

(control) infants who had a median TEWL of 10.82 (*FLG* non-AE infants had a median TEWL of 15.99). This implies that *FLG* mutations are associated with barrier dysfunction, but WT individuals with AE may not have significant measurable barrier dysfunction—so what role are emollients designed to replace lipids playing in these individuals? We congratulate the group on its findings and look forward to follow-up data of this cohort and similar studies addressing potential topical sensitization.

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Reply

To the Editor:

We thank Leitch et al¹ for their interest in our pilot study for atopic dermatitis prevention using emollients. Their group made some suggestions for improving our larger studies that are currently in development. In our pilot study,² we offered participants a choice of an oil, a cream/gel, and an ointment to determine parental preferences. They suggest using 1 emollient intervention (rather than several) to reduce variability.

We agree that that approach reduces variability. Indeed, 1 current study under way will use just 1 emollient or 2 very similar emollients to offer parents some degree of choice. A price is paid, however, for this design decision—reduced participant choice, which could affect recruitment and adherence, and reduced generalizability of the results. Surprisingly, there are few patient-oriented outcome data that support the superiority of one emollient over another. A second study is under way that will provide a choice of emollients. Leitch et al¹ also suggest avoiding non-ointment emollient formulations to reduce sensitization to excipients. Our group prefers ointment-based emollients to avoid sensitizers that are more likely to be present in cream formulations, but our parent preference data found that parents prefer creams or gels. After consultation with experts, we chose our emollients on the basis of safety data and formulation, and chose emollients with data from pediatric populations.

Leitch et al¹ also mention that our recruitment strategies were different between countries, which was true. As designed, we gathered important information regarding various recruitment strategies in different settings to help us plan the follow-up trials. They also mention that the prevalence of filaggrin (*FLG*) mutations seemed low in our study of high-risk individuals. Although we did

not gather precise racial or ethnic data on our small cohort, we did have participants of African American and Asian descent—2 populations with *FLG* mutations that would not have been picked up by our *FLG* screening. Our larger studies in progress have more in-depth characterization of the populations with expanded *FLG* screening.

Last, Leitch et al¹ question why participants without *FLG* mutations would be included in a prevention trial using emollients. The answer is 2-fold. First, *FLG* mutations may not be the only barrier defect that leads to atopic dermatitis.³ Second, emollients exert an anti-inflammatory effect and may repair barrier defects induced by early inflammatory skin infiltrates. Thus, emollients address many different pathways leading to atopic dermatitis—they correct *FLG*-barrier defects, they correct skin barrier defects caused by genes yet to be characterized, they may correct skin barrier defects caused by environmental insults (such as overbathing or allergen exposure), and they blunt early inflammatory skin responses in predisposed individuals. A very recent cohort study by Kelleher et al⁴ found that the presence of barrier dysfunction at age 2 months strongly correlated with the development of atopic dermatitis regardless of *FLG* mutation status. These findings argue against screening for *FLG* mutations when determining who would benefit from emollient therapy. Larger trials in various populations are under way to further characterize this promising approach.

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The risk of sensitization to furry animals in patients already sensitized to cat/dog: An *in vitro* evaluation using molecular-based allergy diagnostics

To the Editor:

We greatly appreciate the recent article by Konradsen et al¹ dealing with the important topic of allergic sensitization to furry animals. However, we noticed the lack of information on the risk of developing allergic sensitization to “other” furry animals in subjects already sensitized to common pets (cats/dogs [c/d]).

