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REVIEW ARTICLE

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# Consensus document on dog and cat allergy

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## Abstract

The prevalence of sensitization to dogs and cats varies by country, exposure time and predisposition to atopy. It is estimated that 26% of European adults coming to the clinic for suspected allergy to inhalant allergens are sensitized to cats and 27% to dogs. This document is intended to be a useful tool for clinicians involved in the management of people with dog or cat allergy. It was prepared from a consensus process based on the RAND/UCLA method. Following a literature review, it proposes various recommendations concerning the diagnosis and treatment of these patients, grounded in evidence and clinical experience. The diagnosis of dog and cat allergy is based on a medical history and physical examination that are consistent with each other and is confirmed with positive results on specific IgE skin tests. Sometimes, especially in polysensitized patients, molecular diagnosis is strongly recommended. Although the most advisable measure would be to avoid the animal, this is often impossible and associated with a major emotional impact. Furthermore, indirect exposure to allergens occurs in environments in which animals are not present. Immunotherapy is emerging as a potential solution to this problem, although further supporting studies are needed.

  

KEYWORDS
allergen immunotherapy, allergic sensitisation, furry animals, hypersensitivity

## 1 | INTRODUCTION

The increasing presence of cats and dogs in homes, associated with significant levels of dog and cat allergens in areas where no animals are present (homes, schools, nurseries, places of work), has contributed to an increase in the frequency of allergy to these animals in industrialized countries.[1,2] The percentage of homes with a pet is highly variable: from 20% in Sweden and being as high as 65% in New Zealand.[3,4] Accordingly, the prevalence of sensitization to dogs and cats varies by country, timing of exposure and predisposition to atopy. It has been estimated that, in Europe, the percentages of sensitization in adults consulting for suspected allergy to inhalant allergens are around 26% to cats and 27% to dogs.[5] In the United States, in a population over the age of 6 years, 12.1% were sensitized to cats and 11.8% to dogs.[6] It has also been estimated that around 6% of the Spanish population is sensitized to animals[7] with figures increasing up to 30% in allergic patients. Animals are therefore the third leading cause of allergic asthma, after mites and pollens.[8] In addition to pet owners and their family members, professionals involved in animal care and research are a clearly affected group, representing up to a third of sensitized patients, with 30% of missing working days and 10% of them developing professional asthma.[7]

As dog and cat allergy represents a significant health problem with unresolved questions about clinical management, diagnosis, treatment and prevention, the aim of this document was elaborating recommendations in relation to these matters, based on published evidence when available, or, otherwise, in expert clinical opinion.

## 2 | GATHERING OF EVIDENCE AND PREPARATION OF RECOMMENDATIONS

In a previous consensus meeting, a panel of 14 allergy specialists agreed upon the main issues that should be addressed by the panel. Then, a systematic nonexhaustive literature review was performed to extract the scientific evidence available that could provide answers to the previously agreed questions on the management of patients with dog and cat allergy. The literature search process was performed using specific keywords for each question formulated. Patient/intervention/control/outcome (PICO) methodology was used whenever applicable. Filters used were as follows: English or Spanish language, and last 5 years. The types of publications that were prioritized were clinical practice guidelines, systematic reviews, and consensus documents. The search was performed in PubMed using keywords for each question formulated on diagnosis and treatment (Figure 1) (Key words are shown in Table S1).

Following the literature review, a consensus process based on the RAND/UCLA method was used, with the participation of the entire panel for the preparation of final recommendations (Figure 2). The specialists evaluated the evidence available and drafted recommendations and conclusions for each question, categorizing the level of evidence (LE) and degree of recommendation (DR) according to the 2011 Centre for Evidence-Based Medicine (Oxford) system.[9] Consensus was considered when a percentage of agreement ≥80% was achieved, whereas a percentage of agreement below this threshold was established as a disagreement. Finally, a total of 27 recommendations were approved (Table 2), and diagnostic and therapeutic algorithms for dog and cat allergy were elaborated (Figures 3 and 4).

## 3 | AGREEMENTS AND RECOMMENDATIONS

### 3.1 | Diagnosis of dog and cat allergy

#### 3.1.1 | Characterization of dog and cat allergens and cross-reactivity

Main dog and cat allergens are shown in Table 1. Major dog allergens are Can f 1 and Can f 5[10]; their sensitization frequencies are variable in different geographic regions.[11-13] Although there may be differences between breeds, all dogs produce allergenic proteins found in the epithelium, dander, lingual glands, prostate and parotid glands.[11] Can f 5, also known as prostatic kallikrein, is present in significant quantities only in non-neutered males.[14]

Major cat allergens are Fel d 1 and Fel d 4, although the clinical significance of sensitization to Fel d 4 is unknown.[15] All cats produce quantities of allergens high enough to be considered clinically significant. The sources of allergens are salivary, sebaceous and perianal glands[14] (Table 1). Fel d 1 is associated with hormone production and acts as an uteroglobin. It is found mainly in saliva, but also in sebaceous glands of the skin and in the urine of male cats. Airborne particles that carry Fel d 1 may be $< 5$ μm in diameter. This renders it more likely to be able to reach small bronchioles and induce asthma.

It is common for many patients to be simultaneously sensitized to both animals.[15] These patients show a higher risk of becoming sensitized to other allergens.[16] In fact, 75% of individuals sensitized to a pet are 14 times more likely to be sensitized to other animals.[16] The homology and/or structural similarity between different dog and cat allergens (such as albumins and lipocalins) explain the cross-reactivity between them and with other mammals. They also partly explain the presence of simultaneous sensitization to dogs, cats and

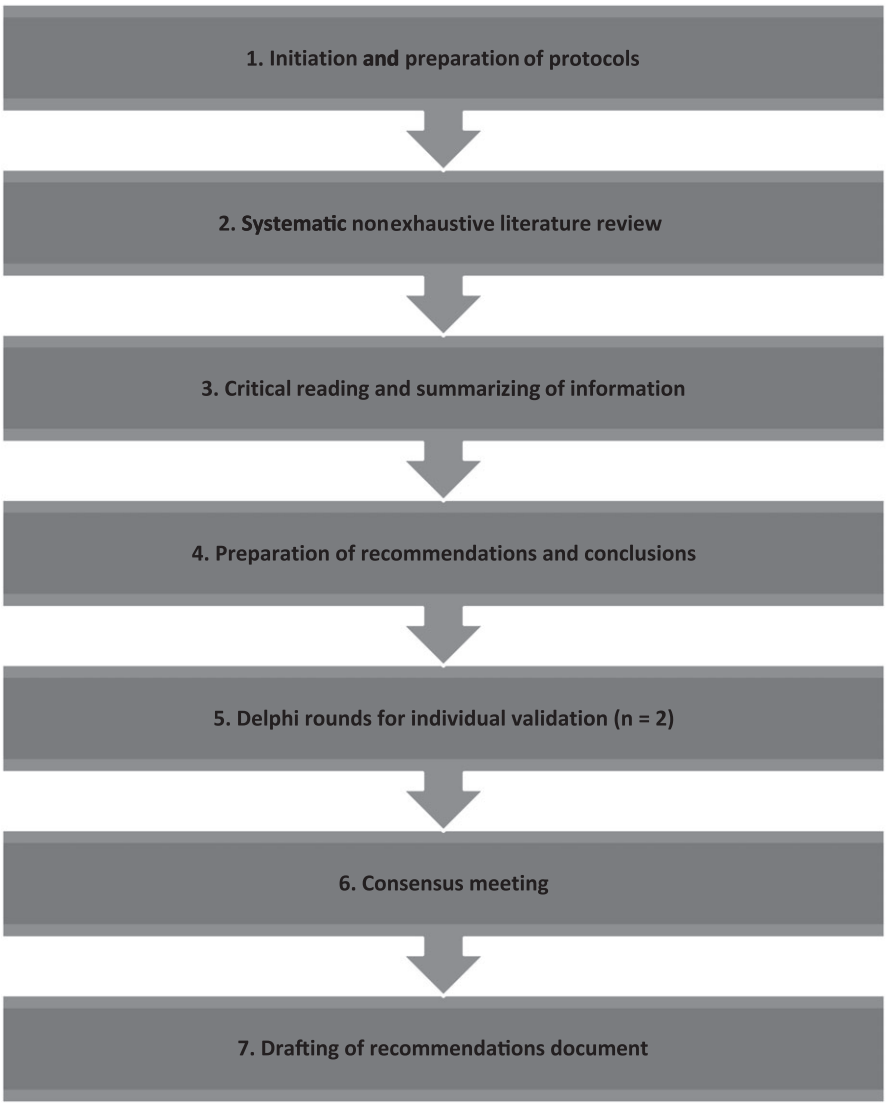


**FIGURE 1** Systematic non-exhaustive literature review

other mammals,[17] regardless of whether there is direct exposure to dogs, cats or both, or no direct exposure to either of them. There may be a significant cross-reactivity between dogs and cats, depending on the allergen(s) to which the patient is sensitized. It is recommended that molecular diagnosis be used to evaluate cross-reactivity [Recommendation 1, Table 2].

