
Optimal skin prick wheal size for diagnosis of cat allergy

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Background: The skin prick test is the diagnostic procedure of choice for determination of immediate hypersensitivity. A wheal diameter of 3 mm or larger is generally accepted as the cutoff for a positive test result, although the validity of this assumption has not been rigorously demonstrated.

Objective: To determine the skin prick wheal size that best identifies clinical allergy to cat.

Methods: Forty-five patients referred for evaluation of rhinoconjunctivitis underwent determination of atopic status by skin testing using the Greer Dermapik device and a combination of other modalities, including history, in vitro determination of specific IgE level, and nasal challenge with standardized cat pelt extract. Parameters evaluated before and after nasal challenge included symptom score and nasal lavage tryptase and prostaglandin D₂ (PGD₂) levels.

Results: The widely accepted 3-mm wheal for a positive skin test result to cat is highly sensitive but only moderately specific for diagnosis of cat allergy as evaluated by history, specific IgE level, postchallenge symptom score, and tryptase and PGD₂ levels. Optimal cutoffs for a positive skin test result to cat based on receiver operating characteristic analysis and 95% positive predictive value were 5.5 mm or greater for each of these parameters. When a true-positive result for cat allergy was defined as a combination of positive history, specific IgE level, postchallenge symptom score, and tryptase and PGD₂ levels and a true-negative result as all of these parameters being negative, a 6-mm cutoff was able to distinguish cat allergic from cat nonallergic individuals.

Conclusion: In a potentially allergic population undergoing skin prick testing with the Greer Dermapik using standardized extracts, a 3-mm skin prick wheal will overestimate the presence of cat allergy. A 6-mm wheal appears to distinguish those individuals who are cat allergic from those who are not.

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INTRODUCTION

The diagnosis of allergic disease is based on a detailed history and physical examination, with demonstration of specific IgE by skin or in vitro tests. References to puncture skin tests have appeared in the European literature since the early 1950s.¹ In the United States, skin prick testing has been the prime diagnostic procedure for confirming allergy for more than 30 years.^{2,3} Skin prick tests have many uses. They are an invaluable tool for the standardization of allergen extracts,^{4,5} evaluation of specific immunotherapy,^{6,7} and pharmacologic studies.⁸ A noted difficulty in utilization of skin prick tests is the wide variation that exists in the interpretation of skin test results among physicians and other investigators.^{9–11} The widely accepted criterion for a positive immediate hypersensitivity skin test result is a 3-mm wheal diameter, yet few scientific data are available to evaluate the validity of this assumption. Furthermore, studies of skin prick tests with histamine demonstrate a wide variation of wheal diameter based on the skin test device used.^{12,13} Thus, a cutoff for a

positive skin test result would only be relevant to the device used for the test.

With the advent of new technologies for not only detecting but also quantifying allergen-specific IgE, such as the Pharmacia-Upjohn CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden), there has been renewed interest in trying to determine whether a positive test result for clinical allergy is related to a threshold amount of specific IgE. This hypothesis has been tested for food allergies, where the double-blind, placebo-controlled food challenge is generally accepted as a gold standard. Sampson and Ho¹⁴ have demonstrated, in children with atopic dermatitis, levels of IgE against peanut, milk, egg, and codfish that will accurately predict a positive response to challenge with these foods. These levels were obtained by calculation of 95% and 90% positive predictive values (PPVs) and negative predictive values (NPVs) using the Bayes theorem with a prevalence of food allergy in their clinic population of 10%. The authors noted that no cutoff level for specific IgE against several other foods could be determined.¹⁴ Cutoff values for skin prick wheal area and serum IgE levels as determined by CAP FEIA (Pharmacia Diagnostics AB) against a variety of inhalant allergens has also been reported.^{15–18} In an Italian study, clinical allergy was determined by history, and results were analyzed by receiver operating characteristic (ROC) analysis.¹⁶ This approach is not as ideal as that used in the studies

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of food allergy by Sampson and Ho,¹⁴ where a true gold standard exists.

