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# Analysis of allergen specific IgE cut points to cat and dog in the Childhood Allergy Study

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**Background:** The application of a single allergen specific IgE (sIgE) cut point, such as 0.35 kU/L, to determine sensitization for all allergens may be suboptimal.

**Objectives:** To analyze self-reported symptoms suggestive of dog and cat allergy in relation to the test performance characteristics of low level, but reliably detectable, sIgE and to compare these cut points to the traditional 0.35-kU/L cut point.

**Methods:** Interviews and blood samples were collected among 564 young adult participants of a general risk birth cohort. Data collected from the participants' parents were analyzed as validation populations. A history of symptoms consistent with allergy on exposure to pets was obtained by standardized questionnaire. Allergen sIgE levels for dog and cat were evaluated with Pharmacia CAP. Receiver operating characteristic curves were constructed and the performance characteristics of the traditional sIgE cut point of 0.35 kU/L were compared with cut points as low as 0.1 kU/L.

**Results:** Using the Youden J criteria, based on the highest sum of sensitivity and specificity for a diagnostic test, cut points of 0.12 kU/L for cat and 0.2 kU/L for dog were identified as performing optimally among the participant population. In 2 validation populations, consisting of the participants' mothers and fathers, the performance of these alternative cut points were superior or similar to the traditional 0.35-kU/L sIgE level.

**Conclusions:** Accurately measured sIgE at levels approaching the lower limit of detection of current assays may be useful in confirming sensitization. Optimal clinical application of these tests will continue to require careful integration of the result and the strength of the patient's history.

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## INTRODUCTION

Patients often consult an allergist to determine whether symptoms are being triggered by common airborne allergens. After obtaining a detailed medical history, allergists typically perform allergy testing to confirm specific allergen sensitivity consistent with their clinical history. For example, when patients report nasal symptoms on pet exposure, confirmatory tests to assess sensitization to cat or dog are often performed. Testing modalities often include skin testing, but in vitro evaluation of allergen specific IgE (sIgE) levels is preferred when patients are unable to discontinue use of antihistamines,

when widespread skin conditions are present, or if preferred by the patient or clinician.<sup>1</sup>

Historically, in vitro allergen test results have been dichotomously interpreted as positive or negative, at a threshold of 0.35 kU/L of sIgE, a level based primarily on the technical limitations of a first generation of sIgE assays. However, recently the precision and reliability of in vitro IgE detection systems have improved markedly.<sup>2</sup> For example, the Pharmacia CAP system can reliably identify sIgE antibody levels as low as 0.1 kU/L.<sup>3</sup> In this report, we determined the extent to which cat and dog sIgE levels lower than the traditional threshold of 0.35 kU/L correlated with self-reported symptoms associated with exposure to these pets. The data for this analysis were systematically collected as part of an ongoing general risk birth cohort study in suburban Detroit, the Childhood Allergy Study (CAS).

## METHODS

### Population

The CAS was conducted among health maintenance organization (HMO) members in metropolitan Detroit and is a general risk birth cohort study of the natural history and environmental determinants of pediatric allergy. All pregnant HMO members 18 years or older, living in a predefined geographic area, with an estimated date of confinement between April 15, 1987, and August 31, 1989, were invited to participate. Only full-term infants (at least 36 weeks' gestation) were included. Therefore, recruitment was based on

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common characteristics, including HMO membership, delivery date, and geographic location.

Of the 1194 eligible study participants, 953 women provided written consent to participate. Infants from 106 women were not further enrolled because their cord blood was not obtained. Of the remaining 847 infants, 6 had cord blood considered contaminated by maternal blood and 6 more were ineligible at subsequent review of entry criteria. Mothers of the remaining 835 children were asked to complete interviews annually through the age of 6 to 7 years when children were invited to complete a clinic visit. In May 2005, the oldest children reached 18 years of age. After their 18th birthday, children and their parents were contacted to obtain information on allergy symptoms, asthma, and other health and exposure histories through telephone interviews. Teens and parents were then invited to provide blood samples for measurement of total IgE and sIgE, including IgE to cat and dog allergen. There were no exclusions for blood collection, such as concurrent medication use or viral illness, and samples were collected throughout the year at the convenience of participants. Teens and parents did not have their blood drawn on the same day as the interview. All aspects of this research were approved by the institutional human subjects boards of review of all participating institutions.

