who might show sIgE against cat dander extract as a result of cross-reactivity. Therefore, screening for IgE to rFel d 1 and other allergens without carbohydrates might identify patients with true cat sensitisation/allergy in parasite-infested areas [21•]. Two newly identified cat allergens are the von Ebner gland protein Fel d 7 and the latherin-like protein Fel d 8 [22].

The dog lipocalin, allergen **rCan f 2**, shows cross-reactivity to the cat allergen Fel d 4 [23, 24]. **rCan f 5**, isolated from dog urine and identified as prostatic kallikrein, shows cross-reactivity with dog dander allergen and human prostate-specific antigen (PSA), and was described as being involved in human seminal plasma allergy [25•]. Can f 6 is a new lipocalin dog allergen that cross-reacts with lipocalins from horse and cat. Can f 6 and homologous allergens may

contribute to multisensitisation and symptoms in individuals allergic to mammals [26].

#### House Dust Mites

In sensitisations towards house dust mites, sIgE to the major allergens of *Dermatophagoides pteronyssinus*, **nDer p 1** and **rDer p 2**, are most frequently found [27]. When investigating over 1,300 patients with mite allergy, patients with sIgE to the tropomyosin **rDer p 10** also reacted to a series of other mite allergens (Der p 1, 2, 5, 7, 10, 21) or showed a rather selective Der p 10 reactivity, while Der p 10-negative patients were primarily sensitised to Der p 1 and/or Der p 2 [28]. Cross-reactions exist between antibodies to Der p 10 of mites and **rPen a 1** from shrimps as well as with Ani s 2 and Ani s 3 from roundworms (*Ascaris*) [29–31].

#### Latex

When sIgE to latex is due to a sensitisation to the profilin (**rHev b 8**), clinical symptoms are unlikely [32]. On the other hand, sIgEs to other latex allergens such as **rHev b 1**, **3**, **5** and **6** are highly likely to be associated with allergy symptoms [30]. Also, sIgE to **rHev b 11** has been shown to be important in patients with a clinical history of cutaneous symptoms due to contact with latex products [33].

#### Cross-Reacting Carbohydrate Determinants (CCD)

Many allergens are glycoproteins which can share significant structural homologies beyond the limits of protein families. As they are prone to extensive cross-reactivity they are called cross-reactive carbohydrate determinants or CCDs. Two types of CCDs are differentiated: while sensitisations to the  $\alpha$ -galactose type are capable of eliciting serious reactions (see also animal food allergies, below) [34], sensitisations to the MUX type (glycoforms containing mannose, glucose and xylose) are often clinically irrelevant. In patients with increased alcohol consumption, elevated IgE levels are thought to be associated with sensitisation to CCD of the MUX type [35, 36]. In a population of 1,025 adults with predominantly sensitisation to mite allergens, CCD sensitisation was shown to be relatively rare and not to be a relevant problem for the diagnosis of patients with suspicion of respiratory allergy [37]. The detection of anti-CCD IgE antibodies of the MUX type is possible with a series of commercially available kits. In addition to detection of sIgE to **MUXF3** (the fucosylated n-glycan of bromelain), other carbohydrate determinants are also used, e.g. bromelain from pineapple (**nAna c 2**), peroxidase from horseradish/MMSF and ascorbate oxidase from zucchini/MMXF) [38].