Regarding the most significant cross-reactivity patterns between cats/dogs and other mammals:

- Some lipocalins have amino acid sequences with up to 60% identity, which explains the cross-reactivity between them, for example, Can f 6 (dog), Equ c 1 (horse), Fel d 4 (cat), Ory c 4 (rabbit), Mus m 1 (mouse), Rat n 1 (rat).[18]
- Serum-specific Immunoglobulin E (sIgE) to Fel d 1 is present in 95% of patients who are allergic to cats and is also present in other feline families such as tigers, jaguars, pumas and lions.[6]
- sIgE to Can f 6 is present in 38% of patients sensitized to dogs; however, it appears in 60% of patients sensitized to both cats and dogs, which could be related to its identity with Fel d 4.[19]
- Structures of Can f 2 and Equ c 1 are quite similar; however, they do not show cross-reactivity.[19]
- The amino acid sequences of Can f 6 and Equ c 1 have 57% identity.[19]
- In the case of Can f 1, cross-reactivity with the human tear lipocalin has been reported.[10]
- Can f 5 shows a certain homology with prostate-specific antigen (PSA), belonging to the kallikrein family.[6] Therefore, it has been speculated that prior sensitization to Can f 5 from dogs could be associated with a greater propensity for developing allergic reactions to human seminal fluid.[20]

### 3.1.2 | Usefulness of skin tests, determination of specific IgE and molecular diagnosis

Skin prick testing with standardized extracts, along with a targeted medical history and physical examination, should be used to ruling out discarding or confirming a suspected IgE-mediated allergy to animals.[21]

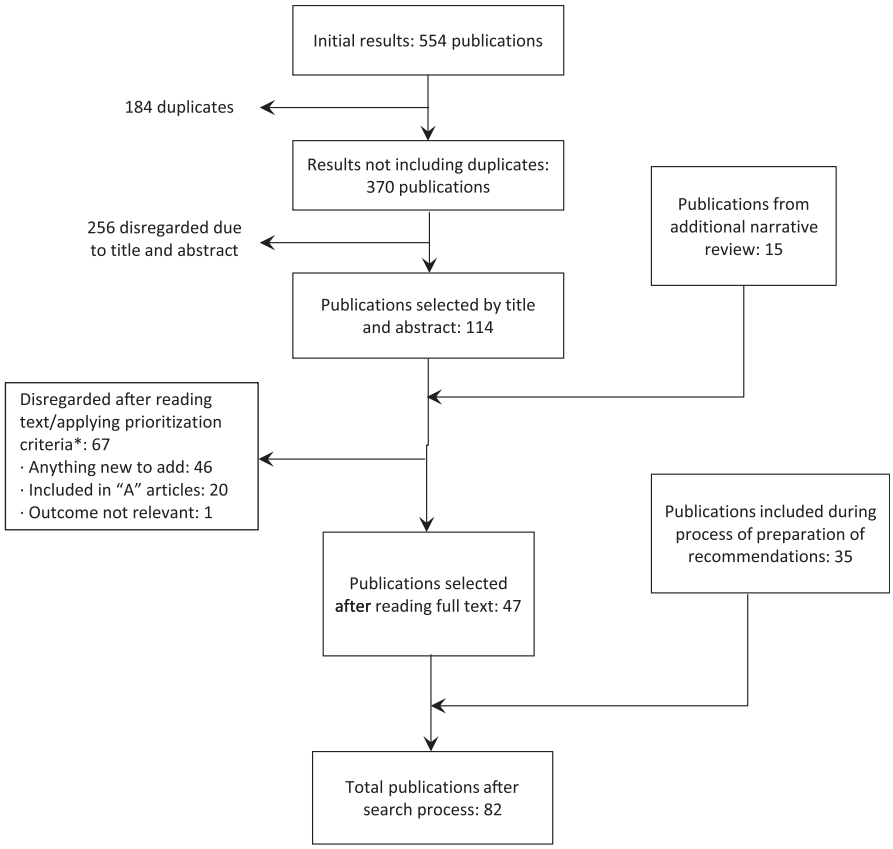


**FIGURE 2** Phases of consensus process.*Prioritization of the selected articles according to the type of publication. A: Review article and/or guide, consensus document. B: Study, essay or primary article. C: Expert opinion, case report

Skin prick tests extracts are mostly prepared by extracting allergens from several natural sources (like hair, dander, saliva, urine and/or epithelium) and contain a variety of allergenic and nonallergenic proteins.[22] Allergen extract standardization has been recommended to increase comparability and consistency between products from different manufacturers.[22] Nevertheless, in the case of dog allergy, for example, Curin et al[23] studied different commercial dog SPT extracts, founding a 20-fold variation regarding the total protein content. In addition, the concentration of Can f 1 and of Can f 2 varied considerably between the extracts, which was undetectable by immunoblotting in some extracts. The authors also observed great variability in the contents of Can f 3, albumin. Altogether, this variability between extracts should be taken into account in the evaluation of patients.

These tests are inexpensive, simple and quick to perform and should be used as an initial test. The performance of skin prick tests depends on methodological factors and factors related to the quality of the allergenic extract used [Recommendations 2 and 3, Table 2].

Serum-specific IgE against extract is considered to be a marker of sensitization, but it is not reliable enough to predict whether the patient is allergic or just sensitized. It should be particularly used when patient's symptoms and skin test results are contradictory, especially before recommending allergen-specific immunotherapy (AIT)[24] [Recommendation 4, Table 2]. In the case of cats, the determination of sIgE is a highly sensitive test, but there is a likelihood of false positives; therefore, it is less accurate than skin prick tests.[25]

Molecular diagnosis refers to the diagnostic use of purified or recombinant allergens.[26,27] It has clear advantages over the use of a complete extract, especially in polysensitized individuals, given its usefulness for distinguishing between sensitizations specific to singular species and sensitizations due to cross-reactivity.[27] It therefore aids in establishing recommendations for avoidance and assessing the choice and composition of immunotherapy. It might also be useful for predicting clinical symptoms and their severity[28] (Table 3). The performance of molecular diagnosis is different in the case of dog and cat allergy. Although the allergen Fel d 1 is a predictive marker of allergy to cats,[29] the performance of determining sIgE against complete cat extract and against Fel d 1 is similar.[29] In the case of dogs, Can f 1 and Can f 5 are highly predictive of dog allergy, although other allergens such as Can f 4 and Can f 6 could also be clinically significant[28] [Recommendations 5-9, Table 2].

### 3.1.3 | Usefulness of specific exposure tests

Specific exposure tests can be used to assess the clinical significance of sensitization to an allergen, when there are discrepancies between the medical history and the diagnostic or serological skin tests, in studies of allergies of occupational origin, in medical/legal assessments, or to assess treatment efficacy [Recommendation 10, Table 2]. In the case of inhaled allergens, there are 3 types of specific exposure tests: conjunctival, nasal and bronchial provocation [Recommendation 11, Table 2].

However, there is little evidence of the actual value of specific exposure tests in dog and cat allergy, and in most published studies,

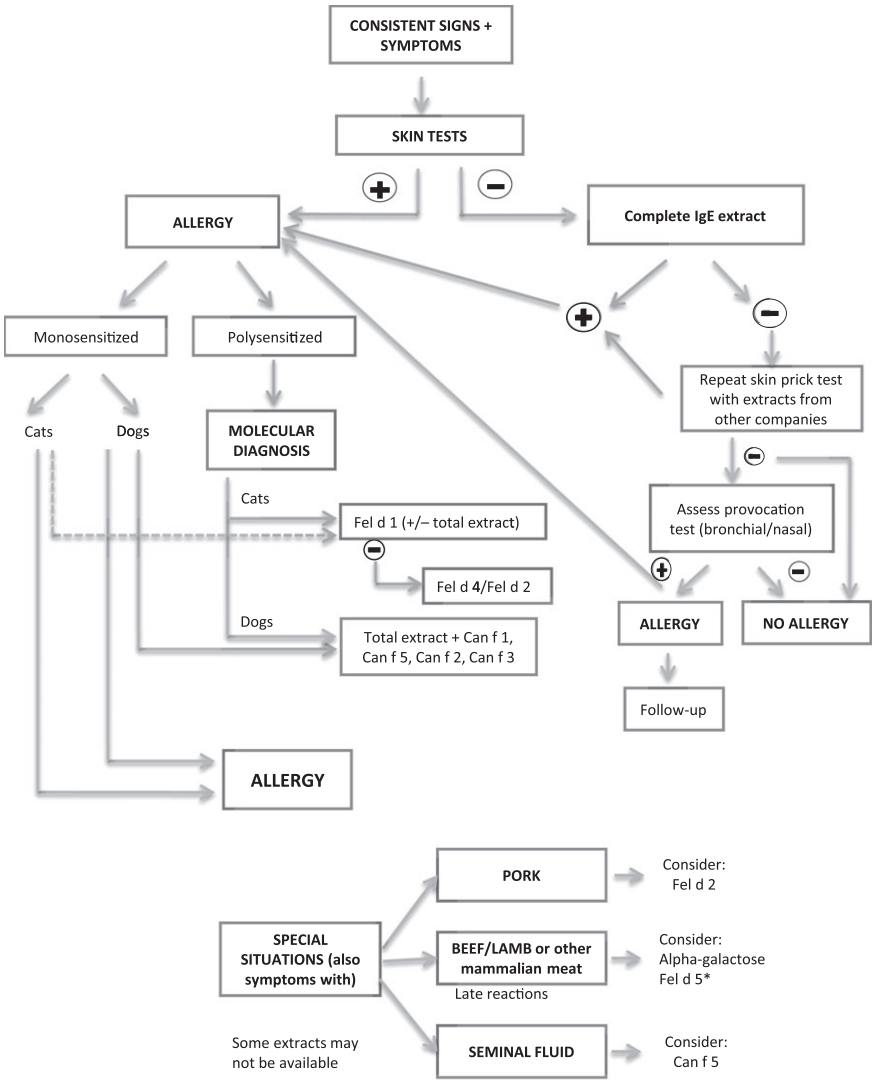


**FIGURE 3** Diagnostic algorithm for dog or cat allergy. *Fel d 5 corresponds to cat IgA, as an oligosaccharide epitope on cat IgA has been described[43]

specific exposure tests have been used to evaluate response to AIT treatments in exposure chambers.[30]

## 3.2 | Characteristics of sensitization to dogs or cats and its influence on allergic diseases

### 3.2.1 | Factors that predict sensitization and development of dog and cat allergy

The timing of exposure to allergens seems to be critical for inducing sensitization. In the case of dogs and cats, some data have suggested that exposure during the first year of life, along with other genetic and environmental risk factors, may decrease the risk of developing allergic asthma.[31,32] By contrast, when the exposure occurs after the first year of age, the risk of sensitization and development of an allergic disease seem to be increased.[33,34] However, further studies are needed to confirm this finding.