### *Symptoms*

Participating CAS teens and their parents were asked at the teen's 18-year visit whether they ever developed any of the following symptoms on exposure to cats or dogs: cough, wheeze, chest tightness, shortness of breath, runny/stuffy nose or sneezing, itchy or watery eyes, or hives/itchy red bumps on the skin.

On the basis of these 7 symptoms, study participants were initially classified, *a priori*, into 4 categories (as symptoms ever being present or absent in relation to cat or dog exposure): (1) any pet-related (cat or dog) symptom report (yes to any of the 7 symptoms); (2) set-related rhinoconjunctivitis symptoms (yes to runny/stuffy nose or sneezing and/or itchy or watery eyes); (3) pet-related lower respiratory tract or asthma symptoms (yes to at least 1 of cough, wheeze, chest tightness, and/or shortness of breath); or (4) pet-related skin symptom (yes to hives/itchy red bumps on the skin).

### *sIgE Assessment*

Venous blood was collected for assessment of sIgE and stored at  $-80^{\circ}\text{C}$  until assayed. Measurements of sIgE were performed following the standard manufacturer's protocols using the Phadia UniCAP system (Phadia AB US, Portage, Michigan). Allergen sIgE was analyzed for dog and cat and a battery of other allergens. One percent of all assays were repeated in a different assay run on a different day to provide estimates of interassay reliability. The geometric mean coefficient of interassay variation was 5.9% for all 6 allergens.

### *Analysis*

We created receiver operating characteristic (ROC) curves<sup>4</sup> to evaluate the predictive ability of cat and, separately, dog sIgE

levels in relationship to the gold standard of patient report of symptoms when around cat(s) or dog(s). The curve was constructed by using each unique value of the predictor variable, in our case, pet sIgE as a possible cut point, calculating the corresponding sensitivity and specificity based on that cut point, and then plotting sensitivity vs  $1 - \text{specificity}$ . Using the ROC analysis, we selected the optimal cut point by using the value that maximized the sum of sensitivity plus specificity. This is equivalent to using the Youden J index.<sup>5</sup> We compared the sensitivity and specificity for the selected cut point to the traditional threshold value of 0.35 using the McNemar test.

We present the positive predictive value (PPV) and negative predictive value (NPV) for descriptive purposes. These should be interpreted with care because they depend directly on the prevalence of the disease (symptoms in our case). Individuals were categorized as misclassified if they had an sIgE level greater than or equal to the corresponding cut point and had no symptoms or conversely if they had symptoms but their sIgE level was less than the selected IgE cut point.

Three separate but not independent samples for analysis are included: teen ( $n = 564$ ), mother ( $n = 470$ ), and father ( $n = 364$ ). We decided *a priori* to use these samples as separate analysis data sets and selected the teen data as the sample in which to determine the optimal cut points (sometimes called the training sample). The teen sample was selected for 2 reasons: (1) the teens were the primary focus of the research and (2) they provided the largest sample size. After the analyses were completed for each symptom group among the teens, the mother and father data sets were used for validation.

## **RESULTS**

Five hundred sixty-four teenagers were interviewed about symptoms that occurred concomitantly with pet exposure. Of these, 29.6% (95% confidence interval [CI], 25.9%–33.6%) reported having any symptoms around cats, whereas 11.3% (95% CI, 8.9%–14.3%) reported asthma symptoms around cats, and 4.3% (95% CI, 2.7%–6.3%) reported skin symptoms around cats (Table 1). Only 1 teen reported rhinoconjunctivitis symptoms that had not already been classified as being in the any symptom category around cat; therefore, the rhinoconjunctivitis symptom classification was not meaningfully different from the any symptom category, and we thus excluded that classification group from further analysis. (Tables illustrating data specific for respiratory vs cutaneous symptoms can be viewed in the online supplement.)

