PURINA Institute

Advancing Science for Pet Health

# A TRANSFORMATIONAL APPROACH

## To Managing Fel d 1, The Major Cat Allergen

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Allergies to cats are the most common animal-origin allergies in humans and can impair quality of life for allergy sufferers by interfering with daily activities as well as performance at work and school. They can also limit the interactions between the allergic person and their cat, and allergy to cats is a commonly provided reason for relinquishment to shelters as well as a barrier to cat adoption and ownership.

Based on more than a decade of research, a novel approach uses a feline diet that neutralizes the major cat allergen, Fel d 1, in the cat's mouth as (s)he chews the food: neutralized Fel d 1 is unable to trigger an allergic response. This cat-safe approach provides a means of reducing allergenic Fel d 1 through the simple act of feeding. As part of a comprehensive allergen management plan, this approach can help reduce the major cat allergen while keeping the cat in its loving home.

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# THE ROLE OF FEL D 1 IN HUMAN ALLERGIES TO CATS

Allergies to cats are the most common mammal-origin allergy in humans,[1-3] affect 7-25% of the population, and represent a growing public health concern as these rates increase.[3-5] The prevalence of cat allergy varies among countries,[5] but it is estimated that approximately 1 in 5 adults worldwide are affected.[1-3]

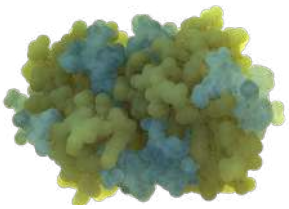
To date, eight cat allergens have been identified and registered through the World Health Organization/International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-Committee.[1,6] **Fel d 1 is the major cat allergen, accounting for up to 96% of human allergic sensitization to cats and 60-100% of the overall antigenicity of cats and cat dander.**[1,4,5,7-9] It was first identified as a major cat allergen in the early 1970s.[10]

**Table 1:** Human sensitization rates to feline-origin allergens. (Excerpted from EAACI Molecular Allergology User's Guide 2.0)[7]

| Allergen | Biochemical name | Prevalance of allergen-specific IgE among human patients (%) | Molecular weight (kDa) |
|---|---|---|---|
| Fel d 1 | secretoglobin | >90 | 18 |
| Fel d 2 | serum albumin | 14-23 | 69 |
| Fel d 3 | cystatin-A | 10 | 11 |
| Fel d 4 | lipocalin | 63 | 22 |
| Fel d 5 | immunoglobulin A | 20-40 | 400 |
| Fel d 6 | immunoglobulin B | not reported | 800-1000 |
| Fel d 7 | lipocalin | 38 | 17.5 |
| Fel d 8 | latherin | 19 | 24 |

**All cats produce Fel d 1** regardless of breed, age, hair (length, color or pattern), sex (male or female; neutered or intact), housing (indoors vs outdoors), or body weight; there are no truly allergen-free or hypoallergenic cats.[1,5,11-14] Fel d 1 production varies widely among individual cats, and may vary widely throughout the year in the same cat.[11,15] Bastien et al[11] observed an 80-fold difference in salivary Fel d 1 levels between the lowest-producing and highest-producing cats in a 64-cat group, and up to a 76-fold difference between the lowest and highest salivary Fel d 1 levels in individual cats over the course of a year. Studies have shown that male cats produce 3-5 times less Fel d 1 after neutering; these findings, combined with observations that Fel d 1 production could be restored to pre-neutering levels with the administration of exogenous testosterone, suggest an influential role of testosterone on Fel d 1 production.[1,2]

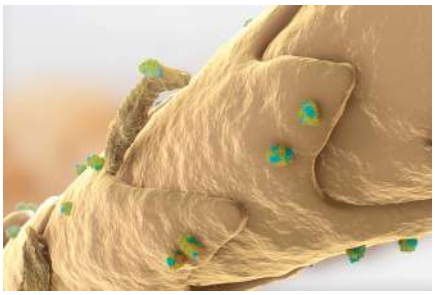
All cats, even hairless cats, produce Fel d 1



Fel d 1

Fel d 1's function for the cat has not been definitively determined, but proposed roles include pheromone/chemical signaling, epithelial defense, lipid regulation and immunoregulation.[16-18]

Fel d 1 easily becomes and remains airborne in dander and dust particles; up to 60% of Fel d 1 is carried by particles less than 5 microns in diameter.[1,5] Fel d 1's molecular structure also allows it to stick to many surfaces such as clothing, carpet and upholstered furniture. As a result, the allergen is ubiquitous and has been documented in private vehicles as well as public transportation and buildings at levels that exceed the threshold value associated with sensitization and may worsen allergic symptoms in sensitized individuals.[1,2,4,8,19-22]