These observations could be specific for cat and dog and could not occur with other mammals such as rodents. In this case, it has been described that the exposure could even increase the risk of developing nonatopic asthma.[32]

### 3.2.2 | Course of sensitization to dogs and cats throughout life

There is not enough available evidence to predict whether sensitization to dogs or cats will be associated or not to clinical allergy. However, sensitization to Can f 1 or Fel d 1 and polysensitization to cat and dog allergens during childhood have been associated to the development of subsequent allergy to dogs and cats.[35] Some studies have confirmed a decrease in sIgE levels after removing the source of exposure, but without significant association with clinical manifestations.[36] In addition, and although studies confirming this observations are pending, it has been described that some patients develop a lower clinical response when they are continuously exposed to significant allergen levels.[7] Thus, in patients allergic to cats, it has been reported that concentrations of Fel d 1 over 44 μg per gram of powder may cause them tolerating the presence of their pets, although

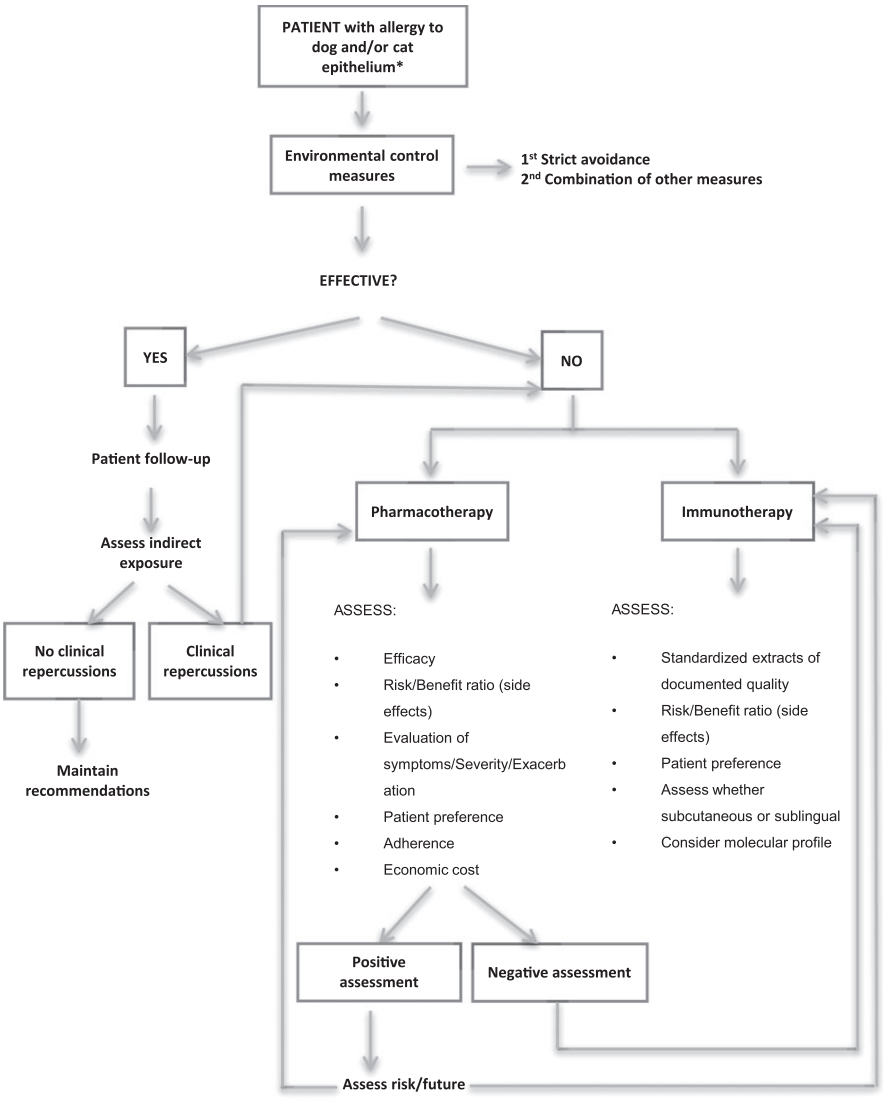


**FIGURE 4** Therapeutic algorithm for dog or cat allergy. *Primary sensitization should be considered before to initiating immunotherapy

they tend to have severe respiratory signs and symptoms again after having a time without exposure.[7]

From studies reviewed,[10,14,28,37,38] it could be concluded that sensitization to certain allergens seems to be associated with severity and persistence of clinical symptoms and that sensitization to more than 1 allergen or sensitization to albumins seems to be associated with more severe respiratory symptoms.[29]

### 3.2.3 | Exposure to dogs and cats and risk of developing sensitization or clinical symptoms upon exposure to other mammalian allergens

It is unclear whether sensitization to dogs or cats is a risk factor for sensitization to other aeroallergens. Regarding other mammals, there seems to be an increased risk of sensitization to horses and mice in patients previously sensitized to cats/dogs, which could be related to cross-reactivity of lipocalins or albumins.[27] Therefore, in such cases it would be preferable to avoid any exposure to other mammals, although it is unknown whether cross-reactivity necessarily leads to the development of clinical symptoms [Recommendation 12, Table 2]. In addition, it has been described that mite-allergic patients could have a higher risk of developing sensitization to dogs if they own or have previously owned a dog.[33]

### 3.2.4 | Main food allergy syndromes in patients sensitized to dogs or cats

The existence of potential cross-reactivities in patients sensitized to dogs and cats may trigger food allergy syndromes that are difficult to manage and diagnose. In patients who are allergic to cats, the main food allergy syndrome is pork-cat syndrome, secondary to the cross-reactivity of Fel d 2 with other albumins from mammals, leading to anaphylactic reactions after consuming pork, especially raw or undercooked.[39]

Other syndrome is "delayed anaphylaxis due to IgE to galactose-alpha-1,3-galactose (alpha-gal)." In this case, the allergenic carbohydrate epitope (alpha-gal) is present on cat IgA and IgM (designated Fel d 5 and Fel d 6, respectively).[40] This carbohydrate

**TABLE 1** Characteristics of dog and cat allergens[a]

| Allergen | Protein family | Allergen source | Molecular mass (kDa) | Sensitisation (%) | Glycosylation |
|---|---|---|---|---|---|
| Can f 1 | Lipocalin | dander, epithelium, saliva | 23-25 | 40-70 | Yes |
| Can f 2 | Lipocalin | dander, saliva | 19 | 25-30 | Yes |
| Can f 3 | Albumin | dander, saliva, serum | 69 | 15-35 | No |
| Can f 4 | Lipocalin | dander, saliva | 18 | 15-35 | No[b] |
| Can f 5 | Kallikrein (arginine esterase) | dander, urine | 28 | 70 (Spanish population) | Yes |
| Can f 6 | Lipocalin | dander, saliva | 27-29 | 35-40 | Yes[b] |
| Can f 7 | Recognition of MD2-like lipids | - | 16 | 10-20 | Yes |
| Fel d 1 | Secretoglobin | saliva | 38 | 60-100 | Yes |
| Fel d 2 | Serum albumin | dander, serum, urine | 69 | 14-54 | No |
| Fel d 3 | Cysteine protease | dander | 11 | 10 | Yes[b] |
| Fel d 4 | Lipocalin | saliva | 22 | 61-63 | Yes[b] |
| Fel d 5 | IgA | saliva, serum | 38 | 24-38 | Yes |
| Fel d 6 | IgM | saliva, serum | 800-1000 | 38 | Yes |
| Fel d 7 | Lipocalin - von Ebner's gland protein | saliva | 17.5 | 38 | No[b] |
| Fel d 8 | Latherin-like | saliva | 24 | 19-20 | No[b] |

[a]Table adapted from[11,15,98]

[b]Presence or absence of glycosylation deduced from sequence analysis, not based on experimental evidence.

is well-described evoking allergic symptoms after tick bites,[41] cetuximab infusion[42] and in mammalian red meat delayed allergic symptoms.[43]

### 3.2.5 | Influence of dog and cat allergy on atopic dermatitis

Due to the lack of uniformity (exposure time, duration and dose, type of pet, family history of allergy, etc.) of studies that have evaluated the role of dog and cat exposure in the development of atopic dermatitis, no definitive conclusions can be drawn. Some guidelines recommend avoiding or limiting contact with dogs and cats in patients with atopic dermatitis, depending on the severity of the signs and symptoms and the psychological stress that getting rid of the pet may cause.[44] Nevertheless, according to a recent meta-analysis, exposure to dogs from birth may decrease the risk of suffering from atopic dermatitis by 25%.[45] Regarding cats, neither a protective effect nor an increase of atopic dermatitis has been found in exposed children, except in those at high risk of developing atopic dermatitis. Concerning remission of atopic dermatitis in children, no protective effect of exposure to dogs or cats has been demonstrated.[45-53] As family members share microbiota with each other and with their dogs, living with a dog, although not with a cat, would alter the child's intestinal microbiota.[6,54]

Concerning exposure to cat or dog and the development or remission of atopic dermatitis, the expert panel did not achieve to a consensus on a specific recommendation.

## 3.3 | Quality of life in dog and cat allergy

Although no specific studies evaluating the repercussions of allergy to animals for quality of life have been found, exposure to mammals represents a significant cause of occupational allergy.[55,56] The expert panel believes that dog or cat allergy could have a negative impact on quality of life and that it is an important aspect to be considered.[2,7,8] As no specific studies have been found on the impact on the quality of life of patients who are allergic to dogs and cats, recommendations are inferences from the quality of life of patients who suffer from allergic respiratory disease [Recommendations 13 and 14, Table 2].

