Component-resolved diagnostics in pet allergy: Current perspectives and future directions

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Furry mammals kept as pets are important allergen sources. The prevalence of sensitization to dander from various animals appears to be increasing worldwide. Several mammalian allergens from diverse species and distinct protein families have been characterized, and some are available for component-resolved diagnostics (CRD). This review presents an overview of mammalian aeroallergens, with a focus on cat, dog, and horse allergens. The potential of CRD in fine-tuning the diagnostic workup following traditional methods based on whole- allergen extracts and allergen immunotherapy is discussed. The review highlights the clinical utility of CRD, particularly as a marker/predictor of increased asthma risk and disease severity. Finally, several perspectives of the future implications of CRD are offered in the context of furry animal allergens. (J Allergy Clin Immunol 2021;147:1164-73.)

Key words: *Pet allergy, dog, cat, horse, component-resolved diagnostics, asthma risk*

Abbreviations used
AIT: Allergen immunotherapy
CRD: Component-resolved diagnostics
FENO: Fractional exhaled nitric oxide
sIgE: Specific IgE
SPT: Skin prick test

Allergy to cats and dogs has been recognized for many years as a major risk factor for the development of asthma and allergic rhinitis.[1] In Europe and the United States, 24% to 38% of households own dogs and 25% own cats.[2,3] In the United States, only 0.7% own horses.[3] These estimates indicate that there is a high exposure in households to furred animals, in particular cats and dogs, at least in the Western world. Allergens from pet animals are mainly present in their fur, saliva, and urine and are spread into the environment through shedding of hair and dander.[4] A national survey of 831 random homes in the United States found that all homes contained dog allergen (100%) and most contained cat allergen (99.9%), even homes without pets.[5]

Over the past decades, the prevalence of allergy to furry animals[6] and the prevalence of asthma and allergic rhinitis[7,8] have been increasing. Allergy to cat is the most common mammalians-origin allergy in humans,[9] and sensitization to cat is found in up to 1 in 5 adults worldwide.[10] The diagnosis of cat allergy has proven rather uncomplicated, probably because most patients react to 1 main protein, Fel d 1.[11] The cat skin prick test (SPT) extracts contain mainly Fel d 1, but might differ in content of Fel d 4, which needs further investigation.

The diagnosis of dog allergy is more challenging; self-reporting misclassifies allergic status in many patients,[12] and the protein content in SPT extracts vary up to 20-fold within different manufacturers.[13]

Component-resolved diagnostics (CRD) is beginning to gain greater recognition for pet allergy diagnostics. CRD identifies specific IgE (sIgE) responses to specific molecular targets, and several molecular allergy components have been identified for cat, dog, and horse. However, this dimension also increases the complexity of diagnostics because some components may represent cross-reactive sensitizations.[14,15]

The aim of this review was to provide an overview of the symptomology and epidemiology of pet allergy. The focus is on CRD for cat, dog, and horse allergens, with a description of the different proteins, frequency of sensitization, and the clinical utility of pet components. A search was performed in PubMed to identify studies on CRD for pet components (cat, dog, and horse allergen components) published between 1997 and mid-2020.

PET ALLERGY: FREQUENCY, TREND, AND IMPACT ON ALLERGIC DISEASES

An international survey of more than 27,000 participants from 22 countries estimated that 57% of the population has at least 1 pet at home, most commonly dogs (33%) and cats (23%)[16] (Fig 1). A survey of almost 13,000 German children reported a sensitization rate of 12.6% to animal dander. The prevalence increased with age from 5.7% in 3- to 6-year-olds to 11.5% in 7- to 10-year-olds, and reached 17.2% in 14- to 17-year-olds.[17] A Swedish birth cohort study of more than 4000 children reported a similar increase in sensitization rates to horse, cat, and dog from

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4 to 20 years, reaching 9.8%, 19.6 %, and 17.0 %,[18,19] respectively. High prevalence of sensitization to common airborne allergens, including cats and dogs, has also been observed in adults,[20] although the prevalence in adults is lower and monosensitization is more frequent than in children.[21] In Brazil, sensitization to furry animals, especially to dog, increased dramatically among allergic children and adolescents between 2004 and 2016, seemingly reflecting a sedentary "indoor lifestyle."[22]

Geographic variation in the prevalence of allergic sensitization to furry animals has been attributed to cultural differences, environmental factors, and rate of pet ownership.[23,24] A large international multicenter study in adults reported a sensitization rate to cat of 8.8% (range, 1.2%-22.4%) as measured by SPT[10] and the sensitization rate for dog was 20.4% among adult Korean subjects.[25] Approximately 26% of European adults coming to the clinic for suspected allergy to inhalant allergens are sensitized to cat and 27% to dog, according to another large patient-based study of SPT for aeroallergens (Global Asthma and Allergy European Network).[24,26]