Of the 564 teenagers surveyed, 14.5% (95% CI, 11.7%–17.7%) reported any symptoms around dogs, whereas 5.7% (95% CI, 3.9%–7.9%) reported asthma symptoms around dogs, and 3.4% (95% CI, 2.0%–5.2%) reported skin symptoms around dogs (Table 1). Similarly, only 9 teens reported rhinoconjunctivitis symptoms that had not already been classified as having any symptom around dogs; so again, that classification group was excluded from dog analyses. Table 1

Table 1. Prevalence of Symptoms When Exposed to Pets

| Symptoms                                               | No. (%) of patients (95% CI) |                        |                       |
|--------------------------------------------------------|------------------------------|------------------------|-----------------------|
|                                                        | Teen (n = 564)               | Mother (n = 470)       | Father (n = 346)      |
| Individuals reporting symptoms related to cat exposure |                              |                        |                       |
| Any symptoms                                           | 167 (29.6) (25.9–33.6)       | 120 (25.5) (21.6–29.7) | 67 (19.4) (15.3–23.9) |
| Asthma symptoms (cats)                                 | 64 (11.3) (8.9–14.3)         | 73 (15.5) (12.4–19.1)  | 37 (10.7) (7.6–14.4)  |
| Skin symptoms                                          | 24 (4.3) (2.7–6.3)           | 28 (6.0) (4.0–8.5)     | 8 (2.3) (1.0–4.5)     |
| Individuals reporting symptoms related to dog exposure |                              |                        |                       |
| Any symptoms                                           | 82 (14.5) (11.7–17.7)        | 58 (12.3) (9.5–15.7)   | 28 (8.1) (5.4–11.5)   |
| Asthma symptoms                                        | 32 (5.7) (3.9–7.9)           | 40 (8.5) (6.1–11.4)    | 16 (4.6) (2.7–7.4)    |
| Skin symptoms                                          | 19 (3.4) (2.0–5.2)           | 16 (3.4) (2.0–5.5)     | 6 (1.7) (0.6–3.7)     |

Abbreviation: CI, confidence interval.

also gives the prevalence data for the mothers (n = 470) and fathers (n = 346).

Table 2 summarizes results of the ROC analysis using cat sIgE level as a predictor of any of the 7 previously mentioned symptom categories when exposed to cat. The optimal cut point, as selected by the Youden J index (the sum of the sensitivity and specificity) in the teen data, was 0.12 kU/L. As expected, there was greater sensitivity for the 0.12-kU/L cut point of 63.5% (95% CI, 55.7%–70.8%), which was statistically higher than the sensitivity for the traditional 0.35-kU/L cut point of 49.1% (95% CI, 41.3%–56.9%;  $P < .01$ ). The tradeoff for this higher sensitivity was the requisite lower specificity for the 0.12-kU/L cut point of 85.9% (95% CI, 82.1%–89.2%) compared with 91.9% (95% CI, 88.8%–91.4%;  $P < .01$ ) for the 0.35-kU/L cut point. The misclassification rates were identical, again reflecting the inherent inverse relationship between sensitivity and specificity.

Table 3 gives similar results when dog sIgE was analyzed among the teen population. In this case, an optimal cut point of 0.20 kU/L was selected using the Youden J index. Notably, the sensitivity of sIgE was lower for dogs compared with cats across each sIgE cutoff level.

In general, the parental validation population analyses for both cat and dog mirrored that of the teens, with the sensitivity of any sIgE level being lower in the maternal analysis

when compared with teens or fathers (Tables 2 and 3). For example, regarding cat-related symptoms, the sensitivity at the 0.12-kU/L cut point (55%; 95% CI, 45.7%–64.1%) compared favorably with the 0.35-kU/L level (38.3%; 95% CI, 9.6%–47.6%), as did the sum of sensitivity and specificity among the maternal validation population. A similar pattern was also seen among fathers, providing evidence of replication of the lower cut points in the 2 validation populations (Table 2).

The parental validation results for the 0.2-kU/L sIgE cut point for dog-related symptoms among teens showed a similar overall pattern of relative performance. However, in fathers, a slightly higher Youden J index was observed at the traditional 0.35-kU/L level compared with the 0.2-kU/L level, although the difference was minimal (Table 3).