## 3.4 | Therapeutic management of dog and cat allergies

### 3.4.1 | Measures for avoidance

Described measures for avoiding pet allergens are as follows: removing the pet from home,[14,57,58] regularly washing the pet,[57,59] keeping the pet out of the bedroom,[14,60,61] air purifying using HEPA filters,[62] regularly using and maintaining of high-efficiency vacuum cleaners,[14] using covers and cases for mattresses and pillows,[14,63] removing pillows and other items that may act as a reservoir,[14] using bleach and tannic acid,[64] using night-time temperature-controlled laminar airflow,[59] applying topical lotions to the animal's fur[7] and combining several of these measures.[14] Although removing the animal from the home is the most commonly recommended measure, it may be so difficult for patients to agree to this that measures focused on decreasing exposure to allergens while keeping the pet at home, although less effective, can be more practical. The alternative described measures should preferably be applied in combination and sustained over time, although they do not ensure a current clinical benefit or a clinical benefit in disease progression [Recommendations 15-20, Table 2]. As data on the effect of spaying and neutering dogs and cats are inconsistent, no specific recommendations have been made in this regard.[14]

**TABLE 2** Evidence-based consensus recommendation statements

| No. | Recommendation[a] | LE/DR | % A (N) |
|---|---|---|---|
| How can the cross-reactivity of the different dog and cat allergens, with each other and with those of other mammals, be assessed? | | | |
| 1 | Molecular diagnosis is strongly recommended to distinguish between simultaneous sensitisation and cross-reactivity, depending on the animals to be studied.<br>Ref.: Based on[99] | 2/B | 92.9% (13) |
| What is the usefulness of skin tests in the diagnosis of dog and cat allergy? | | | |
| 2 | Skin prick tests with standardised extracts are recommended as the initial diagnostic procedure in all patients with clinically suspected dog and cat allergy.<br>Ref.: Based on[21] | 5/D | 100% (14) |
| 3 | Diagnostic extracts should be standardised and it is recommended that at least major allergens be specified.<br>Ref.: Based on expert opinion | 5/D | 100% (14) |
| What is the usefulness of determination of specific IgE with complete extract in dog and cat allergy? | | | |
| 4 | It is recommended that the determination of specific IgE with complete extract be performed in dog or cat allergy:<br>• when patient's medical history and skin test results are contradictory<br>• when skin tests cannot be performed<br>• to support the diagnosis<br>• before starting IT<br>Ref.: Based on[25] | 2/B | 100% (14) |
| What is the usefulness of molecular diagnosis? | | | |
| 5 | It is advisable to use molecular diagnosis in polysensitised patients, to provide recommendations for avoidance and/or to identify allergens that could be significant components in IT.<br>Ref.: Based on[28] | 2/B | 100% (14) |
| 6 | In cases of suspected cat allergy, it is advisable to perform determination of specific IgE against complete extract or Fel d 1, interchangeably.<br>Ref.: Based on[29] | 3/B | 100% (14) |
| 7 | In the case of dog allergy, it is advisable to determine specific IgE against the complete extract and against the largest number of available dog allergens.<br>Ref.: Based on[29] | 3/B | 92.8% (13) |
| 8 | Molecular diagnosis may be useful for attempting to predict clinical symptoms and their severity, especially in patients with asthma and particularly in severe asthma.<br>Ref.: Based on[28] | 2/B | 100% (14) |
| 9 | In women allergic to dog that refer reactions following contact with human seminal fluid, it would be advisable to determine IgE against Can f 5.<br>Ref.: Based on[20,100,101] | 4/C | 100% (14) |
| What is the usefulness of specific exposure tests? | | | |
| 10 | It is recommended that specific exposure tests be performed:<br>• to assess the clinical significance of sensitisation to an allergen,<br>• whenever there are discrepancies between the medical history and diagnostic skin or serum tests,<br>• in the aetiological study of allergic respiratory diseases of occupational origin, in medical/legal situations,<br>• in the assessment of drug efficacy<br>• they can also be considered in the follow-up and monitoring of clinical response to allergen-specific IT.<br>Ref.: Based on expert opinion | 5/D | 100% (14) |
| 11 | Bronchial provocation may be used to confirm or rule out the involvement of an allergen in asthmatic patients, to make an aetiological diagnosis and for research or medical/legal purposes. Very few publications have dealt in particular with specific exposure tests in allergy to epithelia.<br>Ref.: Based on expert opinion | 2/B | 100% (14) |
| Does exposure to dogs and cats have repercussions for sensitisation and clinical signs of exposure to other allergens? | | | |
| 12 | Although more studies are needed, in the case of patients who are allergic to dogs or cats that are sensitised to albumins or lipocalins, it is recommended that further exposure to other mammals be avoided.<br>Ref.: Based on[27] | 5/D | 100% (14) |

(Continues)

**TABLE 2** (Continued)

| No. | Recommendation[a] | LE/DR | % A (N) |
|---|---|---|---|
| What repercussions does dog and cat allergy have for quality of life? | | | |
| 13 | Given the potential effect of dog and cat allergy on quality of life, its evaluation is essential for adopting the measures to improving patient's quality of life.<br>Ref.: Based on[2,7,8] | 5/D | 100% (14) |
| 14 | In patients with dog or cat allergy, it would be appropriate to evaluate quality of life by means of specific questionnaires to apply the appropriate therapeutic/prophylactic measures.<br>Ref.: Based on[102,103] | 1/A | 85.7% (12) |
| What measures for avoidance in allergic respiratory disease due to dogs and cats should be applied/recommended based on efficacy and in disease progression? | | | |
| 15 | It should be recommended that the animal be removed from the patient's environment, as avoidance is believed to be the most effective measure for the management of dog and cat allergy.<br>(Although it would be advisable to avoid exposure, if a causal relationship is demonstrated, the risk/benefit ratio of this measure should be evaluated on a case-by-case basis with consideration for its potential emotional impact.)<br>Ref.: Based on[104] | 4/C | 92.9% (13) |
| 16 | Exposure to dog and cat allergens should be minimised to reduce the likelihood of an asthma exacerbation in sensitised patients with asthma.<br>Ref.: Based on[105,106] | 3/B | 92.9% (13) |
| 17 | The interventions should start as soon as possible in the natural history of the disease.<br>Ref.: Based on[59] | 5/D | 100% (14) |
| 18 | Up to the point of removing the animal from the home, or if the patient does not want to remove it, it is advisable to combine multiple measures to decrease the patient's exposure, since individual measures do not seem to be useful.<br>Ref.: Based on[14] | 5/D | 100% (14) |
| 19 | It is recommended that a combination of some of the following measures, which have demonstrated some usefulness, be used: | | 100% (14) |
| | It is recommended that dogs and cats be washed regularly, at least twice a week, since this measure has demonstrated a reduction in the quantity of Fel d 1 from cats and Can f 1 from dogs.[57,59,63] | 4/C | |
| | It can be recommended that the pet be kept out of the bedroom, since this seems to decrease allergen levels.[14,60,61] | 5/D | |
| | Whenever possible, the use of air purifiers with HEPA filters may be an effective measure for decreasing exposure to animal epithelia.[62,63] | 5/D | |
| | Regular, sustained use of high-efficiency vacuum cleaners in the homes of patients who are allergic to epithelia may be recommended [14] | 5/D | |
| | The use of certain covers and cases for mattresses and pillows, especially those with a mean pore size equal to or less than 6 μm, may be beneficial for patients who are allergic to epithelia.[14,63] | 5/D | |
| | It is recommended that pillows and other items that may act as a reservoir be removed.[14] | 5/D | |
| | In certain cases it may be recommended that chemical products (sodium hypochlorite, tannic acid) be used for washing pillows and other reservoirs.[14] | 5/D | |
| | The use of night-time temperature-controlled laminar airflow may decrease allergen exposure in patients who are allergic to epithelia, since it displaces aeroallergens from the breathing area.[59] | 2/B | |
| | Application of topical lotions that encapsulate the allergens on the fur of the animal that lives with patients who are allergic to epithelia may be recommended.[7] | 5/D | |
| 20 | Adherence to measures for avoidance may be enhanced with education and monitoring.<br>Ref.: Based on[14] | 5/D | 100% (14) |
| Can indirect exposure to dogs and cats maintain disease? | | | |
| 21 | Although no studies evaluating the efficacy of this measure are available, patients with allergy to epithelia should, as far as possible, avoid indirect exposure to animals and not go to places where animals may have been, even if no animals are present at that time.<br>Ref.: Based on expert opinion | 5/D | 100% (14) |

(Continues)

**TABLE 2** (Continued)

| No. | Recommendation[a] | LE/DR | % A (N) |
|---|---|---|---|
| 22 | Although it is difficult to avoid indirect exposure to animal epithelia, a series of recommendations to attempt to minimise this exposure could be established:<br>• To reduce the dispersion of animal epithelia allergens, people could change their clothes when they travel from places with a high allergen concentration to places with a low allergen concentration.<br>• If people who live with an allergic patient work with or have been in contact with animals, they should change their clothes and shower before returning home.<br>• Family members and friends who have animals should refrain from bringing them to the home of the patient who is allergic to epithelia.<br>• In the case of schools, it would be advisable for students who live with pets to wear clothes that have not come into contact with these pets, and it could be recommended that the presence of animals in classes be avoided.<br>Ref.: Based on expert opinion | 5/D | 100% (14) |
| 23 | For the recommendations above to be effective, they should be followed by most of the population, and they should be strictly followed by those who live with people allergic to the epithelia of these animals. In the case of dogs, there are not enough studies to support this recommendation.<br>Ref.: Based on expert opinion | 5/D | 100% (14) |
| Are so-called "hypoallergenic" animals really "hypoallergenic"? | | | |
| 24 | A "hypoallergenic" pet should not be recommended to patients who are allergic to dogs or cats.<br>Ref.: Based on[14,57,68] | 5/D | 100% (14) |
| 25 | Although there are animals genetically modified not to produce a major allergen (as is the case of Fel d 1), when individual sensitisation is to other clinically significant allergens, this type of animal is not useful for allergen avoidance.<br>Ref.: Based on[14] | 5/D | 100% (14) |
| In which cases should allergen-specific IT be recommended? | | | |
| 26 | IT with cat epithelium would be indicated in patients with allergic respiratory disease under circumstances in which there is exposure, assessing the viability and efficacy of environmental control measures, drug therapy and patient preferences.<br>Ref.: Based on[107] | 5/D | 100% (14) |
| 27 | IT with dog epithelium could be recommended in certain patients under strict follow-up by their prescribing physician and using standardised extracts with the main allergens quantified, assessing the viability and efficacy of environmental control measures, drug therapy and patient preferences.<br>Ref.: Based on[107-109] | 5/D | 100% (14) |

LE/DR, level of evidence/degree of recommendation; % A, percentage of agreement in last round; N, total votes.
[a]Some questions are not shown in this table as they did not generate recommendations.