The severity of induced symptoms of pet allergy varies widely from discomfort associated with rhinitis and conjunctivitis to severe asthma, which can develop into a life-threatening condition.[1] Some studies have found an association between sensitization to cat and dog in early childhood and later development of asthma and allergic rhinitis.[27,28] Another study found no association between early cat and dog exposure and later development of allergic rhinitis to cat and dog, respectively,[29] and one even found neonatal exposure to dog to reduce the risk of atopic dermatitis in early childhood.[30] A number of pet animal components, mostly produced as recombinant proteins, are now available for CRD, offering improved diagnostic workup (Fig 2), particularly in patients with polysensitization and/or severe asthma.[4,31] There is little evidence of the actual value of sIgE and SPTs in dog and cat allergy, and large variability between content of skin-prick extracts has been documented.[13,32] However, the ability of pet allergen CRD can help distinguish between sensitizations specific to singular species and sensitizations due to cross-reactivity.[31]

ALLERGENS AND SENSITIZATION PATTERNS

The World Health Organization/International Union of Immunological Societies[33] lists 36 major mammalian-derived aeroallergens (Table I). They can be classified into the following protein families: lipocalins, secretoglobins, serum albumins, kallikreins, and latherins.[19,23] A major allergen is defined as one to which more than 50% of patients with an allergy to its source react.[18]

Lipocalins

The most important group of mammalian aeroallergens is lipocalins.[34] These allergens are produced in secretory glands and are present in skin, urine, saliva, sweat, and sebum.[34] At least 1 allergen from the lipocalin protein family has been identified in each species (Table I). From the lipocalin family, cats contain Fel d 4 and Fel d 7. Studies have shown that saliva is the main source of these allergens, and that they are deposited through grooming on the fur.[35,36] Fel d 4 levels showed no relation to hair length; however, neutered female cats had significantly higher levels compared with not neutered cats (17.4 vs 2.2 μg/g; $P = .039$). IgE reactivity to cat allergen Fel d 4 has been observed in up to 63% of subjects allergic to cat,[37] and IgE reactivity to Fel d 7 has been reported in 38%.[36] Fel d 7 has high potential to cross-react with Can f 1, with which it shares 62% amino acid identity.[10]

Dogs contain Can f 1, Can f 2, Can f 4, and Can f 6 from the lipocalin family. Dog studies have shown that higher lipocalin levels were detected in saliva than in fur, with Can f 4 showing the highest concentration.[32] Sensitization to Can f 4 has been found in up to 46% of patients allergic to dog.[38] Can f 2 was exclusively found in saliva and is characterized as a minor allergen, with sensitization present in about 20% to 33% of patients allergic to dog.[1,39,40] Among patients allergic to dog, 50% to 90% have antibodies to Can f 1, 20% to 33% to Can f 2,[1,39,40] 35% to 46% to Can f 4,[38,41] and 56% to Can f 6.[42]

Two horse lipocalins, Equ c 1 and Equ c 2, have been identified. In an adult Swedish population, 2% were sensitized to Equ c 1 and 12% among patients with asthma.[21] Up to 76% of patients with horse allergy are sensitized to Equ c 1.[43]

The lipocalins comprise a diverse protein family with specific patterns of cross-reactivity among certain of its members, for example, between Can f 6 and Fel d 4 and Equ c 1,[44-46] Mus m 1 and Rat n 1,[47] Equ c 1 and Mus m 1,[43] and Fel d 7 and Can f 1.[48] Lipocalin allergens Equ c 1, Fel d 4, Can f 6, and Mus m 1 show sequence identities between 47% and 69% (Fig 3, *A*).[18]

Secretoglobins

Two mammalian allergens have been categorized as members of the secretoglobin protein family, namely Fel d 1 from cat and Ory c 3 from rabbit.[43] Fel d 1 is mainly produced in sebaceous and salivary glands and is transferred to fur by grooming.[48] Fel d 1 is the most important allergen in cat allergy, shown to react with IgE from 90% of cat-sensitized individuals, and to account for up to 90% of IgE reactivity to cat dander.[49] Sequence identity between Fel d 1 and Ory c 3 is very low, and no IgE cross-reactivity has been observed.[47]