## DISCUSSION

To our knowledge, this is the first article to report the performance characteristics of allergen sIgE levels between 0.1 and 0.35 kU/L in a general risk population. Our data suggest that dog and cat allergen sIgE levels, when applied below the traditional cutoff value of 0.35 kU/L, are related to self-reported symptoms consistent with clinical allergy and yield performance characteristics similar to or slightly better than the traditionally accepted threshold. Accepting somewhat

Table 2. Cat Specific IgE Levels and Prediction of Any Symptom When Exposed to Cats

| IgE cutoff, kU/L      | Sensitivity rate, % (95% CI)  | Specificity rate, % (95% CI)  | Sum of sensitivity and specificity, % | PPV, % (95% CI)  | NPV, % (95% CI)  | Misclassified, % (95% CI) |
|-----------------------|-------------------------------|-------------------------------|---------------------------------------|------------------|------------------|---------------------------|
| Teen sample (n = 564) |                               |                               |                                       |                  |                  |                           |
| 0.12                  | 63.5 (55.7–70.8) <sup>a</sup> | 85.9 (82.1–89.2) <sup>a</sup> | 149.4                                 | 65.4 (57.6–72.7) | 84.8 (80.9–88.2) | 20.7 (17.5–24.3)          |
| 0.35                  | 49.1 (41.3–56.9) <sup>a</sup> | 91.9 (88.8–94.4) <sup>a</sup> | 141                                   | 71.9 (62.7–79.9) | 81.1 (77.2–84.6) | 20.7 (17.5–24.3)          |
| Mothers (n = 470)     |                               |                               |                                       |                  |                  |                           |
| 0.12                  | 55.0 (45.7–64.1) <sup>a</sup> | 87.4 (83.5–90.7) <sup>a</sup> | 142.4                                 | 60.0 (50.2–69.2) | 85.0 (80.9–88.5) | 20.9 (17.3–24.8)          |
| 0.35                  | 38.3 (29.6–47.6) <sup>a</sup> | 92.9 (89.6–95.3) <sup>a</sup> | 131.2                                 | 64.8 (52.5–75.8) | 81.5 (77.3–85.1) | 21.1 (17.5–25.0)          |
| Fathers (n = 346)     |                               |                               |                                       |                  |                  |                           |
| 0.12                  | 68.7 (56.2–79.4) <sup>a</sup> | 87.1 (82.6–90.8) <sup>a</sup> | 155.8                                 | 56.1 (44.7–67.0) | 92.0 (88.1–95.0) | 16.5 (12.7–20.8)          |
| 0.35                  | 52.2 (39.7–64.6) <sup>a</sup> | 93.2 (89.6–95.9) <sup>a</sup> | 145.4                                 | 64.8 (50.6–77.3) | 89.0 (84.9–92.4) | 14.7 (11.2–18.9)          |

Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

<sup>a</sup>  $P < .01$  comparing specific IgE level of 0.12 kU/L with 0.35 kU/L.

Table 3. Dog Specific IgE Levels and Prediction of Any Symptom When Exposed to Dogs

| IgE cutoff, kU/L      | Sensitivity rate, % (95% CI)  | Specificity rate, % (95% CI)  | Sum of sensitivity and specificity, % | PPV, % (95% CI)  | NPV, % (95% CI)  | Misclassified, % (95% CI) |
|-----------------------|-------------------------------|-------------------------------|---------------------------------------|------------------|------------------|---------------------------|
| Teen sample (n = 564) |                               |                               |                                       |                  |                  |                           |
| 0.20                  | 56.1 (44.7–67.0) <sup>a</sup> | 79.5 (75.6–83.0) <sup>a</sup> | 135.6                                 | 31.7 (24.3–40.0) | 91.4 (88.3–93.9) | 23.9 (20.5–27.7)          |
| 0.35                  | 41.5 (30.7–52.9) <sup>a</sup> | 86.1 (82.7–89.1) <sup>a</sup> | 127.6                                 | 33.7 (24.6–43.8) | 89.6 (86.5–92.3) | 20.4 (17.1–24.0)          |
| Mothers (n = 470)     |                               |                               |                                       |                  |                  |                           |
| 0.20                  | 46.6 (33.3–60.1) <sup>b</sup> | 87.6 (84.0–90.6) <sup>a</sup> | 134.2                                 | 34.6 (24.2–46.2) | 92.1 (89.0–94.6) | 17.4 (14.1–21.2)          |
| 0.35                  | 39.7 (27.0–53.4) <sup>b</sup> | 93.0 (90.0–95.2) <sup>a</sup> | 132.7                                 | 44.2 (30.5–58.7) | 91.6 (88.5–94.1) | 13.6 (10.6–17.1)          |
| Fathers (n = 346)     |                               |                               |                                       |                  |                  |                           |
| 0.20                  | 53.6 (33.9–72.5) <sup>c</sup> | 84.3 (79.8–88.1) <sup>a</sup> | 137.9                                 | 23.1 (13.5–35.2) | 95.4 (92.2–97.5) | 18.2 (14.3–22.7)          |
| 0.35                  | 50.0 (30.6–69.4) <sup>c</sup> | 89.0 (85.0–92.2) <sup>a</sup> | 139                                   | 28.6 (16.6–43.3) | 95.3 (92.2–97.4) | 14.2 (10.7–18.3)          |

Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

<sup>a</sup>  $P < .01$  comparing specific IgE level of 0.20 kU/L with 0.35 kU/L.

<sup>b</sup>  $P < .05$  comparing specific IgE level of 0.20 kU/L with 0.35 kU/L.

<sup>c</sup>  $P = .32$ .

lower yet reliably detected IgE levels than traditionally relied on as evidence of allergen sensitization has direct practical implications regarding patient management. Clinicians often evaluate patients who relate convincing histories consistent with allergy when exposed to easily identifiable allergens, such as pets. However, on occasion, the results of confirmatory testing for sensitization, such as skin prick tests (SPTs) or in vitro testing (using the traditional threshold of 0.35 kU/L), are negative, and the clinician may incorrectly conclude that allergen-specific management strategies, such as avoidance or allergen desensitization, are irrelevant and not discuss these potentially beneficial intervention options. For instance, patients with a strong clinical history of cat allergy yet negative skin test results may have detectable specific IgE levels lower than the traditional threshold. Our data imply that it is likely that some of these patients have symptoms that are truly triggered by cat exposure and may benefit from removal of cats from the environment or desensitization either with cat extract alone or as a component of multiallergen immunotherapy.

Our data should not be interpreted as promoting the concept that low levels of IgE should be used indiscriminately or in isolation to diagnose allergy. We view our results as primarily an opportunity to discuss how it may be possible to refine and potentially improve individual patient management based on a suggestive clinical history taken in the context of a situation where confirmatory allergen testing has known limitations. Experts that have closely analyzed the performance characteristics of allergen sIgE tests, even at relatively high levels, continue to caution that “the most prudent use of a positive specific IgE antibody result is as a risk factor for allergic disease and not as a definitive indicator of the presence of allergic disease.”<sup>2</sup> In fact, it is clear that higher levels of allergen sIgE are more likely to be associated with clinical manifestations of allergy.<sup>6,7</sup> However, this does not mean that the presence of low-level IgE should be ignored as evidence of sensitization, especially in the context of a strong clinical

history. We believe these data support the contention that any level of reliably detected allergen sIgE, in the context of a suggestive history, may indicate true sensitization. The degree to which these low levels of IgE are likely to be linked to allergen-triggered symptoms in an individual patient can best be determined by clinicians who can link the test result with the strength of the patient’s history before a decision is made whether avoidance measures or possible desensitization should be recommended or considered. The definitive answer as to “when” or “whether” one can unquestionably link symptoms to allergen exposure is rarely available to the clinician because neither clinical history alone nor sensitization alone is sufficient to unequivocally diagnose allergic disorders, and even when both are present, a reliable diagnosis may remain elusive.<sup>8</sup> Admittedly, self-reported symptom histories are subjective and, as used in this report, may be suboptimal for defining true clinical sensitivity and specificity of in vivo or in vitro testing.<sup>9–12</sup> Practically, one should be willing to accept somewhat lower levels of allergen sIgE as confirmatory when the clinical history is strongly suggestive. Direct allergen challenge tests would be a more suitable method for validating tests, but even these tests have limitations and are not practical in many settings.<sup>13,14</sup>

The 2008 American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology Diagnostic Testing Practice Parameters suggest that in vitro immunoassays have sensitivities averaging 70% to 75% for most allergens when compared with symptoms induced after natural or controlled organ challenge tests.<sup>1</sup> Studies also cite specificity ranging from 30% to 95%.<sup>1,15</sup> In the current analysis, the sensitivity at the 0.35-kU/L level is lower than this estimate with similar specificity when comparing in vitro sIgE testing with reported clinical symptoms. Symptom reports are clearly not equivalent to allergen challenge, and the observed lower sensitivity is likely due to a number of individuals reporting symptoms that mimic allergy but would prove to be irreproducible on allergen challenge.