Fel d 1 on hair shaft

## CONSEQUENCES OF HUMAN ALLERGIES TO CATS

### Consequences for the human allergy sufferer

Exposure to Fel d 1 can induce nasal and ocular allergy symptoms and can induce asthma symptoms in some individuals. Aside from the clinical symptoms, allergies to cats can also lead to poor sleep quality, fatigue, reduced alertness, lower work productivity and concentration, and mood changes.[23] These impairments may result not only from the allergic condition itself, but also from undesired effects of medications taken for symptom prevention and relief.

### Consequences for the human-animal bond

Cats serve as sources of emotional support, particularly when a strong human-animal bond is present.[24] Cats tend to interact more frequently with people who are available, accessible, and attentive.[25-27] Reduction in any of these factors due to allergen avoidance measures and restricted access to humans could be detrimental for the cat. For example, isolating a cat to one room or an area of the house, excluding a cat from areas commonly inhabited by their bonded humans, and/or reducing interaction time due to cat allergies may deprive the cat of social interactions and lead to a more distant relationship that fails to meet the cat's and/or the owner's needs.[25,28,29] Shorter interaction time between the cat and owner in an attempt to reduce allergen exposure may be associated with reduced relationship quality, diminished attachment, and a compromised perception of the emotional support received from the cat.[29]

### Consequences for cat health and welfare

Allergy to cats directly impacts cat welfare because allergy is a commonly provided reason for relinquishment of cats to shelters[30-34] as well as a barrier to cat adoption and ownership.[30,35]

Inadequate housing and/or handling (e.g., due to attempts to reduce allergen exposure) that fails to meet the cat's needs regarding their micro- and macroenvironment can compromise cats' welfare.[36,37] Poor welfare may contribute to physical deterioration, chronic physiologic stress, illness, and behavioral problems such as house soiling and spraying, aggression and repetitive or destructive behaviors,[36-39] which may lead to an increased risk of relinquishment.[39,40]

## APPROACHES FOR MANAGING CAT ALLERGIES

There are varying options available for individuals looking to find a solution for their cat-related allergies. These range from cleaning supplies to help manage allergen levels in the home to medical intervention for the allergy sufferer. Each of these has varying levels of efficacy, associated cost, and validated scientific support. Combining methods provides better results.[5,9,41,42]

**Research has shown that a combination of methods can have the greatest impact on reducing allergens.**[5,9,41,42]

## Preventive measures

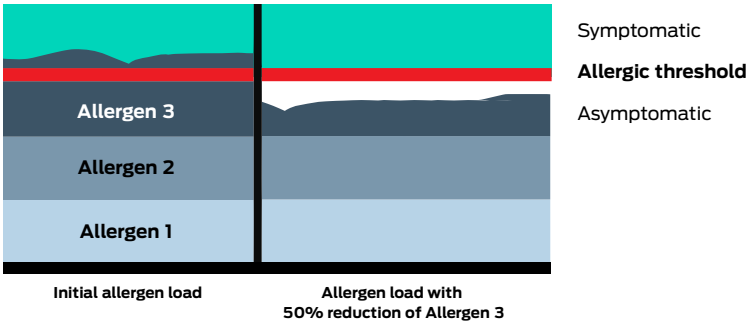
- **Primary prevention:** To date, there is no consensus regarding animal exposure and preventing later onset of asthma or other allergic diseases.[5]
- **Pharmaceutical management:** Patients with a known cat allergy may prevent or mitigate the symptoms with medications.
- **Immunotherapy:** While immunotherapy has been in use for more than 100 years, there is limited evidence regarding its efficacy cat allergies.[43]
- **"Hypoallergenic" cats:** So-called "hypoallergenic pets" have been marketed to allergy sufferers, but their clinical relevance has never been demonstrated.[5,12] While anecdotal evidence may suggest some breeds of cats tend to be less allergenic to some individuals, there are currently no scientifically proven breeds of hypoallergenic dogs or cats.[12] Genetic modification is another method that has been suggested for the creation of truly hypoallergenic cats; two genome-edited cats produced using the CRISPR-Cas9 system to modify the genetic code for Fel d 1 showed significantly reduced Fel d 1 levels compared to a normal cat.[44] Further research is indicated to evaluate the viability and animal welfare impacts of this approach.