Measurement of allergic mediators following nasal challenge with allergen has been used in several studies,^{19–23} but since nasal challenge does not necessarily mimic natural allergen exposure, its use as a gold standard for inhalant allergy is controversial. Thus, most published studies rely on different individual markers for determining true allergic status, including history, symptom score, skin tests, in vitro tests for specific IgE, and measurement of mediators following allergen challenge.^{24,25} The purpose of this study is to validate the scientific basis of the 3-mm wheal as the cutoff for a positive immediate skin test result with the Greer Dermapik (Greer Laboratories, Lenoir, NC) to cat. Because the positive cutoff values determined by Sampson and Ho¹⁴ for serum IgE against peanut, milk, egg, and codfish are all different, it seems unlikely that a single skin prick wheal diameter would serve as a cutoff for a positive test result against different allergens.

PATIENTS AND METHODS

A group of 45 patients with a mean age of 39 years (age range, 25–66 years) took part in a study that was approved by the Institutional Review Board of the Southern California Kaiser Permanente Medical Group. There were 21 men and 24 women. Forty-five patients had a history of rhinoconjunctivitis with or without mild, intermittent asthma. Twenty-one of these individuals had a history of worsening symptoms when exposed to cats. Informed consent was obtained from all 45 patients. Volunteers were enrolled at the time of their first presentation and were excluded only if they had a history of acute or chronic sinusitis, anatomic defects of the nose or sinuses, prior immunotherapy, or a level of asthma severity that required daily inhaled corticosteroids. Only patients without daily exposure to cats were tested. Patients were asked to abstain from using all antihistamines and topical and oral decongestants for 1 week and nasal steroids and cromolyn for 4 weeks.

To ensure consistent potency of allergens, we selected cat pelt at 10,000 BAU/mL (50% glycerin; Hollister-Stier Laboratories, Spokane, WA). Cat extract is a clinically important, well-characterized airborne allergen to which nasal challenge response has been correlated with nasal symptom scores following challenge using an environmental chamber.²⁶ Wood et al²⁷ concluded that a positive skin prick test result and serum IgE result to cat were most often indicative of allergy as evaluated by a natural cat exposure challenge model.

Skin Prick Test

During the first visit, the primary investigator performed skin prick testing on the forearms of patients using the Dermapik device. A true prick technique without twisting was used as recommended by the vendor. The subject was blinded to the composition of the extract being tested. All subjects per-

formed peak flows before and after nasal challenge. The difference between the average net orthogonal diameters of the skin prick wheal induced by allergen and the negative saline control was measured after 20 minutes.

Nasal Challenge Study Design

The technique for nasal challenge has been described previously.^{19,28} Except for one study using the maximal cat allergen dose of 625 BAU/mL,²⁶ to our knowledge, there have been no prior studies using standardized extracts. Patients were able to tolerate starting doses of the standardized cat extract at 1,000 BAU/mL without any significant adverse effects. This shortened the nasal challenge procedure to a total of only 2 dilutions (1,000 BAU and 10,000 BAU/mL), which improved patient recruitment.

After acclimatizing patients for 30 minutes in the testing area, 4 nasal lavages were performed with 5 mL of isotonic sodium chloride solution at room temperature. To preserve nasal airway patency and prevent elevation of nasal airway resistance, 0.05% oxymetazoline hydrochloride (Schering Corp, Kenilworth, NJ) was randomly sprayed into one nostril. This has previously been shown to not effect mediator release.²⁹ Control challenge was performed after 5 minutes with 0.2 mL of diluent (sterile saline with 0.03% human albumin and 0.4% phenol), followed in 10 minutes by nasal lavage with 5 mL of isotonic sodium chloride solution. The nasal secretions were collected through a plastic funnel held under the nose, draining into a polystyrene tube. This was followed by antigen challenge, and symptom score was determined after 10 minutes. If the symptom score was less than 5, a second challenge was performed with a 10-fold increase of the allergen dose. Nasal washes were placed on ice and processed immediately. Specimens were agitated by pipetting and vortex spinning to break up mucus plugs and were immediately centrifuged at 4° C for 15 minutes at 25,000 rpm. The solution was separated from the bottom gel phase and stored at –20° C. Samples were frozen and thawed only once.