Serum albumins

According to the World Health Organization/International Union of Immunological Societies allergen nomenclature database,[33] 6 mammalian serum albumin allergens have been identified, including Bos d 6 (domestic cattle), Can f 3 (dog), Cav p 4 (guinea pig), Equ c 3 (domestic horse), Fel d 2 (cat), and Sus s 1 (domestic pig). Serum albumins are highly abundant proteins present in blood, dander, milk, and other secretions, but are considered minor allergens with low prevalence of IgE reactivity among patients allergic to its source. Serum albumins remain relevant because they are responsible for species cross-reactivity due to high sequence identity (up to 82%),[50] for example, between cat and pig (Fig 3, *B*). In a group of 39 highly sensitized patients allergic to cat, 23% had sIgE to Fel d 2 and more than half of these had sIgE to Sus s 1.[51] Monosensitization to serum albumins seems rare. Sensitization to serum albumins is in most cases observed in combination with sIgE directed against major allergens.[44] Serum albumins may play a significant role as cross-reacting allergens in individuals sensitized to dander of multiple animal species. These mechanisms could explain why some atopic patients develop allergic sensitization to mammalian allergens in the absence of contact with the animals.[52] Indeed, because of cross-reactivity, children with persistent milk allergy

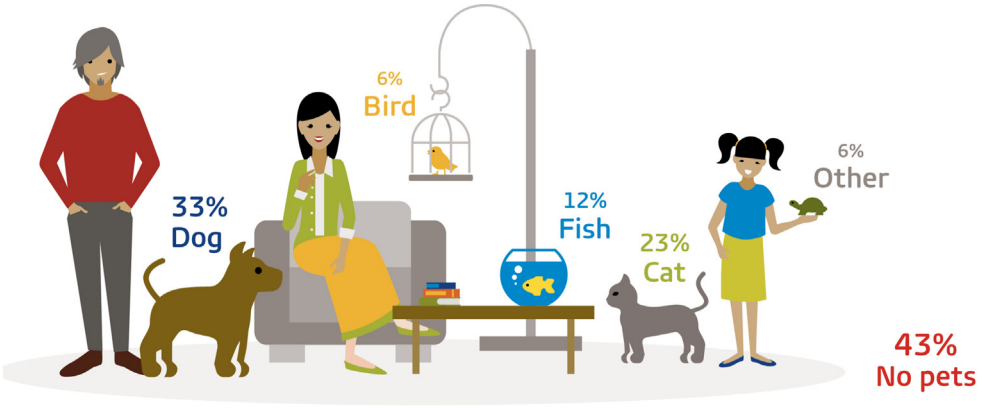

FIG 1. Percentage of people living with pets (Growth from Knowledge survey of >27,000 internet users in 22 countries).[16]

and BSA sensitization show an increased risk of allergy to animal dander with symptoms of rhinoconjunctivitis and asthma.[53]

Kallikrein

Can f 5 is so far the only identified allergen from the kallikrein protein family. The protein is secreted from the prostate and therefore present only in male dogs. The allergen can be isolated from the urine of male dogs, but it is also present in dog hair and dander.[54] Among patients allergic to dogs, 31% to 70% showed IgE reactivity to Can f 5, and up to 58% of these patients were monosensitized to Can f 5 alone[54-59] (Table II). Can f 5 has also been recently reported as the most common dog component sensitization in a Swedish adult population.[21] The Can f 5 amino acid sequence shows no significant similarity to any known animal dander or urinary allergen.[4] Therefore, monosensitization to Can f 5 could be a highly specific marker for allergy to male dogs. Schoos et al[64,65] have recently shown that patients allergic to dogs who are truly monosensitized to Can f 5 are allergic only to male dogs. These patients showed no reaction to SPT or conjunctival allergen provocation test using female dog extract and thereby tolerated female dogs. On the contrary, Käck el al[61] found no correlation between nasal provocation test with dog dander extract and monosensitization to Can f 5. This can be due to the dog extract containing a mix of all the dog components (from both male and female dogs), and possibly very low levels of Can f 5. Can f 5 is a 28-kDa protein prostatic kallikrein that cross-reacts with prostate-specific antigen of human seminal plasma.[54] Because these 2 proteins share substantial structural similarity, 60% sequence identity, it is possible that sensitization to Can f 5 in women might lead to allergic reactions to human seminal fluid during intercourse.[66-69]

Latherins

Two allergens belonging to the latherin protein family, namely Equ c 4 and Fel d 8, have been identified. Equ c 4 is an abundant protein constituent in sweat, saliva, and dander of horses.[70,71] An IgE-binding frequency to Equ c 4 of 77% in horse-sensitized subjects has been reported.[72] Fel d 8 has been found in saliva of cats; however, with an IgE-binding frequency of only 19% among individuals allergic to cat, it is not considered a major cat allergen.[36]

CLINICAL UTILITY OF CRD

Allergy diagnosis is supported by the detection of allergen sIgE antibodies using whole extracts or individual allergenic proteins from animal dander. However, component-based IgE testing can distinguish a primary sensitization from a cross-sensitization to a higher extent than whole-allergen extracts.[17] Although the possibility of using single components to replace whole extracts in daily diagnostic practice has been widely debated,[72,73] a dominating view is that extracts are still needed as first-line testing to ensure the detection of patients sensitized to components other than those that are available for CRD.