## Environmental management and intervention

Individuals who are polysensitized (allergic to two or more allergens) will often show more severe symptoms than mono-sensitized individuals when exposed to environmental allergens, indicating that allergens have an additive effect.[45,46] This reinforces the concept of total allergen load, which represents the sum of the individual allergens in the environment at that time. If the total allergen load exceeds an individual's allergic threshold, that individual develops allergic symptoms.

If the allergen load can be reduced by avoiding or reducing exposure to one or more of the contributing allergens, the cumulative level of allergen exposure may fall below an individual's threshold and improve or prevent allergy symptoms.[45,46] This may be achieved in a number of ways, including complete avoidance of the allergen, altering the immune response to the allergen, and reducing the levels of the offending allergen(s). Combination strategies to reduce allergen exposure are generally more successful.[5,9]

The concept of the allergic threshold. In this case, the sensitized individual is exposed to two allergens (1 and 2) at relatively consistent levels in their home but not at cumulative levels that reach or exceed the individual's allergic threshold. However, sensitization to Allergen 3 sufficiently increases the allergen load that it exceeds the threshold and the individual becomes symptomatic (left side). The right side represents the allergic load if Allergen 3 is reduced by approximately 50%. The allergens do not need to be eliminated to produce clinical relief; relief is experienced when the allergic load is reduced and remains below the allergic threshold.



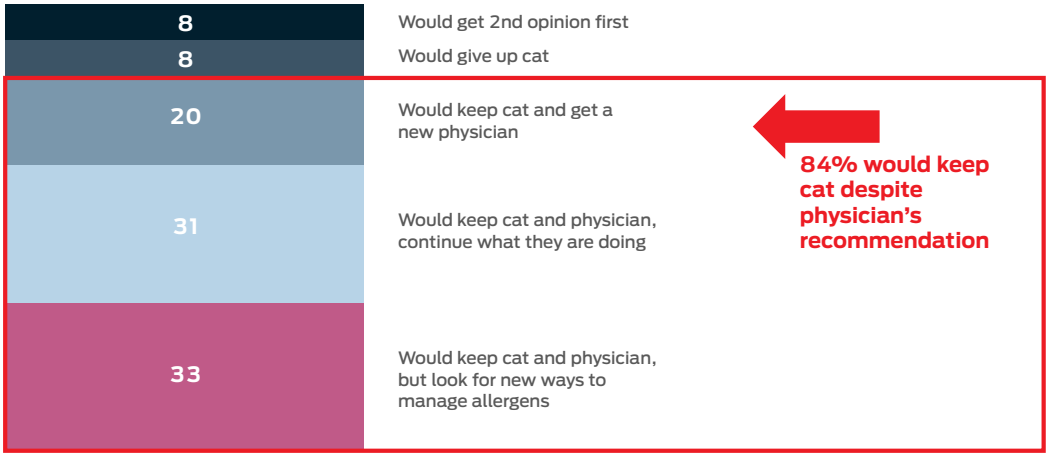

### *Allergen avoidance*

The most common allergist recommendation for those suffering from allergies to cats is to remove the cat from the home, thereby avoiding the allergen.[5,9,14] This measure is not supported by evidence[5,9,14,47] and many cat owners refuse or fail to comply.[5,48-51] Pets are often considered part of the family[52] and removing a pet from the home is associated with emotional consequences that many, if not most, pet owners are unwilling to accept. A study of 341 adults diagnosed as allergic to dogs or cats revealed that only 21% complied with the recommendation and removed their pet from the home.[49] In addition, in a subset of 122 subjects whose pet had died since the patient's pet allergy diagnosis, 70% had acquired a new pet.[49] A recent survey of 1,002 cat-allergic cat owners showed that 84% would

keep their cat despite their physician's recommendation, including 20% who replied they would keep their cat but find a new physician.[53]

**Many pet owners accept the physical discomfort associated with their allergic symptoms in order to keep their pets.[49,61]**

**Reaction to physician's advice to remove cat from home**




Fel d 1 is a "sticky" allergen and it may take months for symptoms to improve following removal of the cat from the household, particularly if the household is carpeted.[42] Wood et al[42] observed that up to 20 weeks were required following removal of the cat for Fel d 1 levels to reduce to those found in homes without cats. In addition, the ubiquitous nature of Fel d1 makes it nearly impossible to avoid the allergen altogether, even if there is no cat in the home.