## Hymenoptera Venom Allergy

Currently, sIgE antibodies to the following allergens are available: **rApi m 1**, **nApi m 4**, **rVes v 1**, **rVes v 5** and **rPol d 5**. Most hymenoptera venom allergens possess CCD that are responsible for a portion of the IgE cross-reactivity between bee and wasp venom [39]. The cross-reactivity can, however, also be based on common protein epitopes, when allergens of bee and wasp venom display a high degree of sequence homology (e.g. hyaluronidases **Api m 2** and **Ves v 2** and the dipeptidyl-peptidases **Api m 5** and **Ves v 3**) [40]. Detection of sIgE to **rApi m 1** and **rVes v 5** was identified as being the most reliable diagnostic procedure to discriminate between true double sensitisation and cross-reactivity in patients with double-positive IgE results to venom extracts in the presence of sIgE against CCDs [41–44]. However, the major honeybee venom allergen, **rApi m 1**, was shown to have a limited clinical usefulness for the detection of honeybee venom allergy because of its low diagnostic sensitivity (60 %) [45]. **Api m 10**, not being available for routine diagnostics, was recently identified as being another major allergen in bee venom-allergic patients [46]. In *Vespa* allergic subjects, sIgE to **rVes v 5** were demonstrated in 87 % of 100 patients [40]. Additional use of **Ves v 1** was shown to significantly enhance the sensitivity of diagnostic tests based on recombinant yellow jacket venom allergens [47]. Sensitisation to cohabiting wasps *Polistes dominulus* and *Vespa* species (mainly in the Mediterranean region) was proposed to be discriminated by investigating sIgE for antigen 5s (**Pol d 5/Ves v 5**) and the phospholipases (**Pol d 1/Ves v 1**) of both *V. vulgaris* and *P. dominulus* [48]. It can be expected that the spectrum of recombinant insect allergen for diagnostic purposes will soon be expanded.

## Plant Food Allergies

The important plant food allergens belong to a few protein families (Table 1), the most well known of which are the Bet v 1 homologues, lipid transfer proteins (LTP), profilins and storage proteins [49]. Great progress has already been made in applying the CRD to well-defined patients' collectives verified by DBPCFC.

### Leguminosae (Peanut, Soy) and Nuts

The pattern of allergenic component recognition varies in peanut-sensitised patients from different geographical areas, reflecting different pollen and dietary exposures. In the USA, peanut-allergic patients are commonly sensitised to storage proteins **rAra h 1**, **2** and **3**, in Spain to LTP **rAra**

**h 9** and in Sweden to Bet v 1 homologue **rAra h 8** [50•]. Molecular allergy diagnostics was shown to predict if the patients must expect severe or milder reactions when eating peanuts [49, 50•, 51]; for example, sensitisation to the storage proteins **rAra h 1**, **2** and **3**, which are also resistant to heat and digestion, is associated with severe immediate-type reactions [52–54]. **Ara h 2** was shown to be the component with the highest accuracy for discriminating between allergy or tolerance to peanut in 81 children with positive oral provocation test [50•]. In mice, **Ara h 2** and **6** were shown to be the major elicitors of anaphylaxis and were used to effectively desensitise peanut-allergic mice [55].

In 12 peanut-allergic patients with a history of combined walnut allergy, no cross-inhibition was seen for peanut allergens **Ara h 1**, **Ara h 2** and **Ara h 3** and walnut allergens **Jug r 1**, **Jug r 2** and **Jug r 4** [56]. This observation does not support the idea of relevant cross-reacting IgE antibodies between peanut and walnut [56].

Sensitisations to hazel allergens **rCor a 8** (LTP), **nCor a 9** (storage protein) and **Cor a 11** (cupin family) are associated with severe immediate-type reactions and are mostly seen in children [57]. Sensitisation to the Bet v 1 homologue **rCor a 1** more likely leads to mild symptoms of an OAS and is typically seen in adults [49, 56].

In soy allergy, sensitisations to the soy storage proteins **rGly m 5** and **rGly m 6** were shown to be associated with severe anaphylactic reactions [58]. In Europe, the Bet v 1-associated soy allergy is more frequent, especially in adults. Patients with birch allergy were reported to have partly severe reactions after consumption of protein rich soy food (i.e. drinks), which is due to a cross-reaction to the Bet v 1 homologue soy allergen **rGly m 4** [59]. A prospective multicentre clinical trial, initiated by the University of Leipzig and funded by the German Federal Ministry of Education and Research, is currently investigating if birch-associated food allergy in patients with Bet v 1 sensitisation can be effectively treated with subcutaneous SIT to the hypoallergenic folded variant of Bet v 1 [60].

### Wheat and Vegetables

A sensitisation to the storage protein **rTri a 19** ( $\omega$ -5-gliadin) is observed in wheat-dependent exercise-induced anaphylaxis (WDEIA) [61]. The improved versions of the ImmunoCAP ISAC™ (Phadia/Thermo Fisher Scientific) was shown to be as adequate as detection of sIgE by enzyme immunoassay ImmunoCAP™ (Phadia/Thermo Fisher Scientific) in the detection of sIgE against  $\omega$ -5-gliadin in ten patients with suspected WDEIA [62].