The availability of allergen component tests has driven new epidemiological studies to analyze the prevalence and clinical relevance of sIgE directed against individual molecular allergens. Thus, CRD may be useful in detecting atypical sensitization profiles that involve minor allergen components. It can also be used to describe patient-specific IgE profiles to establish predictive risk markers and to develop strategies for therapeutic intervention.[1,44] When clinical history and investigations are inconclusive, molecular allergology can add valuable clinical information in the diagnostic workup (Fig 2).[12] CRD may further prove useful in terms of improved clinical sensitivity in cases in which a relevant allergen is scarcely represented in the natural allergen extract, as is the case of PR-10 allergens in certain plant foods such as fruits and nuts. Superior clinical specificity of component IgE testing compared with whole-extract testing has been demonstrated for allergies to several foods, including peanut,[74] hazelnut,[75,76] and cashew nut.[77,78]

PET ALLERGEN COMPONENTS AS MARKERS OF INCREASED DISEASE RISK AND DISEASE SEVERITY

CRD could provide markers of increased asthma risk. Sensitization to Equ c 1 has been associated with severe childhood asthma.[31] Furthermore, asthmatic children with cat allergy have higher Fel d 1 sIgE levels than children with rhinitis only.[79] Another study of 696 Swedish children allergic to cat found that asthma symptoms on contact with cat were significantly associated with sIgE to cat allergens Fel d 1 and Fel d 4.[57] Among dog-sensitized children, most were sensitized to more than 1 dog component, and cosensitization to Can f 5 and Can f 1/2 conferred