When patients refuse to comply with the recommendation to remove the cat(s) from the home, commonly proposed compromises include excluding the cat(s) from the bedroom and other frequently used areas of the home, and restricting the cat(s) to specific rooms or areas of the house.[5] Although these measures can reduce allergen exposure, they may reduce the frequency, duration, and quality of owner-cat interactions and can compromise cat health and welfare as previously described.

### *Environmental controls*

Environmental control measures are also recommended in order to reduce environmental allergen levels, and measures implemented in cat-sensitized households may include keeping the cat outdoors;[9] using HEPA filters in vacuums and HVAC systems;[5,9,14] removing carpets;[9,41,42] removing or covering upholstered furniture;[5,42] and regular, intensive cleaning.[41,42]

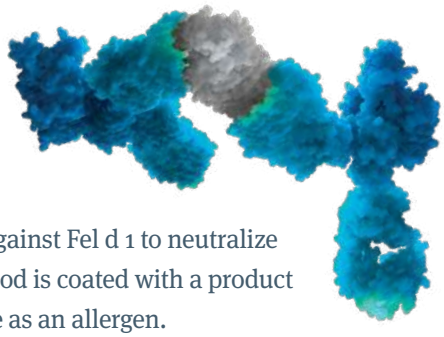
Although these measures may reduce the allergen load,[41] they are effort-intensive, costly, and may be difficult to sustain long-term.[47] In addition, the effects may be transient.[9,14]

### *Bathing the cat*

Allergists' recommendations may include washing the cat to physically remove allergens from its hair.[1,5,54,55] This recommendation has poor compliance,[41] due largely to the feline species' aversion to bathing. In addition, although immersion bathing is effective for lowering allergen levels on the cat's hair, the effects of bathing are transient; allergen levels return to baseline within 24 hours of bathing.[1,14,54,55]

# A TRANSFORMATIONAL NUTRITIONAL APPROACH TO MANAGING FEL D 1

Fel d 1 bound by two anti-Fel d 1 IgY



A new approach developed by Nestlé Purina scientists leverages avian-origin IgY antibodies against Fel d 1 to neutralize it after its production but before it enters the environment. A complete and balanced dry cat food is coated with a product containing anti-Fel d 1 IgY that binds and neutralizes the allergen, rendering it unrecognizable as an allergen.

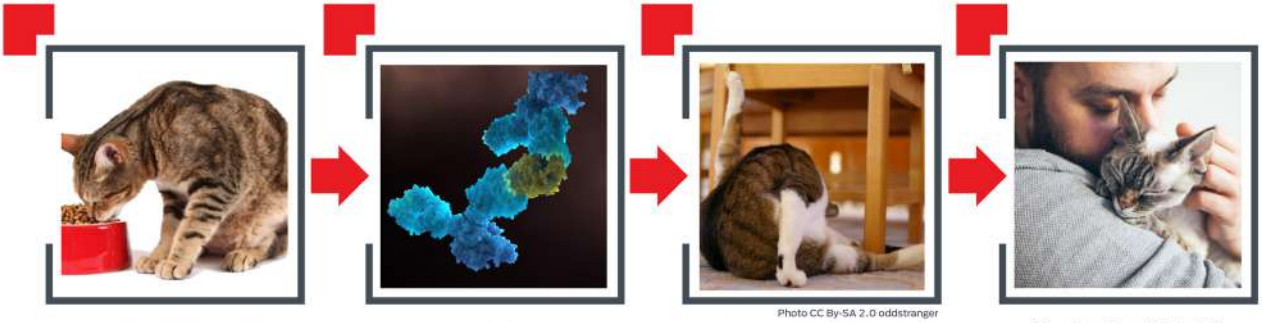


Photo CC By-SA 2.0 oddstranger

Cat eats diet coated with an egg product containing anti-Fel d 1 IgY antibodies

Anti-Fel d 1 IgY binds to salivary Fel d 1 in the cat's mouth as the cat chews the food

During grooming, neutralized Fel d 1 is distributed on the cat's hair and skin

Neutralized Fel d 1 is no longer recognizable as an allergen when released into the environment

## Anti-Fel d 1 IgY

Egg products containing specifically targeted IgY, an avian-origin immunoglobulin comparable to mammalian IgG, have been used safely in human and veterinary medicine.[56-59] This approach uses a concentrated IgY that targets and binds Fel d 1.