In addition, regarding indirect exposure, Fel d 1 has been reported to be distributed throughout the community, including schools and homes in which there are no cats.[6] Pet allergens are passively transferred from homes with pets to homes without pets and to public spaces, especially in populations in which pets are more common.[61] The extent of indirect contact is significant, as the prevalence of allergy to cats in patients who have never had a cat in their home may be as high as 34%.[65] This would require allergic patients to avoid indirect exposures using some specific measures, which is nearly impossible.[66] Houses in which there is a dog or cat have very high concentrations of allergens, even if the animal is not present at that time, and so patients can develop symptoms even in the absence of the animal.[7] It may be said that concentrations of 1-8 μg/g powder of Can f 1 and Feld 1 of 2-20 nanograms per cubic metre in the air seem to be associated with a higher risk of developing sensitization to dogs and cats as well as causing symptoms in allergic individuals.[7] Long-term exposure to cat allergens at relatively low doses may lead to adverse effects on respiratory health in atopic individuals, even without causing perceptible symptoms[67] [Recommendations 21-23, Table 2].

So-called "hypoallergenic" animals respond to the desire of having a cat or dog in patients sensitized to these animals.[57] Most "hypoallergenic" dogs are advertised as such because they shed less fur or have been bred to produce a lower quantity of Can f 1 or Fel d 1 in their dander. However, decreased shedding does not eliminate exposure to dog/cat saliva nor to minor allergens to which the individual may have been sensitized and that may also play a role in allergy symptoms.[14]

There is no scientific evidence to support labelling certain breeds of cats or dogs as hypoallergenic, as no significant differences have been found between environmental levels of allergens from nonhypoallergenic dogs vs so-called hypoallergenic dogs.[14,57,68]

Therefore, the availability of a genuinely allergen-free dog for allergic individuals who would like to have a dog is questionable.[69]

**TABLE 3** Allergic markers of clinical symptoms[a]

| (A) Markers of severe asthma |
|---|
| • High levels of specific IgE against cats, dogs and horses. |
| • Polysensitisation to all three animals (cats, dogs and horses). |
| • Sensitisation to Can f 2; 1 study found that no patients with controlled asthma were sensitised to this allergen. No patients monosensitised to this allergen were found. |
| • Sensitisation to Can f 5. Not significant, but a trend towards association with more severe asthma has been found. |
| • Polysensitisation to 3 or more lipocalins. Sensitisation to any lipocalin did not confer severity, but combined sensitisation to 3 or more lipocalins did. |
| (B) Described associations of allergens to asthma, rhinitis and other respiratory symptoms |
| • Can f 1 with persistent rhinitis. |
| • Can f 2 with a diagnosis of asthma. |
| • Can f 3 with moderate/severe rhinitis and a diagnosis of asthma. |
| • Can f 5 with moderate/severe persistent rhinitis. |
| • Fel d 2 with moderate/severe rhinitis and a diagnosis of asthma. |
| • Fel d 4 with a diagnosis of asthma. |
| • Sensitisation to 2 or more allergens was associated with more severe respiratory symptoms. |
| • Sensitisation to albumins was associated with more severe respiratory symptoms. |
| • In the case of dogs and horses, sensitisation to more than 1 allergen was associated with more severe rhinitis and asthma. |

[a]Table adapted from[28,29]

Patients should not be advised on the safety of acquiring a "hypoallergenic" dog or cat[14,57,68] [Recommendations 24 and 25, Table 2].

### 3.4.2 | Immunotherapy in dog and cat allergy

The literature on cases in which allergen-specific IT (AIT) against aeroallergens should be prescribed is extensive, and multiple international consensuses have been reached. Such studies particularly review IT with pollens and/or mites. In the case of AIT, there are few studies, and most of them performed with cat extracts. In this regard, the expert panel for this document has established the recommendations shown in Table 2 [Recommendations 26-27, Table 2].

#### Dog allergy

Available studies on subcutaneous immunotherapy (SCIT) with dog are limited and mixed. There are only 3 double-blind, placebo-controlled, randomized studies. SCIT with a complete dog extract has demonstrated a reduction in the size of skin tests and an increase in serum IgG and IgG4 in adults and children with rhinoconjunctivitis and asthma, but not a significant clinical efficacy.[70-72] This could be due to the quality of extracts and/or to confounding factors such as sensitization to other aeroallergens.[70,72,73] Regarding the dose, a study conducted in 2006 concluded that a dose containing 15.0 μg Can f 1 per 0.5 mL maintenance dose produced the most consistent response[72] (Table 4).

#### Cat allergy

SCIT with cat extracts has demonstrated a statistically significant improvement in specific conjunctival, nasal and bronchial provocation with cat in adults with rhinoconjunctivitis and asthma after 12 months of treatment,[73-75] as well as a significant, dose-dependent increase in total IgG and IgG4, and a reduction in the size of the skin tests.[73,76,77] Regarding clinical improvement, in two placebo-controlled, randomized clinical trials, SCIT with cat extracts induced significant clinical improvement in adults with rhinoconjunctivitis and asthma after 12 months of treatment.[74,75] Even so, more clinical trials should be conducted to confirm this improvement. Only two studies have evaluated the effect of SCIT with cat extracts in children, finding a significant improvement in specific bronchial provocation with cat and in skin test reactivity, as well as an increase in specific IgG and IgG4.[73,78] Therefore, more studies should be conducted in paediatric populations. The optimal dose of Fel d 1 in SCIT with cat extract seems to be a maintenance dose of 15.0 μg[73-77,79] (Table 5). Sublingual immunotherapy (SLIT) with a cat extract has demonstrated significant improvement in nasal, eye and bronchial symptoms in adult patients after 12 months of treatment.[80]

### 3.4.3 | Other forms of Immunotherapy

In order to improve the safety and efficacy of the current IT regimens, different lines of research are being pursued to optimize the outcome of allergen IT. At present, the only studies on IT with dog are in a preclinical phase. However, although more phase 3 studies are needed to confirm efficacy and safety, in the case of cat IT in patients with allergy to cats, the use of Fel d 1 peptides[81-86] and the intralymphatic route for the administration of recombinant Fel d 1 bound to a translocation sequence (MAT) have been evaluated.[87] Regarding other forms of IT such as hypoallergenic recombinant allergens,[88-90] fusion proteins to transport peptides[91,92] and the use of different coadjuvants (immunomodulating molecules, vitamin D and carbohydrates),[93-96] clinical studies are required to verify their efficacy and safety. Concomitant or prior use of omalizumab has demonstrated certain usefulness with other aeroallergens, but more outcomes that confirm its clinical efficacy and cost-effectiveness are needed.[97]

The satisfactory outcomes of new forms of IT should be confirmed with further multicentre clinical studies with larger numbers of patients that reproduce the usual exposure to cats of allergic patients.