Measurement of Prostaglandin D₂

Prostaglandin D₂ (PGD₂) was assayed by enzyme immunoassay using a commercially available kit (Cayman Chemical, Ann Arbor, MI) according to the method of Macclouf et al.³⁰ The limit of detection is 30 pg/mL, and an increase of more than twice the baseline has been considered to be a positive result.²⁴

Measurement of Tryptase

The concentration of tryptase in nasal lavage fluid was assayed using the Pharmacia-Upjohn UniCAP system (Kalamazoo, MI). The samples were assayed according to the protocol provided by the vendor. The concentration of mast cell tryptase in all prechallenge nasal lavage samples was below the detection limit of 1.0 µg/L. Tryptase concentrations of more than 2 µg/L in the postchallenge samples were considered to be a positive result.^{22,23}

Table 1. Postchallenge Symptom Score*

Symptoms	Score†
Sneezing	
3–4	1
≥5	3
Rhinorrhea	
Anterior and moderate	1
Posterior	1
Both symptoms	2
Important anterior and posterior	3
Nasal blockade	
Breathe freely	0
Difficult breathing	1
One nostril blocked	2
Both nostrils blocked	3
Pruritus	
Nose only	1
Palate and/or ear	1
Eyes	1

* Data are from Lebel et al.²⁴

† Scores range from 1 to 12.

Specific IgE

The Pharmacia CAP FEIA method was used to detect allergen-specific IgE. A value greater than or equal to 0.35 kU_A/L was considered indicative of the presence of allergen specific IgE.

Symptom Score

Evaluation of symptoms, including sneezing, rhinorrhea, nasal block, or nasal, ocular, ear, or palate pruritus, was determined at baseline, after diluent, and after allergen challenges based on the Lebel scoring system (Table 1).²⁴ Symptom scores, including sneeze counts, were recorded for each patient, and a score of 5 or more points was considered significant for a positive response.

ROC Curves

Optimal skin prick wheal cutoffs were determined using ROC curves, constructed by plotting sensitivity vs 1 – specificity at various skin prick wheal diameters using the True Epistat computer program.³¹ True-positive and true-negative designations were based on the following references: clinical history, IgE level, postchallenge symptom score, mast cell tryptase level, and PGD₂ level.

PPVs and NPVs

Both PPVs and NPVs^{14,31} were calculated using Bayes theorem based on a prevalence of respiratory allergy in our clinic population of 69%. We derived this number from the clinical evaluation during a 1-year period of 100 randomly reviewed patient records. Optimal skin prick wheal cutoffs based on 95% PPV and 95% NPV were extrapolated from a plot of PPV or NPV vs skin prick wheal diameter.

RESULTS

The raw data for all patients are given in Table 2. There were 24 patients with a negative history of cat sensitivity. All 24 had negative cat specific IgE results by CAP FEIA (<0.35 KU_A/L) Twenty-one of these 24 individuals had completely negative nasal challenges, 1 patient had an elevated symptom score without a measurable increase in mediators, and 2 others had a rise in PGD₂ but not tryptase or symptom score following nasal challenge. All but 3 (wheal sizes 5, 6, and 7 mm, respectively) of these 24 subjects had skin wheal diameters less than 3 mm (data not shown). Of the 21 patients with a history of cat allergy, 16 had skin prick wheal diameters of 6 mm or greater. Eleven history-positive patients had cat specific IgE levels by CAP FEIA at least 0.35 kU_A/L and completely positive nasal challenges as evaluated by positive symptom scores and significant postchallenge increases in tryptase and PGD₂ levels. All 11 of these individuals had skin