## Anti-Fel d 1 IgY effectively neutralizes active Fel d 1 in vitro and ex vivo

Anti-Fel d 1 IgY blocked the binding of salivary Fel d 1 to Fel d 1-specific IgE in a dose-dependent manner and prevented mast cell degranulation.[60]

## Anti-Fel d 1 IgY is safe for cats

Many cat owners view their cats as part of the family[24,52] and will often go to great lengths to keep their cat in the home despite allergies.[61] However, although many allergic owners will compromise their own health to keep their cat, they are unlikely to accept approaches that they feel may put their cat's health and well-being at risk.

The anti-Fel d 1 IgY is safe for cats, based on a comprehensive safety study that fed an egg product ingredient with multiple levels of anti-Fel d 1 IgY, including levels many times higher than those used in efficacy studies.[62] A subsequent study confirmed the ingredient's safety for kittens.[63]

Because the biological function of Fel d 1 is not definitively known, the potential health and welfare effects of stopping its production are also unknown. Based on the principle of allergen load reduction, complete elimination of Fel d 1 production is not necessary. **This approach does not neutralize 100% of the cat's Fel d 1.** Cats produce varying levels of Fel d 1 depending on neuter status, sex, and genetics and can be healthy regardless of their Fel d 1 levels;[15] our approach preserves some biologically available Fel d 1 while reducing the active allergen.

## Diet coated with anti-Fel d 1 IgY reduces active Fel d 1 in cats' saliva

Salivary active (allergenic) Fel d 1 was significantly reduced by Week 3 in the cats receiving the diet coated with anti-Fel d 1 IgY.[64]

## Diet coated with anti-Fel d 1 IgY reduces active Fel d 1 on cats' hair

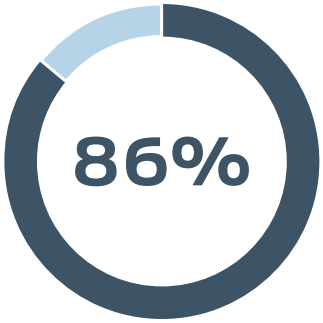
Fel d 1 (active and neutralized forms) originating in the saliva is distributed on the cat's hair during grooming and enters the environment through shed hair and dander; therefore, the next step in the validation process was to determine the effects of anti-Fel d 1 IgY on active Fel d 1 levels in the cat's hair and dander.

Active Fel d 1 levels in the hair and dander collected by brushing were significantly reduced starting in Week 3 of the test period and sustained their reduced levels for the remainder of the treatment period. The reduction in active Fel d 1 ranged from 31-77%, with an average reduction of 47%.[65]

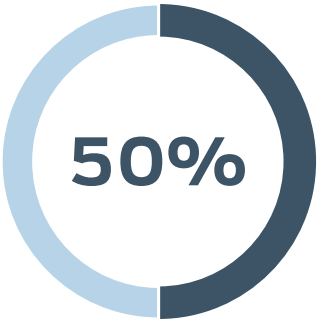
## Preserving the human-animal bond

In an open-label, survey-based trial, 82.5% of veterinary team participants with self-reported allergy to cats reported improvements in perceived quality of life and allergen management after feeding their cats the diet coated with anti-Fel d 1 IgY. Improvements were most commonly observed starting in the fourth week of feeding the diet. In addition, respondents reported they were more able to interact physically with their cat(s) as much as they wanted to and they were able to be as close to their cats as they wanted to be.[66]

**Beginning in the third week of feeding a diet coated with an egg product containing anti-Fel d 1 IgY:**

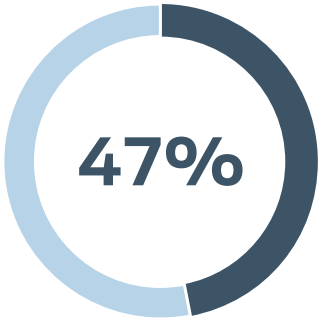



of cats showed at least 30% reduction in active Fel d 1




of cats showed at least 50% reduction in active Fel d 1

**Active Fel d 1 on hair and dander was significantly reduced starting with the third week of feeding the diet, and continued through the end of the study.**




average reduction in active Fel d 1 levels (weeks 3-10) (range 33-71%)