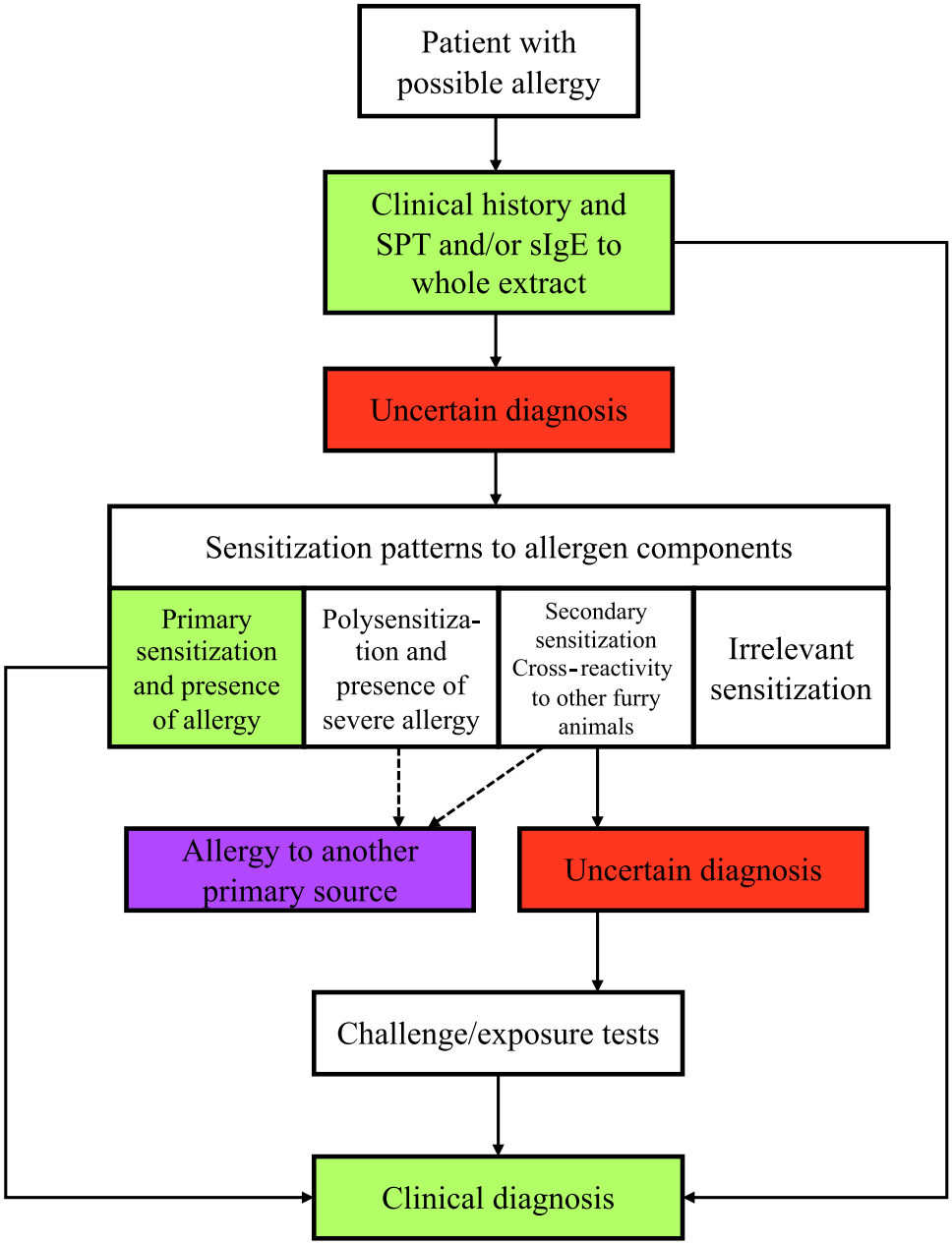

FIG 2. Algorithm for diagnostic workup of patients allergic to animal dander (adapted from Gerth van Wijk[12]).

the greatest risk for asthma.[57] Furthermore, the study confirmed that asthma was associated with higher levels of component sensitization. Progression of allergic sensitization over time has been shown to involve IgE recognition of an increasing number of components from the sensitizing allergen source, forming the basis for the concept of molecular spreading, in which sensitization to a greater number of components from the same allergen source correlates with disease severity.[80] A recent study reported that asthmatic pediatric patients with IgE to Fel d 2 serum albumin and Fel d 4 and Fel d 7 lipocalins were more likely to have persistent type 2 inflammation.[81] A longitudinal study of 398 children found that sensitization to dog, cat, and horse throughout childhood was significantly associated with asthma at age 7 years.[82] Similarly, a small early-stage study comparing children with severe asthma *versus* children with controlled asthma demonstrated that those with severe asthma had higher levels of IgE antibodies toward cat, dog, and horse components.[31] Along those lines, a cross-sectional cohort study of 269 children found that sensitization to members of the lipocalin protein family, mainly derived from cat, dog, and horse, was associated with current asthma.[83] The relationship between sensitization to specific allergen components and disease has been investigated by Simpson et al,[84] who identified patterns of response to allergen component groups and investigated associations with asthma in children.

TABLE I. Pet allergen components (www.allergen.org)

Animal	Component	Protein type
Domestic cattle	Bos d 2	Lipocalin
	Bos d 3	S100 calcium-binding protein A7
Dog	Can f 1*	Lipocalin
	Can f 2*	Lipocalin
	Can f 3*	Serum albumin
	Can f 4*	Lipocalin
	Can f 5*	Arginine esterase, prostatic kallikrein
	Can f 6*	Lipocalin
	Can f 7	Epididymal secretory protein E1, or Niemann Pick type C2 protein
Guinea pig	Cav p 1	Lipocalin
	Cav p 2	Lipocalin
	Cav p 3	Lipocalin
	Cav p 4	Serum albumin
	Cav p 6	Lipocalin
Donkey	Equ a 6	Lysozyme
Domestic horse	Equ c 1*	Lipocalin
	Equ c 2	Lipocalin
	Equ c 3*	Serum albumin
	Equ c 4	Latherin
	Equ c 6	Lysozyme
Cat	Fel d 1*	Secretoglobin (uteroglobin, chain 1)
	Fel d 2*	Serum albumin
	Fel d 3	Cystatin
	Fel d 4*	Lipocalin
	Fel d 5w	IgA
	Fel d 6w	IgM
	Fel d 7*	Lipocalin (Von Ebner gland protein)
	Fel d 8	Latherin-like protein
Golden hamster Syrian hamster	Mes a 1	Lipocalin
Mouse	Mus m 1*	Lipocalin/urinary prealbumin
Rabbit	Ory c 1	Lipocalin
	Ory c 3	Secretoglobin (lipophilin)
	Ory c 4	Lipocalin
Siberian hamster	Phod s 1	Lipocalin
Rat	Rat n 1	Alpha-2u-globulin/lipocalin
Domestic pig	Sus s 1	Serum albumin

*Mammalian allergens currently available for CRD.

Sensitization to a group that included 27 components of plant, animal, and fungal origin from 12 protein families was most strongly associated with asthma and decreased lung function (lower FEV_1, $P < .001$).[84] Similar results have been reported in several subsequent studies.[60,85] In another study, polysensitization to 3 or more animal-derived components (lipocalins, kallikrein, and secretoglobin) was associated with severe asthma, increased bronchial inflammation, and a trend toward more courses of oral corticosteroid treatment.[86] Similar findings were recently reported in a study of dog-sensitized children,[61] where Käck et al[61] found an association between sensitization to an increasing number of dog allergen components and a positive nasal challenge result.