Similarly, the populations analyzed in allergen challenge studies are likely to differ from our population where symptom reports may relate to clinical conditions that would not be of sufficient effect to prompt evaluation or consideration for allergen challenge. However, the interview data we collected regarding symptoms of pet allergy are similar to the information that would be collected by clinicians in daily practice. However, in practice the timing and recency of symptoms with pet exposure and sIgE measurement would likely be closely correlated.

In vitro tests must discriminate low allergen sIgE levels from nonspecific background binding. Standardization of IgE antibody assays should take into account the quality and performance of the reagents, reproducibility of the test results, and the clinical sensitivity and specificity documented on routine samples.<sup>2,16</sup> Technology has improved remarkably over the years from the initial radioallergosorbent test to the current state-of-the-art, quantitative, third-generation assays (Turbo RAST, Immulite, and ImmunoCAP).<sup>17-19</sup>

However, even among these advanced technologies, there is variability in their ability to detect IgE at the 0.35-kU/L level.<sup>20</sup> In the present analysis we used ImmunoCAP, which has a reported limit of detection of less than 0.1 kU/L for 95% of included allergens.<sup>3</sup> Our data suggest that consideration be given to accepting a lower detectable level of sIgE as evidence of sensitization when the relationship is clearly suggested by history.

To some extent, consideration of low sIgE levels is analogous to the use of intradermal skin tests (IDSTs) when a clinical history of airborne allergen sensitization is suggestive but the results of epicutaneous SPTs are negative or equivocal. It is accepted that the IDST is more sensitive than the SPT.<sup>1,14,21,22</sup> In a recent editorial, Oppenheimer and Marshall<sup>14</sup> address the question of differentiating a true-positive from a false-positive IDST result and emphasize the importance of interpreting this test result in the context of clinical history while recognizing the difficulty allergists face in interpreting the meaning of a positive IDST result paired with a negative SPT result. In fact, an IDST, with inherently lower specificity compared with the SPT, is recommended when the overall intent of the evaluation is to maximize sensitivity, such as in anaphylaxis to medications or stinging insects.<sup>23,24</sup> Similar to the IDST, perhaps the higher level of sensitivity afforded by using lower-than-traditional sIgE levels could also be helpful in the context of supporting recommendations for a diagnostic or therapeutic trial away from suspected high-level workplace allergen exposure.

Our study has several limitations. Self-reported symptoms in response to an interviewer's directed questions regarding pet-related symptoms may lead to different rates of reporting in comparison to an evaluation in a clinician's office where a patient has sought evaluation. Population-based samples likely elicit a less biased distribution of a history of symptoms because it is not based on a patient-prompted office visit. However, the last date of a symptom-pet exposure episode was not collected; thus, a gap in time between such an

episode and sIgE measurement is not known. Provocative challenge to cat or dog would have been preferable for confirming clinical hypersensitivity and as the standard to evaluate IgE test performance. Also, the results of SPTs or IDSTs would have been useful to evaluate in conjunction with the clinical histories and in vitro testing. In addition, the study population was not diverse with regard to geographic location, age group, or ethnicity, which may affect whether these results are reflective of the general population. Finally, we chose to analyze clinical and laboratory data related to only 2 allergens, dog and cat. Typically, patients are aware of times when they are exposed to these pets; therefore, they can more accurately link allergen exposure to symptom onset. It is likely that different allergens would yield different test performance characteristics in terms of best-performing threshold values and their strength of association with clinical symptoms.

In conclusion, we may need to reevaluate a dichotomous view of sIgE cut points. In our opinion, it may be appropriate to accept that any reliably detected level of allergen sIgE, even those somewhat below those traditionally used in clinical practice, may indicate sensitization. Therefore, when the clinical history is strongly suggestive of clinical allergy to a specific allergen, these lower levels of allergen sIgE may be appropriate to use as a criterion to guide individual patient management decisions that rely on allergen identification, including specific allergen avoidance strategies or consideration of allergen immunotherapy.