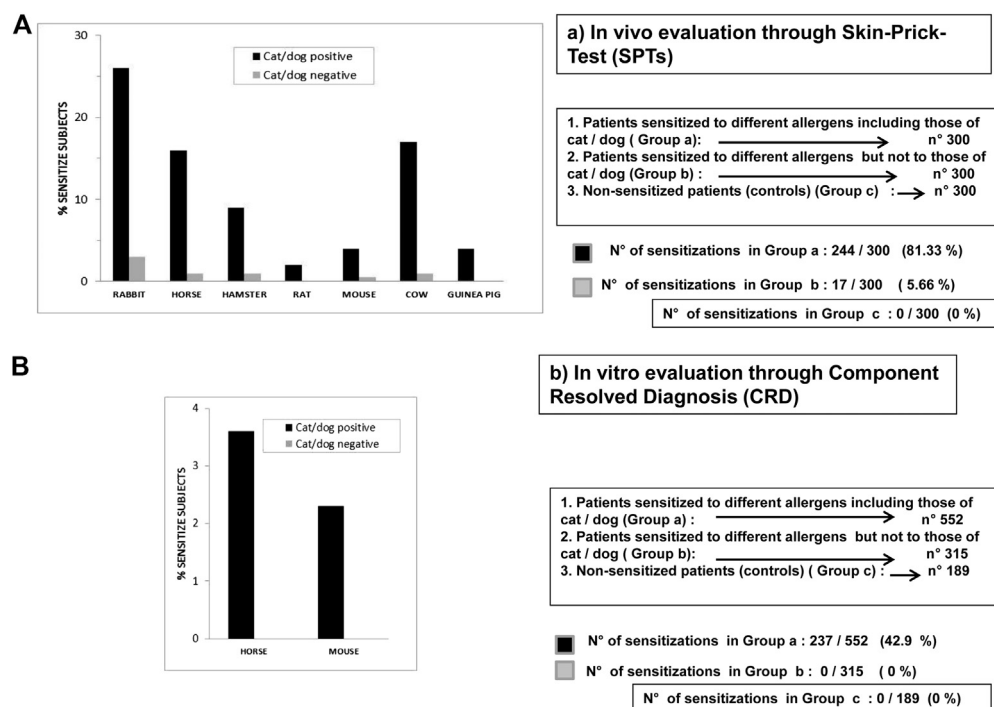


FIG 1. Sensitization to some furry animals in individuals sensitized or not to cat and/or dog. A comparison between the use of skin prick tests (A) and component-resolved diagnosis (B). Fig 1, A is reprinted with permission from Liccardi et al.⁴

In addition to c/d, in all industrialized countries, more and more people become owners of less common or “exotic” animals especially mammals.²

The key question is: how can we estimate the risk of sensitization after exposure to furry animals (eg, small mammals as pets or horses for leisure/sport) in patients already sensitized to c/d or in those having already removed common pets from their homes? These issues are particularly crucial if the pet-sensitized patients are children who wish to own a new pet (eg, hamsters, rabbits, and guinea pigs) or to come into contact with big animals in other settings such as zoos, circuses, and farms.

We have previously shown that allergic sensitization to furry animals such as rabbits, hamsters, guinea pigs, rats, horses, cows, and mouse is also frequent in individuals without direct contact³ and that allergic sensitization to c/d, evaluated by skin prick tests, increases by about 14-fold the risk of developing sensitization to these furry animals.⁴ We thought to evaluate whether the same results could be obtained by using component-resolved diagnosis, which allows the mapping of some cross-reacting allergens such as lipocalins.^{5,6} We retrospectively evaluated specific IgE data obtained with the microarray technique ImmunoCAP ISAC (Thermo Fisher Scientific-Immuno-Diagnostics, Uppsala, Sweden) in 741 subjects referred to the Allergy Unit of Fondazione Salvatore Maugeri in the last 2 years. Patients were divided into the same 3 groups of the previous study⁴: (a) individuals sensitized to different aeroallergens including those of c/d (n = 552), (b) individuals sensitized to different aeroallergens but not to those of c/d (n = 315), and (c) nonsensitized individuals (negative controls) (n = 189).

The sera of subjects with sensitization to c/d (group a) contained IgE to Equ c1 and Mus m1 (42.9%); none of these lipocalins was found in the sera of groups b and c (Fig 1).

Present *in vitro* and previous *in vivo*⁴ data suggest that allergic sensitization to c/d increases the risk of sensitization to horse and mouse because of the presence of lipocalins. Because lipocalins show a certain degree of cross-reactivity,⁵ a similar finding for other furry animals is likely. This risk should be taken into account by susceptible individuals before acquiring new pets after removal of common pets or beginning a contact for working/leisure activity with a common as well as uncommon animal.

As a consequence, skin prick tests and/or evaluation of specific IgE also to less common mammalian allergens could be recommended in these individuals to identify the occurrence of allergic sensitization and consequently to avoid future exposures.⁷ In this context, the use of component-resolved diagnosis might be very useful to evaluate the possibility of sensitization to animal cross-reacting allergens.