Other than asthma, high levels of IgE antibodies to Fel d 4 and also Fel d 2 have been associated with atopic dermatitis in children with cat allergy.[87] This is the only study found so far regarding measurements of IgE antibodies to pet components in individuals with atopic dermatitis. It is an interesting finding that needs to be verified by larger studies.

The use of allergen components compared with whole extracts as predictors of disease severity was evaluated by Asarnoj et al[60] in a large longitudinal population-based pediatric study. Sensitization to Fel d 1 and Can f 1 at age 4 years and molecular polysensitization to cat or dog components predicted allergy to cat and dog at age 16 years significantly better than did IgE to whole cat or dog extracts. In addition, Patelis et al[72] showed that adults sensitized to both cat extract and 1 or more of cat components Fel d 1, Fel d 2, and Fel d 4 had higher fractional exhaled nitric oxide (FENO) ($P = .008$) and more bronchial responsiveness ($P = .002$) than subjects sensitized to the extract but not to any of the cat components tested. Furthermore, subjects who were sensitized to the tested cat components were more likely to develop asthma ($P = .005$) and rhinitis ($P = .007$) over a 12-year period than those who were not, highlighting the value of CRD in predicting disease severity.[72] Another study of adults found that sensitization to furry animal allergen components, sensitization patterns, and clusters were associated with a substantially increased risk of asthma, rhinitis, and concomitant asthma/rhinitis. Sensitization to Fel d 1, Can f 1, Can f 2, and Can f 3 and polysensitization (ie, sensitization to more than 2 components) were further associated with increased FENO and eosinophil levels. The impact of polysensitization was also confirmed when a data-driven approach was used to cluster sensitization to the allergen components. Here, individuals who fell into the

A Lipocalins

	Bos d 23k	Bos d 2	Mus m 1	Equ c 2	Equ c 1	Fel d 7	Fel d 4	Can f 6	Can f 4	Can f 2	Can f 1
Can f 1	22	26	21	23	28	63	26	26	24	24	100
Can f 2	24	20	26	26	26	23	25	24	26	100	
Can f 4	37	32	28	35	29	23	27	26	100		
Can f 6	28	27	47	30	57	24	69	100			
Fel d 4	28	31	50	31	68	20	100				
Fel d 7	21	23	21	23	26	100					
Equ c 1	28	33	47	34	100						
Equ c 2	46	32	28	100							
Mus m 1	27	30	100								
Bos d 2	33	100									
Bos d 23k	100										

B Serum albumins

	Sus s 1	HSA	Fel d 2	Equ c 3	Cav p 4	Can f 3	Bos d 6
Bos d 6	79	76	78	74	70	76	100
Can f 3	78	80	87	76	73	100	
Cav p 4	72	72	76	72	100		
Equ c 3	76	76	78	100			
Fel d 2	79	82	100				
HSA (human serum albumin)	75	100					
Sus s 1	100						

FIG 3. Amino acid sequence identity (adapted from Matricardi et al[18]) for (**A**) lipocalins and (**B**) serum albumins.

"multiple sensitization" cluster were at increased risk of asthma and rhinitis and had higher levels of FENO and eosinophils than those in other clusters. Thus, sensitization to furry animal allergen components is an important predictor of asthma outcome and an indicator of severity.[88] Taken together, available data indicate that measuring component sIgE offers insights into the progression and severity of asthma and allergic rhinitis.

New clinical implications and future perspectives

Monosensitization to Can f 5 could be a highly specific marker for allergy to male dogs. The only study supporting this theory so far is the Danish study by Schoos et al that shows that individuals monosensitized to Can f 5 show different reactions to male and female dog allergen provocation.[64,65] Their findings are indirectly supported by Liccardi et al[62] who found that monosensitization to Can f 5, as well as high levels of IgE to Can f 5, was associated with a prevalent exposure to male dog. The authors conclude that for such patients, the correct prescription of allergen immunotherapy (AIT) and the possibility to own a female dog should be considered. In theory, neutering the male dog could also be a possibility to stop the production of Can f 5; however, this has never been tested in practice. The low cross-reactivity between Can f 5 and the other dog components[4] explains why patients monosensitized to Can f 5 did not react on exposure to female dog extracts.[64,65] Moreover, the possibility of developing an allergy to female dogs is not likely to be increased. An epidemiological study from Sweden studied whether different dog characteristics modify the risk of asthma among children (n = 23,585) exposed to dogs during their first year of life.[89] Children exposed to female dogs had a lower risk of asthma compared with those exposed to male dogs. They were also able to analyze the impact of the breed and interestingly they found that exposure to so-called hypoallergenic dogs was associated with a higher risk of allergy; however, this association became nonsignificant when adjusting for parental allergy, but still with a trend of an association (odds ratio, 1.20; 95% CI, 0.98-1.47). Monosensitization to Can f 5 has been based on evaluation of 4 dog components (Can f 1, 2, 3, and 5), and it varies in frequencies (Table II). IgE to Can f 4 and Can f 6 are now commercially available,[90] which changes the definition of monosensitization in future studies, and the "true" number of patients monosensitized to Can f 5 will be lower than today's estimate.