## Cat diet coated with anti-Fel d 1 IgY reduces the allergic response in sensitized individuals

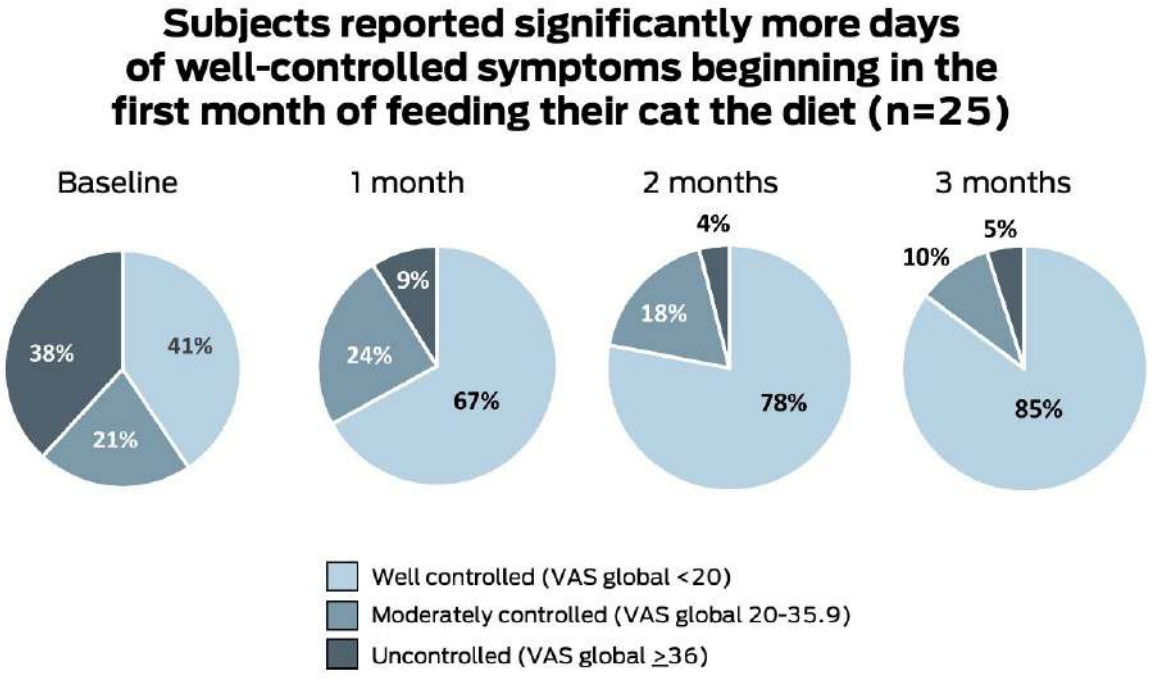
### *Environmental chamber study*

Reducing the levels of active Fel d 1 in a cat's saliva and hair can reduce the amount of cat allergens shed into the environment on hair and dander, thereby reducing the total allergen load in the environment. If the allergen load is reduced to a level below the individual's allergic threshold, clinical allergy symptoms may be prevented.

A pilot study utilizing individual environmental chambers demonstrated that feeding cats a diet with an egg product ingredient containing anti-Fel d 1 IgY decreased the environmental Fel d 1 levels in a controlled environment and produced a significant improvement in Total Nasal Symptom Score and some ocular symptoms in cat-allergic human subjects.[67]

### *Test diet coated with anti-Fel d 1 IgY reduces overall, nasal, and ocular symptoms and increases well-controlled symptom days in cat-allergic individuals*

An open-label proof-of-concept study using MASK-air®, a mobile health app, evaluated allergic symptoms in 42 cat allergen-sensitized individuals while their cats were fed the diet coated with anti-Fel d 1 IgY for 4 months.[68] The visual analog scale (VAS) for global (overall) allergy symptoms was significantly improved. The VAS scores for nose, eye, and asthma symptoms were significantly improved by the end of the first month of feeding the test diet. The combined percentage of moderately controlled and uncontrolled symptom days (VAS >20/100) decreased from 64% at baseline to 35% at one month and 14% at 3 months.



When presented with a cat-allergic, cat-owning patient, allergists are often compelled to recommend removal of the cat from the home in order to reduce the environmental allergen load and relieve clinical symptoms of allergy. However, this recommendation is often met with resistance because cat owners consider their cats to be members of the family and are not willing to re-home or relinquish their cat.

Based on more than a decade of research, this new approach uses a complete and balanced dry feline diet that neutralizes Fel d 1 in the cat's mouth as (s)he chews the food: neutralized Fel d 1 is unable to trigger an allergic response. This reduces active Fel d 1 in the cat's saliva and on their shed hair and dander, subsequently reducing active Fel d 1 in the environment and improving clinical symptoms in cat-sensitized individuals. This cat-safe approach provides a means of reducing allergenic Fel d 1 through the simple act of feeding. **As part of a comprehensive allergen management plan, this approach can help reduce the major cat allergen while keeping the cat in its loving home.**

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