**TABLE 4** Main studies conducted with SCIT in dog allergy

| Reference | Design | Results/Conclusions | LE |
|---|---|---|---|
| Valovirta E et al 1984[70] | First placebo-controlled double-blind clinical trial with SCIT with dog extract that enrolled 27 children with asthma and dog allergy. It evaluated symptom score, conjunctival provocation and bronchial provocation at the start and after 12 mo of treatment. | A significant improvement in conjunctival provocation and a nonsignificant improvement in bronchial provocation and symptom score were seen in the active group compared to the placebo group. | 2 |
| Valovirta E et al 1986[110] | Placebo-controlled, randomized, double-blind study. Study conducted with 27 asthmatic children who did not have pets. | They observed an increase in specific IgG and a reduction in intradermal tests in the active group, with a statistically significant difference vs placebo. | 2 |
| Bertelsen A et al 1989[78] | Open-label study comparing skin tests, specific IgE, IgG4 and specific bronchial provocation in a group of asthmatic children who maintained their symptomatic medication and received SCIT for 9 mo, vs a control group of asthmatic children who received symptomatic medication only. | The authors found lower reactivity in the skin test and better tolerance in bronchial provocation in the active group, in both cases with a significant difference vs the control group. | 3 |
| Bucur J et al 1989[111] | Group of 11 patients allergic to dogs who received IT for 12 mo. No control group. | After 3 mo of treatment, significant changes with respect to size of the skin test and better tolerance in conjunctival provocation were observed. A significant decrease in specific IgE after a year of treatment was also observed. | 3 |
| Danish group of Sundin B and Hedlin G (1986-1995) [71, 73, 79, 112, 113] | Second placebo-controlled, double-blind clinical trial enrolling 22 asthmatic adult and child patients with allergy to animals (7 allergic to dogs) and 17 control patients. The parameters to be evaluated were as follows: changes in symptom score, bronchial provocation with allergen, bronchial provocation with histamine, conjunctival provocation, skin tests, IgE, IgG and IgG4. | The authors concluded that there were no clear efficacy data supporting the use of IT with dog extract:<br>• After 12 mo of treatment: In patients with allergy to dogs only, a significant reduction was seen in the skin test, and a significant increase in IgG and IgG4, but no significant improvement was found in symptom score, conjunctival provocation or specific bronchial provocation.[71,73]<br>• After 1 y of treatment, the trial was unblinded, and a total of 11 patients who were allergic to dogs completed 2 y of treatment. After 2 y and after 3 y of treatment, no change or significant improvement was seen with respect to the measurements made after 1 y of treatment.[112,113]<br>Long-term follow-up of these patients[79]: 5 y after completion of IT with dog extract, 3 of 4 patients reported sustained clinical improvement, and 5 of 6 patients who underwent specific bronchial provocation experienced worsening compared to the time of completion of IT. | 2 |
| Smith DM and Coop CA 2016[11] | Systematic review of studies conducted to date on IT with dog epithelium | These studies observed a reduction in symptoms and better tolerance of exposure to the animal in the patients treated. However, the improvement seen was based on subjective symptoms only, as there was no control group. The authors concluded that no clearly reproducible scientific evidence has been demonstrated to confirm its efficacy in improving the symptoms of rhinitis and asthma. It seems that this lack of efficacy could be due to the quality of the extracts and the variability of the profiles of sensitization of patients allergic to dogs. | 1 |

IT, Immunotherapy; SCIT subcutaneous immunotherapy.

## 4 | CONCLUSIONS

The diagnosis of dog and cat allergy is based on a consistent medical history and physical examination and is confirmed with a positive skin test result or sIgE. It is often necessary and advisable to perform molecular diagnosis, especially in polysensitized patients. A proper diagnosis is essential for achieving short- and long-term symptom management.

There are many measures directed to reduce exposure to dog or cats. Although the most advisable measure would be a complete avoidance of the animal, this is often impossible (not to mention the emotional impact), as there are animal allergens in environments in which animals are not present.

AIT is emerging as a potential alternative. However, a review of the scientific literature offered very modest results with respect to

**TABLE 5** Main studies conducted with SCIT in cat allergy

| Reference | No. of pts., age, underlying disease | Fel d 1 dose | Treatment duration | Clinical course | Test results | LE |
|---|---|---|---|---|---|---|
| Sundin B et al 1986 [73]<br>Hedlin G et al 1986 [71] | 39 adults and children. Asthma ± RC | 17.3 μg | 12 mo | Trend towards improvement | Significant improvement in specific bronchial provocation test<br>Significant improvement in skin reactivity<br>Increase in IgG and IgG4 | 2 |
| Van Metre TE Jr et al 1988 [114] | 22 adults. Asthma | 4.56 FDA units | 12 mo | - | Significant improvement in specific bronchial provocation test<br>Significant improvement in skin reactivity<br>Increase in IgG (cat, Fel d 1, Albumin) | 2 |
| Lilja G et al 1989, Hedlin G 1991 [112,113] | | 17.3 μg | 2 y | Sustained improvement | Sustained improvement over the next 2 y (specific bronchial test)<br>Sustained improvement in skin reactivity | 2 |
| Álvarez-Cuesta E et al 1994 [75] | 28 adults. RC and asthma | 13.2 μg | 12 mo | Significant improvement | Significant improvement in conjunctival provocation test<br>Significant improvement in the specific bronchial provocation test and nonsignificant improvement in the nonspecific bronchial provocation test<br>Significant improvement in skin reactivity | 2 |
| Hedlin et al 1995 [79] | 30 adults and children. Asthma ± RC | 17.3 μg | 5 y after end of IT | Nonsignificant improvement | At the end of treatment, significant improvement in the sensitivity in specific bronchial provocation was seen and there were no changes in nonspecific bronchial provocation.<br>There were no significant changes in IgG4 or specific IgE. | 3 |
| Varney et al 1997 [74] | 28 adults. RC and asthma | 15 μg | 12 mo | Significant improvement | Significant improvement in conjunctival provocation test<br>Significant improvement in skin reactivity | 2 |
| Ewbank PA et al 2003 [76] | 28 adults. RC ± asthma | 0.6 μg<br>3 μg<br>15 μg | 5 wks | - | Bronchial provocation was not performed.<br>Nasal provocation was performed, with no significant changes.<br>Dose-dependent significant improvement in skin reactivity<br>Dose-dependent increase in cat IgG4.<br>Increase in $CD4^+/IL4^+$ PBMCs with the highest dose.<br>Nonsignificant differences for nasal IL-4, IL-5 and IFNγ | 2 |
| Nanda A et al 2004 [77] | 26 adults. RC ± asthma | 0.6 μg<br>1.3 μg<br>15 μg | 12 mo | - | Bronchial provocation was not performed.<br>Nasal provocation was performed with significant improvement with the highest dose.<br>Dose-dependent significant improvement in skin reactivity<br>Dose-dependent increase in cat IgG4.<br>Nonsignificant differences in nasal IL-4, IL-5 and IFNγ<br>Nonsignificant differences in $IL4^+/CD4^+$ PBMCs. | 2 |

LE, level of evidence; Pts, patients; RC, rhinoconjunctivitis.

the clinical efficacy of AIT with dog extracts due to the use of low-quality extracts, the variability of their allergenicity and the complexity of the allergenic profile of dogs. Regarding IAT with cat extracts, the literature consulted showed both clinical and laboratory improvements. However, although there are double-blind placebo-controlled, randomized clinical trials, not all have an optimal design and the number of patients enrolled was limited. Furthermore, as it is known, each IT product is different, and so it is likely that the results achieved with a particular product cannot be extrapolated to all other products on the market with the same allergen.

This document is intended to be a tool to aid in decision-making by professionals who care for people with dog or cat allergy when

establishing diagnostic and therapeutic strategies, and thus improving the quality of life of the people who suffer from them. However, we believe that there is still work to be carried out due to the lack of conclusive evidence in some regards such as the benefits of early exposure, the course of sensitization, the repercussions of allergy to pollen or mites, the significance of cross-reactivity and polysensitization, molecular diagnosis and IT.

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## AUTHOR CONTRIBUTIONS

All the authors of this document have intellectually contributed in this work and have read and approved the final version. They comply with the corresponding ethical considerations in this kind of work.

## CONFLICTS OF INTEREST

Dr. Dávila reports personal fees from STALLERGENES, personal fees from ALK, grants and personal fees from THERMOFISHER DIAGNOSTICS, during the conduct of the study; personal fees from NOVARTIS, personal fees from SANOFI, personal fees from ASTRAZENECA, outside the submitted work. Dr. Dominguez-Ortega reports personal fees from STALLERGENES, personal fees from ALK, personal fees from LETI, personal fees from GSK, personal fees from TEVA, personal fees from ASTRA ZENECA, personal fees from MUNDIPHARMA, personal fees from ZAMBON, outside the submitted work. Dr. Navarro reports personal fees from STALLERGENES, ALK, MEDA, LETI, TEVA, GSK, MERCK, CHIESI, ASTRA ZENECA, ORION, FAES, MUNDIPHARMA, MSD, MENARINI, ALLERGY THERAPEUTICS. Dr. Antolín-Amérigo reports grants from MERK-Serono-Fundación 2000, other from DIATER LABORATORIOS, other from LETI LABORATORIOS, other from NOVARTIS, other from SANDOZ, other from GSK, other from ASTRA ZENECA, other from MUNDIPHARMA, other from MERCK, other from STALLERGENES, grants from PFIZER, other from ALK, other from MEDA, other from STALLERGENES, outside the submitted work. Dr. Eloina reports personal fees from ALK, personal fees from MERK, personal fees from STALLERGENES outside the submitted work. The rest of the authors declare that they have no relevant conflict of interests.