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Reply

To the Editor:

We read with great interest the correspondence from Liccardi et al,¹ which adds valuable information to the review on allergy to furry animals recently published in the journal.² Liccardi et al used molecular allergy diagnostics on 741 subjects and found that sensitization to the lipocalins Equ c 1 (from horse) and Mus m 1 (from mouse) occurred only in those subjects who were also sensitized to cats and/or dogs. The authors suggest that allergic sensitization to cats and/or dogs might be a risk factor for sensitization to horse and mouse.

Applying a similar approach, using an experimental research ISAC prototype (Thermo Fisher Scientific, Uppsala, Sweden) containing 111 allergen components,³ we explored the pattern of sensitization to inhalant allergens in a cohort of school-age children (n = 92) with controlled persistent or severe uncontrolled asthma. We found that 60 children (63%) were sensitized to inhalant allergens, including allergens from cats (Fel d 1, 2, 4) and dogs (Can f 1, 2, 3, 5), 14 children (15%) were sensitized to other inhalant allergens, but not allergens from cats and/or dogs, and 21 children (22%) were not sensitized to any inhalant allergen. Twenty-nine children were sensitized to Equ c 1, and all these were also sensitized to allergens from cats and/or dogs, and of these children 72% (21 of 29) were sensitized to both Equ c 1 and Fel d 4. Eight children were sensitized to Mus m 1, and 7 of these were sensitized to cats and/or dogs. All these 7 children were sensitized to Fel d 1, 6 were sensitized to Fel d 4, and 6 were sensitized to Equ c 1. Two patients were Equ c 1 negative and Mus m 1 positive.

In addition, we investigated 694 randomly selected children (age, 11-12 years) from a population-based study in Northern Sweden (The Obstructive Lung Disease in Northern Sweden [OLIN] longitudinal pediatric study) with sensitization to inhalant allergens. Using extract-based methods (Immunocap, Thermo Fisher Scientific), we found that sensitization toward horse occurred in 54% (106/196) of the children who were sensitized to both cats and dogs, in 41% (114 of 281) of those who were sensitized to either cat or dog, and in 10% (8 of 82) of the children without sensitization toward cats and/or dogs.

These Swedish results from *both* a highly selected population of children with persistent or severe asthma and from a

population-based study support the results provided by Liccardi et al to some extent. Sensitization to horse and/or mice seems to be associated with sensitization toward cats and/or dogs, and a likely explanation is cross-reactivity due to the homogeneity between the lipocalins from cat, dog, mouse, and horse. Amino acid identity between Equ c 1 and Fel d 4 is 67%, between Mus m 1 and Fel d 4 is 49%, between Equ c 1 and Can f 6 it is 57%, and between Mus m 1 and Can f 6 is 47%.⁴

However, it should be emphasized that both Liccardi et al's and our data are cross-sectional and it is currently not possible to state that sensitization to cats and/or dogs increases the risk of sensitization to horse and mouse. Furthermore, it is not clear whether this IgE-cross-reactivity is related to clinical symptoms. We have previously shown that IgE antibodies to some lipocalins are more common in severe childhood asthma,⁵ but clearly more studies are needed to clarify whether clinical symptoms are likely to arise upon exposure to horse or mice in this case.

The clinical relevance of low levels of IgE to Equ c 1 or Mus m 1 is also unknown. Low levels of IgE might not give rise to clinical symptoms, but could possibly, upon regular horse or mice contact, contribute to an amplification of the allergic response over time and lead to epitope spreading and ultimately to clinical symptoms.

We certainly do agree with Liccardi et al that more research is needed on the complex relationship between allergen exposure, the development of allergic sensitization, and allergic diseases. One example of the complexity of these processes was shown in a longitudinal analysis from the OLIN studies. In this study, exposure to cats at home protected against sensitization not only toward cats but also in general. Furthermore, the incidence data from OLIN demonstrate that sensitization to an increasing number of allergens is developed throughout childhood.⁶

With this in mind, it is our understanding that to answer the interesting research question posed by Liccardi et al, longitudinal population-based studies with repeated analysis of IgE antibodies and meticulous data on exposure are needed.

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