Carrot allergy has been observed mainly in relation to a concomitant pollen allergy [62]: 98 % of Central European carrot allergic patients were sensitised to the Bet v 1

homologue in carrots, Dau c 1.0104, and 38 % of the patients recognised the carrot profilin, Dau c 4 [62]. **Dau c 1** isoforms display distinct IgE epitope heterogeneity, and a quantitative enzyme immunoassay for the known carrot allergens, namely Dau c 1.01, Dau c 1.02, and Dau c 4 CRD has been recently developed [64]. Significant differences in IgE sensitisation patterns were detected between geographical regions: i.e. rDau c 1.0104/rDau c 1.0201 (Bet v 1 homologues) for Swiss and Danish carrot allergic patients and rDau c 4 (profilin) for Spanish patients [63]. Among these 49 European carrot allergic patients, rDau c 1.0104 was recognised slightly less frequently than rDau c 1.0201. In this study, among 71 birch or olive pollen allergic controls, the frequency of sensitisation to recombinant carrot components was significantly lower than in the carrot allergic patients, demonstrating a limited cross-reactivity between carrot allergens and homologous pollen allergens [63]. Another isoform, Dau c 1.03, also appears to contribute to the allergenicity of carrots and the manifestation of carrot allergy [63]. The epitope diversity of different Dau c 1 isoforms might be considered for further CRD and is discussed for gene silencing of carrot allergens [65].

Celeriac allergy is highly associated with birch pollen and with mugwort pollen sensitisation [66]. Sensitisations are found to **rApi g 1** (Bet v 1 homologue) as well as to rApi g 4 (profilin) and Api g 5 (glykoprotein)—neither yet routinely testable. To date, no marker for severe reactions in celeriac allergy has been identified [66].

## Fruits

In the Mediterranean region, peach allergies are among the most common food allergies, with the majority of the patients being sensitised to the LTP **rPru p 3** [67]. This sensitisation can lead to cross-reactions to LTP from other fruits and vegetables. Levels of sIgE to the LTP rPru p 3 were correlated with the severity of peach allergy reactions in children [68]. Recently, a peach thaumatin-like protein (TLP) has been identified as major peach allergen [69], and has been suggested to be included in routine diagnosis of peach allergy, at least in the Mediterranean area [69].

Allergic reactions after banana ingestion in 51 children with specific IgE to both banana allergens  $\beta$ -1,3-glucanase (Mus a 5) and TLP (Mus a 4), as well as to peach fruit LTP Pru p 3, was found in over 70 % of sera [70]. Thus, Mus a 4 and LTP were regarded as major allergen in this population in Spain [69]. Mus a 5 was recently identified as being a new candidate for CRD in banana allergy [71].

The prevalence of kiwi allergies appears to be increasing [72]. Allergy can be either due to monosensitisation or it is associated with grass and birch pollen allergy, or latex

allergy. Act d 1 and Act d 3 were identified as potential marker allergens for severe symptoms [72]. Sensitisations to Act d 1 are seen in mono-sensitisations, while sIgE to **rAct d 8** (Bet v 1 homologue) and Act d 9 (profilin) occur in pollen-associated allergies. Sensitisations to **Act d 1** and Act d 3 are associated with the occurrence of severe reactions [73]. Act d 11, purified from green kiwifruit and displaying IgE co-recognitions with allergens of the Bet v 1 family, has been recently identified [74].