## REFERENCES

1. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. *J Allergy Clin Immunol*. 2014;134:350-359.
2. Simpson A, Custovic A. Pets and the development of allergic sensitization. *Curr Allergy Asthma Rep*. 2005;5:212-220.
3. McBride D, Keil T, Grabenhenrich L, et al. The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol*. 2012;23:230-239.
4. Burr ML, Limb ES, Andrae S, Barry DM, Nagel F. Childhood asthma in four countries: a comparative survey. *Int J Epidemiol*. 1994;23:341-347.
5. Heinzerling LM, Burbach GJ, Edenharter G, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy*. 2009;64:1498-1506.
6. Konradsen JR, Fujisawa T, van Hage M, et al. Allergy to furry animals: new insights, diagnostic approaches, and challenges. *J Allergy Clin Immunol*. 2015;135:616-625.
7. de Moral Gregorio A, Carretero Aníbarro P, Mateo Borrega M, Zapata Yébenes J. Capítulo 20: Principales alérgenos de interior. En: Dávila González IJ, Jáuregui Presa I, Olaguíbel Rivera JM, Zubeldia Ortuño JM, eds. *Tratado de Alergología*. 2ª edn, Tomo 1. Madrid, Spain: Ergón, 2015; 287-310.
8. Quirce S. Asthma in Alergológica-2005. *J Investig Allergol Clin Immunol*. 2009;19(Suppl 2):14-20.
9. Oxford Centre for Evidence-Based Medicine (OCEBM). Levels of Evidence Document 2009 (accessed on December 2016).
10. Nilsson OB, van Hage M, Gronlund H. Mammalian-derived respiratory allergens - implications for diagnosis and therapy of individuals allergic to furry animals. *Methods*. 2014;66:86-95.
11. Smith DM, Coop CA. Dog allergen immunotherapy: past, present, and future. *Ann Allergy Asthma Immunol*. 2016;116:188-193.
12. Basagaña M, Luengo O, Labrador M, et al. Component-Resolved Diagnosis of Dog Allergy. *J Investig Allergol Clin Immunol*. 2017;27:185-187.
13. Ukleja-Sokołowska N, Gawrońska-Ukleja E, Żbikowska-Gotz M, et al. Analysis of feline and canine allergen components in patients sensitized to pets. *Allergy Asthma Clin Immunol*. 2016;12:61.
14. Portnoy J, Kennedy K, Sublett J, et al. Environmental assessment and exposure control: a practice parameter–furry animals. *Ann Allergy Asthma Immunol*. 2012;108:223.e1-223.e15.
15. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol*. 2016;27(Suppl 23):1-250.
16. Liccardi G, Passalacqua G, Salzillo A, et al. Is sensitization to furry animals an independent allergic phenotype in nonoccupationally exposed individuals? *J Investig Allergol Clin Immunol*. 2011;21:137-141.
17. Cabanas R, Lopez-Serrano MC, Carreira J, et al. Importance of albumin in cross-reactivity among cat, dog and horse allergens. *J Investig Allergol Clin Immunol*. 2000;10:71-77.
18. Hentges F, Leonard C, Arumugam K, Hilger C. Immune responses to inhalant Mammalian allergens. *Front Immunol*. 2014;5:234.
19. Nilsson OB, Binnmyr J, Zoltowska A, Saarne T, van Hage M, Gronlund H. Characterization of the dog lipocalin allergen Can f 6: the role in cross-reactivity with cat and horse. *Allergy*. 2012;67:751-757.
20. Basagaña M, Bartolomé B, Pastor C, et al. Allergy to human seminal fluid: cross-reactivity with dog dander. *J Allergy Clin Immunol*. 2008;121:233-239.
21. Shah R, Grammer LC. Chapter 1: an overview of allergens. *Allergy Asthma Proc*. 2012;33(Suppl 1):S2-S5.
22. Esch RE. Allergen source materials and quality control of allergenic extracts. *Methods*. 1997;13:2-13.
23. Curin M, Reininger R, Swoboda I, Focke M, Valenta R, Spitzauer S. Skin prick test extracts for dog allergy diagnosis show considerable variations regarding the content of major and minor dog allergens. *Int Arch Allergy Immunol*. 2011;154:258-263.

24. Hamilton RG, Matsson P, Chan S, et al. Analytical performance characteristics, quality assurance and clinical utility of immunological assays for human immunoglobulin E (IgE) antibodies of defined allergen specificities. approved guideline CLSI. In. Third ed.
25. Asha'ari ZA, Suhaimi Y, Yusof RA, Rushdan I, Maraina CH. Comparison of serum specific IgE with skin prick test in the diagnosis of allergy in Malaysia. *Med J Malaysia*. 2011;66:202-206.
26. Valenta R, Lidholm J, Niederberger V, Hayek B, Kraft D, Grönlund H. The recombinant allergen-based concept of component-resolved diagnostics and immunotherapy (CRD and CRIT). *Clin Exp Allergy*. 1999;29:896-904.
27. Liccardi G, Bilo MB, Manzi F, Piccolo A, Di Maro E, Salzillo A. What could be the role of molecular-based allergy diagnostics in detecting the risk of developing allergic sensitization to furry animals? *Eur Ann Allergy Clin Immunol*. 2015;47:163-167.
28. Konradsen JR, Nordlund B, Onell A, Borres MP, Gronlund H, Hedlin G. Severe childhood asthma and allergy to furry animals: refined assessment using molecular-based allergy diagnostics. *Pediatr Allergy Immunol*. 2014;25:187-192.
29. Uriarte SA, Sastre J. Clinical relevance of molecular diagnosis in pet allergy. *Allergy*. 2016;71:1066-1068.
30. Scadding GW, Eifan A, Penagos M, et al. Local and systemic effects of cat allergen nasal provocation. *Clin Exp Allergy*. 2015;45:613-623.
31. Lodge CJ, Allen KJ, Lowe AJ, et al. Perinatal cat and dog exposure and the risk of asthma and allergy in the urban environment: a systematic review of longitudinal studies. *Clin Dev Immunol*. 2012;2012:176484.
32. Collin SM, Granell R, Westgarth C, et al. Pet ownership is associated with increased risk of non-atopic asthma and reduced risk of atopy in childhood: findings from a UK birth cohort. *Clin Exp Allergy*. 2015;45:200-210.
33. Park YB, Mo EK, Lee JY, et al. Association between pet ownership and the sensitization to pet allergens in adults with various allergic diseases. *Allergy Asthma Immunol Res*. 2013;5:295-300.
34. Pyrhonen K, Nayha S, Laara E. Dog and cat exposure and respective pet allergy in early childhood. *Pediatr Allergy Immunol*. 2015;26:247-255.
35. Asarnoj A, Hamsten C, Wadén K, et al. Sensitization to cat and dog allergen molecules in childhood and prediction of symptoms of cat and dog allergy in adolescence: A BAMSE/MeDALL study. *J Allergy Clin Immunol*. 2016;137:813-821.
36. Perfetti L, Hebert J, Lapalme Y, Ghezzo H, Gautrin D, Malo JL. Changes in IgE-mediated allergy to ubiquitous inhalants after removal from or diminution of exposure to the agent causing occupational asthma. *Clin Exp Allergy*. 1998;28:66-73.
37. Nordlund B, Konradsen JR, Kull I, et al. IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobin are markers of bronchial inflammation in severe childhood asthma. *Allergy*. 2012;67:661-669.
38. Grönlund H, Adédoyin J, Reininger R, et al. Higher immunoglobulin E antibody levels to recombinant Fel d 1 in cat-allergic children with asthma compared with rhinoconjunctivitis. *Clin Exp Allergy*. 2008;38:1275-1281.
39. Sabbah A, Lauret MG, Chene J, Boutet S, Drouet M. The pork-cat syndrome or crossed allergy between pork meat and cat epithelia (2). *Allerg Immunol (Paris)*. 1994;26:177-180.
40. Adédoyin J, Grönlund H, Oman H, Johansson SG, van Hage M. Cat IgA, representative of new carbohydrate cross-reactive allergens. *J Allergy Clin Immunol*. 2007;119:640-645.
41. van Nunen S. Tick-induced allergies: mammalian meat allergy, tick anaphylaxis and their significance. *Asia Pac Allergy*. 2015;5:3-16.
42. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol*. 2007;25:3644-3648.
43. Grönlund H, Adédoyin J, Commins SP, Platts-Mills TA, van Hage M. The carbohydrate galactose-alpha-1,3-galactose is a major IgE-binding epitope on cat IgA. *J Allergy Clin Immunol*. 2009;123:1189-1191.
44. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol*. 2012;26:1045-1060.
45. Pelucchi C, Galeone C, Bach JF, La Vecchia C, Chatenoud L. Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. *J Allergy Clin Immunol*. 2013;132:616-622.
46. Gern JE, Reardon CL, Hoffjan S, et al. Effects of dog ownership and genotype on immune development and atopy in infancy. *J Allergy Clin Immunol*. 2004;113:307-314.
47. Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. *Arch Dermatol*. 2007;143:1570-1577.
48. Lodge CJ, Lowe AJ, Gurrin LC, et al. Pets at birth do not increase allergic disease in at-risk children. *Clin Exp Allergy*. 2012;42:1377-1385.
49. Nafstad P, Magnus P, Gaarder PI, Jaakkola JJ. Exposure to pets and atopy-related diseases in the first 4 years of life. *Allergy*. 2001;56:307-312.
50. Brunekreef B, Von Mutius E, Wong G, et al. Exposure to cats and dogs, and symptoms of asthma, rhinoconjunctivitis, and eczema. *Epidemiology*. 2012;23:742-750.
51. Zirngibl A, Franke K, Gehring U, et al. Exposure to pets and atopic dermatitis during the first two years of life. A cohort study. *Pediatr Allergy Immunol*. 2002;13:394-401.
52. Bufford JD, Reardon CL, Li Z, et al. Effects of dog ownership in early childhood on immune development and atopic diseases. *Clin Exp Allergy*. 2008;38:1635-1643.
53. Waser M, von Mutius E, Riedler J, et al. Exposure to pets, and the association with hay fever, asthma, and atopic sensitization in rural children. *Allergy*. 2005;60:177-184.
54. Song SJ, Lauber C, Costello EK, et al. Cohabiting family members share microbiota with one another and with their dogs. *Elife*. 2013;2:813-821.
55. Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL. Natural history of sensitization, symptoms and occupational diseases in apprentices exposed to laboratory animals. *Eur Respir J*. 2001;17:904-908.
56. Knoeller GE, Mazurek JM, Moorman JE. Health-related quality of life among adults with work-related asthma in the United States. *Qual Life Res*. 2013;22:771-780.
57. Butt A, Rashid D, Lockey RF. Do hypoallergenic cats and dogs exist? *Ann Allergy Asthma Immunol*. 2012;108:74-76.
58. Kilburn S, Lasserson TJ, McKean M. Pet allergen control measures for allergic asthma in children and adults. *Cochrane Database Syst Rev*. 2003:CD002989.
59. Custovic A, Simpson A. The role of inhalant allergens in allergic airways disease. *J Investig Allergol Clin Immunol*. 2012;22:393-401.
60. Crocker DD, Kinyota S, Dumitru GG, et al. Effectiveness of home-based, multi-trigger, multicomponent interventions with an environmental focus for reducing asthma morbidity: a community guide systematic review. *Am J Prev Med*. 2011;41:S5-S32.
61. Custovic A, Green R, Fletcher A, et al. Aerodynamic properties of the major dog allergen Can f 1: distribution in homes, concentration, and particle size of allergen in the air. *Am J Respir Crit Care Med*. 1997;155:94-98.
62. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. *Am J Respir Crit Care Med*. 1998;158:115-120.
63. Krouse HJ. Environmental controls and avoidance measures. *Int Forum Allergy Rhinol*. 2014;4(Suppl 2):S32-S34.
64. Barnes CS, Kennedy K, Johnson L, et al. Use of dilute sodium hypochlorite spray and home cleaning to reduce indoor allergen