Table 2. Distribution of Measurements of History, Symptom Score, and Cat Specific IgE, Tryptase, and PGD₂ Levels in Patients Undergoing Nasal Challenge with Cat Pelt Extract*

No. of patients	Clinical history	Symptom score	Specific IgE	Tryptase	PGD ₂	Average skin prick wheal size, mm	
						<6	≥6
11	Positive	Positive	Positive	Positive	Positive	0	11
1	Positive	Positive	Positive	Positive	Negative	0	1
1	Positive	Positive	Positive	Negative	Positive	0	1
1	Positive	Positive	Negative	Positive	Positive	1	0
1	Positive	Positive	Positive	Negative	Negative	0	1
1	Positive	Positive	Negative	Negative	Positive	0	1
1	Positive	Negative	Positive	Positive	Negative	1	0
1	Positive	Positive	Negative	Negative	Negative	1	0
3	Positive	Negative	Negative	Negative	Negative	2	1
1	Negative	Positive	Negative	Negative	Negative	1	0
2	Negative	Negative	Negative	Negative	Positive	0	2
21	Negative	Negative	Negative	Negative	Negative	21	0

Abbreviation: PGD₂, prostaglandin D₂.

* Only the permutations representing our 44 patients are shown.

Table 3. Sensitivity and Specificity of Skin Prick Test to Cat Dander Using a 3-mm Wheal Diameter Cutoff

Standard	Sensitivity, %	Specificity, %	Efficiency, %	PPV, %	NPV, %
History	85.7	70.8	84.4	86.7	69.0
Symptom score	100	74.1	91.1	89.6	100
Specific IgE	93.3	63.3	82.2	85.0	80.9
Tryptase	91.7	57.6	73.3	82.8	75.7
PGD ₂	100	69.0	86.7	87.8	100

Abbreviations: NPV, negative predictive value; PGD₂, prostaglandin D₂; PPV, positive predictive value.

prick wheal diameters of 6 mm or greater. One patient with a history of cat allergy, a positive nasal challenge result, and a negative cat specific IgE result by CAP FEIA (<0.35 KU_A/L) had a skin prick wheal diameter to cat extract of 5.5 mm.

Table 3 illustrates the performance of the traditional 3-mm wheal criterion for a positive skin test result to cat using, alternately, history, symptom score, and specific IgE, post-challenge nasal tryptase, and PGD₂ levels as reference stan-

dards. The data indicate that the widely used 3-mm cutoff exhibits excellent sensitivity but only fair specificity.

Figure 1 and Table 4 demonstrate the determination of optimal decision points for a positive skin test result using ROC analysis. The optimal cutoff wheal diameter for a positive skin test result to cat dander was 6.0 mm using specific IgE, post-challenge tryptase, or PGD₂ levels or 5.5 mm using symptom or clinical history as reference standards for cat allergy.