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eTable 1. Cat specific IgE levels and prediction of 47 any respiratory symptoms around cat

| Cutoff (kU/L)           | Rate (95% CI)          |                        |                  |                  |                  |
|-------------------------|------------------------|------------------------|------------------|------------------|------------------|
|                         | Sensitivity            | Specificity            | PPV              | NPV              | Misclassified    |
| Teen sample (N = 564)   |                        |                        |                  |                  |                  |
| 0.12                    | 76.6 (64.3-86.2)       | 77.4 (73.5-81.0)       | 30.2 (23.3-37.9) | 96.3 (93.9-97.9) | 22.7 (19.3-26.4) |
| 0.35                    | 62.5 (49.5-74.3)<br>** | 85.2 (81.8-88.2)<br>** | 35.1 (26.4-44.6) | 94.7 (92.2-96.6) | 17.4 (14.3-20.8) |
| Mother sample (N = 470) |                        |                        |                  |                  |                  |
| 0.12                    | 65.8 (53.7-76.5)       | 84.4 (80.4-87.8)       | 43.6 (34.2-53.4) | 93.1 (89.9-95.5) | 18.5 (15.1-22.3) |
| 0.35                    | 50.7 (38.7-62.6)<br>** | 91.4 (88.2-94.0)<br>** | 52.1 (39.9-64.1) | 91.0 (87.7-93.6) | 14.9 (11.8-18.4) |
| Father sample (N = 346) |                        |                        |                  |                  |                  |
| 0.12                    | 70.3 (53.0-84.1)       | 82.1 (77.4-86.3)       | 32.1 (22.2-43.4) | 95.8 (92.7-97.9) | 19.1 (15.1-23.7) |
| 0.35                    | 56.8 (39.5-72.9)<br>*  | 89.6 (85.7-92.8)<br>** | 39.6 (26.5-54.0) | 94.5 (91.3-96.8) | 13.9 (10.4-18.0) |

\*\*  $P < .01$ ; \*  $P < .05$  in comparison of 0.12 kU/L to 0.35 kU/L.

eTable 2. Cat specific IgE levels and pr 72 ediction of cutaneous symptoms when around cat\*

| Cutoff (kU/L)           | Rate (95% CI)    |                  |                  |                  |                  |
|-------------------------|------------------|------------------|------------------|------------------|------------------|
|                         | Sensitivity      | Specificity      | PPV              | NPV              | Misclassified    |
| Teen sample (N = 564)   |                  |                  |                  |                  |                  |
| 0.12                    | 95.8 (78.9-99.9) | 74.2 (70.3-77.9) | 14.2 (9.2-20.5)  | 99.8 (98.6-100)  | 24.9 (21.3-28.4) |
| 0.35                    | 87.5 (67.6-97.3) | 82.7 (79.3-85.8) | 18.4 (11.8-26.8) | 99.3 (98.1-99.9) | 17.1 (14.0-20.4) |
| 0.16                    | **               |                  |                  |                  |                  |
| Mother sample (N = 470) |                  |                  |                  |                  |                  |
| 0.12                    | 78.6 (59.0-91.7) | 80.0 (76.0-83.7) | 20.0 (13.0-28.7) | 98.3 (96.4-99.4) | 20.0 (16.5-24.0) |
| 0.35                    | 53.6 (33.9-72.5) | 87.3 (83.8-90.3) | 21.1 (12.3-32.4) | 96.7 (94.5-98.2) | 14.7 (11.6-18.2) |
| ** **                   |                  |                  |                  |                  |                  |
| Father sample (N = 346) |                  |                  |                  |                  |                  |
| 0.12                    | 75.0 (34.9-96.8) | 77.5 (72.7-81.9) | 7.3 (2.7-15.2)   | 99.2 (97.3-99.9) | 22.5 (18.2-27.3) |
| 0.35                    | 75.0 (34.9-96.8) | 85.8 (81.6-89.3) | 11.1 (4.2-22.6)  | 99.3 (97.5-99.9) | 14.5 (10.9-18.6) |
| 0.99                    | **               |                  |                  |                  |                  |

\*\*  $P < .01$ ; \*  $P < .05$  in comparison of 0.12 kU/L to 0.35 kU/L.