levels and improve asthma health parameters. *Ann Allergy Asthma Immunol*. 2008;101:551-552.
65. Ichikawa K, Iwasaki E, Baba M, Chapman MD. High prevalence of sensitization to cat allergen among Japanese children with asthma, living without cats. *Clin Exp Allergy*. 1999;29:754-761.
66. Sanchez J, Diez S, Cardona R. Pet avoidance in allergy cases: Is it possible to implement it? *Biomedica*. 2015;35:357-362.
67. Luczynska CM, Li Y, Chapman MD, Platts-Mills TA. Airborne concentrations and particle size distribution of allergen derived from domestic cats (Felis domesticus). Measurements using cascade impactor, liquid impinger, and a two-site monoclonal antibody assay for Fel d I. *Am Rev Respir Dis*. 1990;141:361-367.
68. Vredegoor DW, Willemse T, Chapman MD, Heederik DJ, Krop EJ. Can f 1 levels in hair and homes of different dog breeds: lack of evidence to describe any dog breed as hypoallergenic. *J Allergy Clin Immunol*. 2012;130:904-909.
69. Smallwood J, Ownby D. Exposure to dog allergens and subsequent allergic sensitization: an updated review. *Curr Allergy Asthma Rep*. 2012;12:424-428.
70. Valovirta E, Koivikko A, Vanto T, Viander M, Ingeman L. Immunotherapy in allergy to dog: a double-blind clinical study. *Ann Allergy*. 1984;53:85-88.
71. Hedlin G, Graff-Lonnevig V, Heilborn H, et al. Immunotherapy with cat- and dog-dander extracts. II. In vivo and in vitro immunologic effects observed in a 1-year double-blind placebo study. *J Allergy Clin Immunol*. 1986;77:488-496.
72. Lent AM, Harbeck R, Strand M, et al. Immunologic response to administration of standardized dog allergen extract at differing doses. *J Allergy Clin Immunol*. 2006;118:1249-1256.
73. Sundin B, Lilja G, Graff-Lonnevig V, et al. Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma. *J Allergy Clin Immunol*. 1986;77:478-487.
74. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy*. 1997;27:860-867.
75. Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Blanco-Quiros A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. *J Allergy Clin Immunol*. 1994;93:556-566.
76. Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind, placebo-controlled immunotherapy dose-response study with standardized cat extract. *J Allergy Clin Immunol*. 2003;111:155-161.
77. Nanda A, O'Connor M, Anand M, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. *J Allergy Clin Immunol*. 2004;114:1339-1344.
78. Bertelsen A, Andersen JB, Christensen J, Ingemann L, Kristensen T, Ostergaard PA. Immunotherapy with dog and cat extracts in children. *Allergy*. 1989;44:330-335.
79. Hedlin G, Heilborn H, Lilja G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J Allergy Clin Immunol*. 1995;96:879-885.
80. Alvarez-Cuesta E, Berges-Gimeno P, Gonzalez-Mancebo E, Fernandez-Caldas E, Cuesta-Herranz J, Casanovas M. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study. *Allergy*. 2007;62:810-817.
81. Norman PS, Ohman JL, Long AA, et al. Treatment of cat allergy with T-cell reactive peptides. *Am J Respir Crit Care Med*. 1996;154:1623-1628.
82. Oldfield WL, Larché M, Kay AB. Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial. *Lancet*. 2002;360:47-53.
83. Worm M, Lee HH, Kleine-Tebbe J, et al. Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. *J Allergy Clin Immunol*. 2011;127:89-97.
84. Patel D, Couroux P, Hickey P, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol*. 2013;131:103-109.
85. Couroux P, Patel D, Armstrong K, Larche M, Hafner RP. Fel d 1-derived synthetic peptide immuno-regulatory epitopes show a long-term treatment effect in cat allergic subjects. *Clin Exp Allergy*. 2015;45:974-981.
86. Larché M, Patel D, Patel P. Safety and efficacy of Fel d 1 derived peptide immunotherapy in a double-blind, placebo-controlled environmental exposure chamber (EEC) study. *Allergy*. 2012;67(Suppl 96):1-97.
87. Senti G, Crameri R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol*. 2012;129:1290-1296.
88. Saarne T, Kaiser L, Grönlund H, Rasool O, Gafvelin G, van Hage-Hamsten M. Rational design of hypoallergens applied to the major cat allergen Fel d 1. *Clin Exp Allergy*. 2005;35:657-663.
89. Saarne T, Neimert-Andersson T, Grönlund H, Jutel M, Gafvelin G, van Hage M. Treatment with a Fel d 1 hypoallergen reduces allergic responses in a mouse model for cat allergy. *Allergy*. 2011;66:255-263.
90. Nilsson OB, Adedoyin J, Rhyner C, et al. In vitro evolution of allergy vaccine candidates, with maintained structure, but reduced B cell and T cell activation capacity. *PLoS One*. 2011;6:e24558.
91. Schmitz N, Dietmeier K, Bauer M, et al. Displaying Fel d1 on virus-like particles prevents reactogenicity despite greatly enhanced immunogenicity: a novel therapy for cat allergy. *J Exp Med*. 2009;206:1941-1955.
92. Niespodziana K, Focke-Tejkl M, Linhart B, et al. A hypoallergenic cat vaccine based on Fel d 1-derived peptides fused to hepatitis B PreS. *J Allergy Clin Immunol*. 2011;127:1562-1570.
93. Zhu D, Kepley CL, Zhang K, Terada T, Yamada T, Saxon A. A chimeric human-cat fusion protein blocks cat-induced allergy. *Nat Med*. 2005;11:446-449.
94. Terada T, Zhang K, Belperio J, Londhe V, Saxon A. A chimeric human-cat Fcgamma-Fel d1 fusion protein inhibits systemic, pulmonary, and cutaneous allergic reactivity to intratracheal challenge in mice sensitized to Fel d1, the major cat allergen. *Clin Immunol*. 2006;120:45-56.
95. Jeffery LE, Burke F, Mura M, et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol*. 2009;183:5458-5467.
96. Grundström J, Neimert-Andersson T, Kemi C, et al. Covalent coupling of vitamin D3 to the major cat allergen Fel d 1 improves the effects of allergen-specific immunotherapy in a mouse model for cat allergy. *Int Arch Allergy Immunol*. 2012;157:136-146.
97. Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol*. 2010;125:383-389.
98. Khurana T, Newman-Lindsay S, Young PR, Slater JE. The NPC2 protein: a novel dog allergen. *Ann Allergy Asthma Immunol*. 2016;116:440-446.
99. Hilger C, Swiontek K, Arumugam K, Lehners C, Hentges F. Identification of a new major dog allergen highly cross-reactive with Fel d 4 in a population of cat- and dog-sensitized patients. *J Allergy Clin Immunol*. 2012;129:1149-1151.
100. Sublett JW, Bernstein JA. Characterization of patients with suspected seminal plasma hypersensitivity. *Allergy Asthma Proc*. 2011;32:467-471.

101. Basagaña M, Bartolome B, Pastor-Vargas C, Mattsson L, Lidholm J, Labrador-Horrillo M. Involvement of Can f 5 in a case of human seminal plasma allergy. *Int Arch Allergy Immunol*. 2012;159:143-146.
102. Camelo-Nunes IC, Sole D. Allergic rhinitis: indicators of quality of life. *J Bras Pneumol*. 2010;36:124-133.
103. Everhart RS, Kopel SJ, Esteban CA, et al. Allergic rhinitis quality of life in urban children with asthma. *Ann Allergy Asthma Immunol*. 2014;112:365-370.
104. Custovic A, Murray CS, Gore RB, Woodcock A. Controlling indoor allergens. *Ann Allergy Asthma Immunol*. 2002;88:432-441.
105. Janson C, Kalm-Stephens P, Foucard T, Norback D, Alving K, Nordvall SL. Exhaled nitric oxide levels in school children in relation to IgE sensitisation and window pane condensation. *Respir Med*. 2005;99:1015-1021.
106. Almqvist C, Wickman M, Perfetti L, et al. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med*. 2001;163:694-698.
107. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136:556-568.
108. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol*. 1998;102:558-562.
109. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127:S1-S55.
110. Valovirta E, Viander M, Koivikko A, Vanto T, Ingeman L. Immunotherapy in allergy to dog. Immunologic and clinical findings of a double-blind study. *Ann Allergy*. 1986;57:173-179.
111. Bucur J, Dreborg S, Einarsson R, Ljungstedt-Pahlman I, Nilsson JE, Persson G. Immunotherapy with dog and cat allergen preparations in dog-sensitive and cat-sensitive asthmatics. *Ann Allergy*. 1989;62:355-361.
112. Lilja G, Sundin B, Graff-Lonnevig V, et al. Immunotherapy with cat- and dog-dander extracts. IV. Effects of 2 years of treatment. *J Allergy Clin Immunol*. 1989;83:37-44.
113. Hedlin G, Graff-Lonnevig V, Heilborn H, et al. Immunotherapy with cat- and dog-dander extracts. V. Effects of 3 years of treatment. *J Allergy Clin Immunol*. 1991;87:955-964.
114. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, et al. Immunotherapy for cat asthma. *J Allergy Clin Immunol*. 1988;82:1055-1068.


## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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