It is perceived that sensitization to Can f 5 confers an increased risk of development of allergic reactions to human seminal fluid, but that proposition needs to be elucidated. A number of case reports have been published supporting this hypothesis.[54-56] In

TABLE II. Can f 5 monosensitization in different populations

Year	Country	Characteristics of studied population	Can f 1	Can f 5	Mono Can f 5*	n†	Reference
2009	Spain, the United States, and Sweden	Dog-allergic, adult patients	57%	70%	33%	37	54
2015	Sweden	General cohort, age 11-12 y, n = 219 positive dog sensitization	39%	47%	10%	696	57
2016	Spain	Asthma/rhinitis + positive dog/cat/horse sensitization	66%	33%	19.5%	159	55
2016	Sweden	General cohort, age 16 y	6%	12.6%	56%	779	60
2016	Poland	Allergy patients mean age 35 y + positive pet sensitization	40%	33%	17%	70	56
2017	Spain	Dog-allergic, age 10-61 y	41%	67%	37%	70	58
2017	Japan	Food allergy cohort, age 13 mo, n = 111 positive dog sensitization	81%‡	36%	4%	304	28
2018	Sweden	Patients allergic to dog, age 10-18 y and positive dog sensitization	65%	62%	12%	60	61
2020	Italy	Allergy patients tested with ISAC, age 4-64 y	59%	69%	58%	1403	62
2019	Sweden	Random population, age 16-75 y	2.9%‡	3.3%	49%	1103	21
2019	Sweden	Asthma, age 16-75 y	14%‡	8.7%	37%	769	21
2020	Czech Republic	Allergy patients tested with ISAC, age 1-68 y	13.9%	16.4%	9.8%	1255	63

*Percentage of monosensitization is calculated from the population sensitized to dog extract but not the components Can f 1-3.
†The numbers extracted from the respective population or through communication with authors.
‡Sensitization to Can f 1 or Can f 2.

view of the high number of patients sensitized to Can f 5 and the potential consequences in females, González-de-Olano et al[69] studied the prevalence of allergic symptoms to human seminal plasma during intercourse among 27 women sensitized to Can f 5 with a male dog at home. They found a high prevalence of allergy to human seminal plasma among this group of women, and it seemed that the presence of allergic symptoms was related to the level of Can f 5. Based on these findings, it would be appropriate to ask women with higher titers of sIgE to Can f 5 about symptomatology during intercourse apart from respiratory symptoms.

In a relatively new approach, the introduction of anti–Fel d 1 immunoglobulin Y in cat food has shown a reduction in immunologically active Fel d 1 in cat saliva, hair, and dander, which in turn leads to reduction in Fel d 1 level in the environment.[91] This provides an opportunity for Fel d 1–sensitized cat owners to treat their cats to reduce their cat-allergic symptoms. Hypothetically, this treatment of the cat would work only if the cat owner is monosensitized to Fel d 1. If the allergic cat owner is polysensitized to Fel d 2, Fel d 4, or Fel d 7, the owner would still be having reactions. The effect of this new interesting treatment needs to be explored further.

Multiplex CRD tests do not only provide detailed information on the patient's sensitization profile in the clinic but are used in clinical and epidemiological research. The number of peer reviewed publications in PubMed has constantly increased over the years. By December 2019, 288 articles were posted on PubMed using the ImmunoCAP ISAC microarray chip technology. CRD has proven to be a useful tool in describing pet sensitization profiles on a population level and thus provides an opportunity to make comparisons across populations. Yamamoto-Hanada et al[92] found that IgE sensitization to Fel d 1 was found in 26% at age 9 years in an unselected Japanese cohort. This finding is in contrast with an unselected Swedish cohort of adolescents in which 16% of subjects were sensitized to Fel d 1. Correspondingly, 10% *versus* 4% were sensitized to Can f 1 in the Japanese *versus* Swedish cohort and 2% *versus* 3% were sensitized to Equ c 1.[93] CRD arrays for multiple components generate complex and rich data sets, which warrants application of novel techniques such as machine learning to analyze the data. These methodologies have identified clusters of component sIgEs to multiple allergenic proteins associated with high risk of asthma in cross-sectional and longitudinal studies. For example, Roberts et al[94] applied clustering methods to identify co-occurring patterns of components and patterns of sensitization among participants. Furthermore, they used network analysis techniques to explore the connectivity structure of component sIgE, and differences in component sIgE interactions between patients with severe and mild/moderate asthma. They found that participants with severe asthma had higher connectivity among components (ie, more connections between different components), but these connections were weaker. The mild/moderate network had fewer connections, but the connections were stronger. Interestingly, connections among animal components showed higher correlations in severe asthma in both adults and children than in mild to moderate asthma. This analysis provides a strong indication that computational data analysis will be essential to uncovering the nuances of complex sensitization patterns of emerging CRD-based allergens of furry animals, which will constitute important steps for future research.