eTable 3. Dog specific IgE levels and prediction of 96 any respiratory symptoms around Dog

| Cutoff (kU/L)           | Rate (95% CI)    |                  |                  |                  |                  |
|-------------------------|------------------|------------------|------------------|------------------|------------------|
|                         | Sensitivity      | Specificity      | PPV              | NPV              | Misclassified    |
| Teen sample (N = 564)   |                  |                  |                  |                  |                  |
| 0.2                     | 68.8 (50.0-83.9) | 76.9 (73.1-80.4) | 15.2 (9.8-22.1)  | 97.6 (95.7-98.8) | 23.6 (20.1-27.3) |
| 0.35                    | 50.0 (31.9-68.1) | 84.0 (80.6-87.0) | 15.8 (9.3-24.4)  | 96.5 (94.4-98.0) | 17.9 (14.8-21.3) |
| *                       | **               |                  |                  |                  |                  |
| Mother sample (N = 470) |                  |                  |                  |                  |                  |
| 0.2                     | 60.0 (43.3-75.1) | 87.4 (83.9-90.4) | 30.8 (20.8-42.2) | 95.9 (93.5-97.6) | 14.9 (11.8-18.4) |
| 0.35                    | 52.5 (36.1-68.5) | 92.8 (89.9-95.0) | 40.4 (27.0-54.9) | 95.5 (93.0-97.2) | 10.6 (8.0-13.8)  |
| 0.08                    | **               |                  |                  |                  |                  |
| Father sample (N = 346) |                  |                  |                  |                  |                  |
| 0.2                     | 62.5 (35.4-84.8) | 83.6 (79.1-87.4) | 15.6 (7.8-26.9)  | 97.9 (95.4-99.2) | 17.4 (13.5-21.8) |
| 0.35                    | 56.3 (29.9-80.2) | 88.1 (84.2-91.4) | 18.8 (8.9-32.6)  | 97.6 (95.2-99.0) | 13.3 (9.9-17.4)  |
| 0.32                    | **               |                  |                  |                  |                  |

\*\*  $P < .01$ ; \*  $P < .05$  in comparison of 0.20 kU/L to 0.35 kU/L.

eTable 4. Dog specific 121 IgE levels and prediction of cutaneous symptom around Dog

| Cutoff (kU/L)           | Rate (95% CI)    |                  |                 |                  |                  |
|-------------------------|------------------|------------------|-----------------|------------------|------------------|
|                         | Sensitivity      | Specificity      | PPV             | NPV              | Misclassified    |
| Teen sample (N = 564)   |                  |                  |                 |                  |                  |
| 0.22                    | 78.9 (54.4-93.9) | 78.2 (74.5-81.6) | 11.2 (6.4-17.8) | 99.1 (97.6-99.7) | 21.8 (18.5-25.4) |
| 0.35                    | 63.2 (38.4-83.7) | 83.7 (80.3-86.7) | 11.9 (6.3-19.8) | 98.5 (96.9-99.4) | 17.0 (14.0-20.4) |
| 0.08                    | **               |                  |                 |                  |                  |
| Mother sample (N = 470) |                  |                  |                 |                  |                  |
| 0.22                    | 62.5 (35.4-84.8) | 86.8 (83.3-89.8) | 14.3 (7.1-24.7) | 98.5 (96.8-99.4) | 14.0 (11.0-17.5) |
| 0.35                    | 56.3 (29.9-80.2) | 90.5 (87.5-93.1) | 17.3 (8.2-30.3) | 98.3 (96.6-99.3) | 10.6 (8.0-13.8)  |
| 0.32                    | **               |                  |                 |                  |                  |
| Father sample (N = 346) |                  |                  |                 |                  |                  |
| 0.22                    | 100* (54.1-100)  | 83.5 (79.2-87.3) | 9.7 (3.6-19.9)  | 100* (98.7-100)  | 16.2 (12.5-20.5) |
| 0.35                    | 100* (54.1-100)  | 87.4 (83.3-90.7) | 12.2 (4.6-24.8) | 100* (98.8-100)  | 12.4 (9.1-16.4)  |
| n/a                     | **               |                  |                 |                  |                  |

\*\*  $P < .01$ ; \*  $P < .05$  in comparison of 0.22 kU/L to 0.35 kU/L.