## Food Allergy to Animal-derived Allergens

### Meat Allergy and Galactose- $\alpha$ -1,3-Galactose-Specific IgE

The  $\alpha$ -galactose epitope (in short:  $\alpha$ -Gal) is a ubiquitous sugar structure on glycoproteins and glycolipids of all mammals except in primates, including man; immunoglobulins as responsible glycoproteins carrying  $\alpha$ -Gal possibly play an important role here. It was also identified as an important IgE epitope on secreted IgA of the cat [20]. It is assumed that sensitisation to  $\alpha$ -Gal can be induced by tick bites or certain parasite infections [75•, 76], as a sensitisation to  $\alpha$ -Gal is found particularly often in the southern states of the USA with a high prevalence of the tick *Amblyomma americanum* (vector for Rocky Mountain spotted fever) [75•]. Clinically, in  $\alpha$ -Gal sensitised patient, delayed immediate-type reactions to red meat (beef, pork) can occur. Also, sensitisation to  $\alpha$ -Gal may be the target of reactivity to meat-derived gelatin [77]. No plausible explanation exists at present for the delayed onset of anaphylactic symptoms. Asthma was not associated with a sensitisation to  $\alpha$ -Gal [78]. The relevance of  $\alpha$ -Gal sensitisation was first noticed after the administration of the chimeric antibody cetuximab, which resulted in severe anaphylactic reactions in the sensitised patients; this was associated with preformed IgE antibodies to  $\alpha$ -Gal on the murine portion of the antibody [33, 75•]. In 14 patients in France, anaphylaxis to pork or beef kidney was related to  $\alpha$ -Gal IgE [79] and in all of them skin test was positive to Cetuximab [79]. Unfortunately, a standardised test for sIgE to  $\alpha$ -Gal will not be available for routine diagnostics in the nearest future. When available, routine tests before administration of cetuximab should be considered.

### Hen's Egg, Cow's Milk and Sea Food

The most important allergens in the egg white are the very thermostable ovomucoid (**nGal d 1**) and the less heat-stable allergens ovalbumin (**nGal d 2**), ovotransferrin (**nGal d 3**) and lysozyme (**nGal d 4**) [80, 81]. Patients with a persistent hen's egg allergy had higher sIgE levels to ovomucoid (nGal

d 1) and ovalbumin (nGal d 2) than children who develop tolerance [82]. Cow's milk contains numerous proteins, eight of which have been characterised as allergens. They include  $\alpha$ -lactalbumin (**Bos d 4**),  $\beta$ -lactoglobulin (**Bos d 5**), bovine serum albumin (BSA) (**Bos d 6**) and casein (**Bos d 8**) [83]. In 104 children with suspected cow's milk or hen's egg allergy, the microarray components Bos d 8 for cow's milk and Gal d 1 and Gal d 2 for hen's egg were the most frequently recognised allergens that had a good ability to predict the food challenge test results [84].

Major allergens to crustaceans (i.e. shrimp: **rPen a 1**) correspond to tropomyosin, an important muscle structure protein of all arthropods and other animals, explaining the cross-reactivities to the tropomyosins from mites (e.g. **rDer p 10**) [85]. High levels of sIgE to tropomyosin seem to be related to the severity of symptoms in patients with shrimp allergy [85]. Specificity of IgE to shrimp tropomyosin (92.8 %) was greater than that of IgE to shrimp (75 %) in seven patients with positive food challenge to shrimp [86]. Comparing patients with negative and positive shrimp challenges, those with clinical reactivity were shown to have a more intense sensitisation and more diverse epitope recognition to the Pacific white shrimp allergens identified to date (Lit v1, Lit v2, Lit v3 and Lit v4) [87].

## Conclusions

Component-resolved allergy diagnostics (CRD) are increasingly entering routine care. It demands new knowledge on the part of the allergist, uncovers molecularly comprehensible cross-reactivities and often allows for better understanding of the disease. In pollen allergies, the determination of the respective major allergens (i.e. Bet v 1: birch; Phl p 1/5: grass) can differentiate clinically relevant sensitisations from those to cross-reacting, clinically less relevant, panallergens such as profilins (i.e. Bet v 2/4, Phl p 7/12). Moreover, these diagnostics may be used to establish a more precise indication for specific immunotherapy. In food allergies, sensitisations to storage (i.e. Ara h 2/peanut) or lipid transfer proteins (i.e. Pru p 3/peach) indicate a high risk of anaphylaxis, while sensitisations to Bet v 1 homologues (e.g. Ara h 8/peanut) are usually associated with milder symptoms. By determination of the major allergens Api m 1 (bee) and Ves v 1 and Ves v 5 (wasp), double sensitisations can already be differentiated from cross-reactivities in hymenoptera venom allergies. Further promising improvements in diagnostics are expected from additional, not yet commercially available, recombinant allergens identifying particular molecules of risk. There is a great need for further clinical studies including well-characterised groups of patients in order to determine the role of CRD in different kind of allergies.

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- Of major importance

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