The chip-based multiplex assay provides interpolate results from an internal calibration curve into semi-quantitative estimates of the IgE antibody as classes or grades.[95] Their analytical sensitivity is generally less than that of singleplex tests. Because of the low density of allergen on the chip dots, nanogram levels of IgE antibody binding can be interfered with ISAC by the presence of microgram quantities of allergen-specific IgG "blocking" antibodies. The optimal application for these assays resides in epidemiologic studies where they can define the atopic status of different populations in geographically diverse regions.

Treatment options for individuals who are allergic to furry animals include allergen avoidance, medication, and AIT.[18] The ability of components to distinguish primary sensitization from cross-sensitization is important when immunotherapy is

envisaged, to choose the primary sensitizing allergen source for therapy. The availability of CRD has raised the possibility of better-targeted AIT, which up to date is the only treatment able to change the natural course of allergic disease. There is a clinical need for improved extracts for pet allergies because both standardized and unstandardized extracts are used for immunotherapy today in the United States.[96] As an example, unstandardized dog allergen extracts exist in the United States in 2 formulations—conventional and "acetone-precipitated." As with all unstandardized allergen extracts, no valid potency measure exists for these dog extracts. In spite of this, some reports and experiences from clinical practice suggest that the use of the acetone-precipitated product will yield better clinical results associated with their higher Can f 1 levels.[97] These suggestions are not based on clinical studies, and a recent report highlights that the immune response to dog is more complex than previously thought.[61] The medical literature on the use of dog extract immunotherapy in patients with hypersensitivity to dog shows poor and conflicting results of clinical efficacy. This has been attributed to poor-quality extracts and the inherent complex allergenic profile of dogs, which remains without a clearly dominant allergen.[98] A recent study showed that the molecular profile (number of allergens to which the patients were sensitized or the quantitative value of sIgE to allergens) was not related to response to subcutaneous immunotherapy with cat or dog extracts.[99] Research into the optimal organism in which to produce recombinant proteins continues. In the future, more potent and patient-specific extracts could be developed from a mixture of organic sources (saliva, urine, and dander) and then hybrid extracts with natural and recombinant allergens could be produced for use in immunotherapy. Component testing and patient-specific hybridized extracts could identify and provide the best therapeutic match to the patient's pattern of sensitization and therefore may offer better chances for effective therapy.

Based on this review, possible future clinical utility of CRD when a patient presents with suspected dog allergy would be measuring all the dog components (Can f 1, 2, 3, 4, 5, and 6) to clarify monosensitization to Can f 5 (female dog tolerance).[65] Furthermore, the more components a patient is sensitized to, the higher the likelihood of a clinical reaction when exposed to dog.[60,61,] Finally, higher levels of dog component sensitization and cosensitization to Can f 5 and Can f 1/2 are associated with current asthma.[57] In patients suspected with cat allergy, Fel d 1, 2, and 4 seem to be the most important components to measure. Sensitization to Fel d 1 is associated with asthma,[57,79] and polysensitization (Fel d 1, 2, and 4) is associated with both clinical reactivity to cat[60] and also bronchial responsiveness and increased FENO.[69] Finally, sensitization to Fel d 2 and Fel d 4 is associated with atopic dermatitis.[87] In patients with suspected horse allergy, only sensitization to Equ c 1 has been found clinically relevant, because it is associated with asthma.[31]

Conclusions

CRD is allowing detailed analysis of patients' sensitization profiles and may ultimately facilitate individualized treatments and patient management options. Some questions however remain to be addressed on the clinical utility of CRD in patients with allergy to furry animals.[1] In the interim, CRD should be considered complementary to extract-based testing rather than a replacement (Fig 2). The role of allergenic molecules as markers and predictors of disease severity needs to be further explored. Further studies are also needed to understand whether CRD could be used to identify patients who are most likely to respond to AIT. CRD may also have a role in monitoring treatment responses following immunotherapy. Debate in the allergy community reveals that the initial skepticism regarding precision allergy molecular diagnostic applications has moved toward the possibility that it could replace SPT in the future.[90] This concern exists especially in areas debating the preparation of SPT reagents in accordance with Good Manufacturing Procedures.

Overall, CRD has a role in developing patient-tailored treatment that could reduce health care costs, save time for patients, reduce adverse effects, and improve patient quality of life.

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