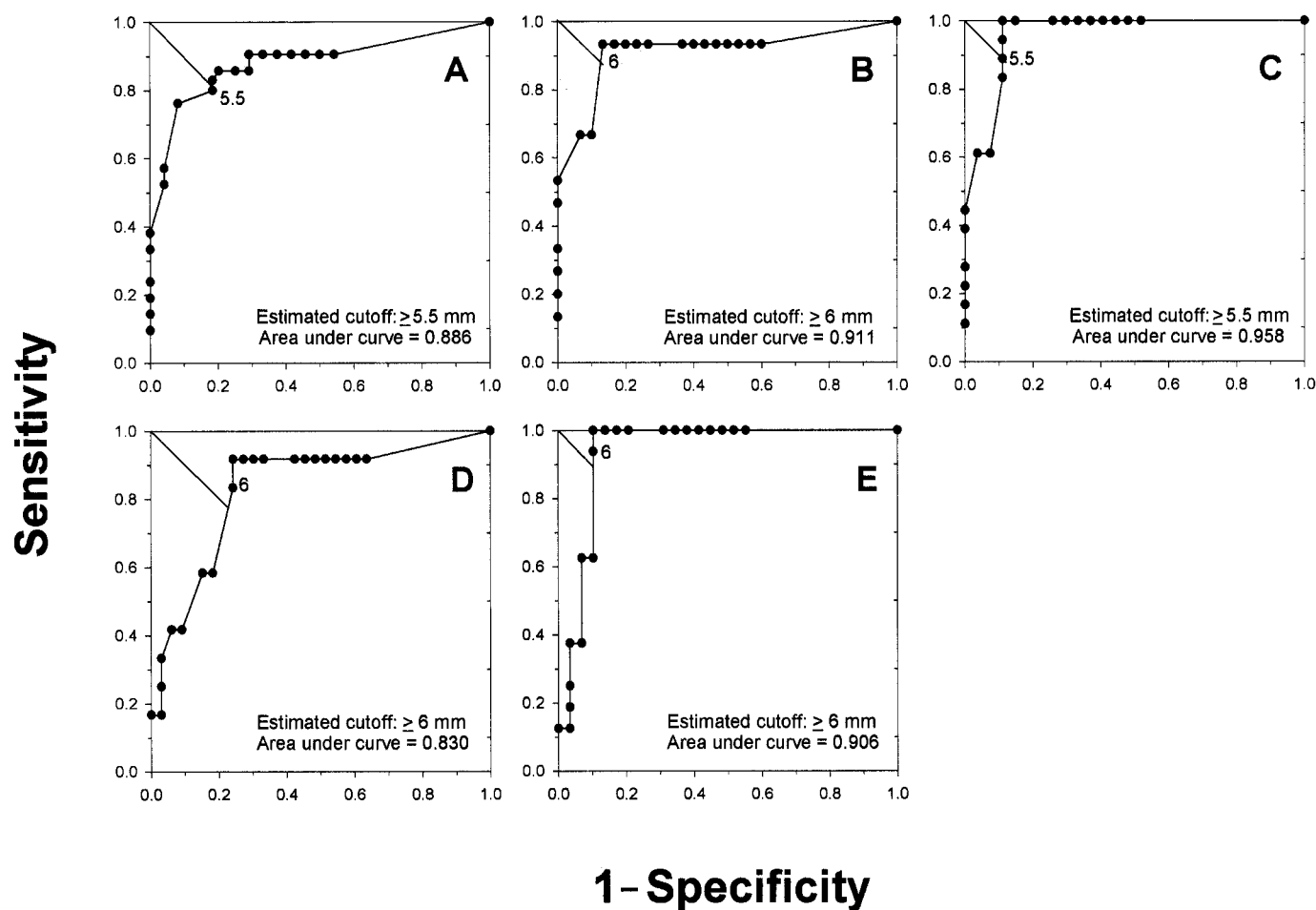


Figure 1. Receiver operating characteristic (ROC) curves (sensitivity vs $1 - \text{specificity}$) are used to obtain optimal cutoffs for a positive skin test wheal diameter to cat allergen. Standards used to calculate true-positive and true-negative results were as follows: (A) clinical history, (B) cat-specific IgE level, (C) nasal challenge symptom score, (D) postchallenge mast cell tryptase, and (E) postchallenge prostaglandin D₂ level. The diagonal solid lines that intersect with the ROC curve on each panel represent the optimal cutoff values for a positive skin test result to cat based on the appropriate standard.

Table 4. Performance Characteristics of Skin Prick Test to Cat Dander Based on Optimal Cutoff Values Determined from Receiver Operating Characteristic Analysis

Standard	Cutoff, mm	Sensitivity, %	Specificity, %	Efficiency, %	PPV, %	NPV, %
History	5.5	81.0	91.7	86.7	95.6	68.4
Symptom score	5.5	88.9	88.9	88.9	94.7	78.3
Specific IgE	6.0	93.3	86.7	91.1	94.0	85.3
Tryptase	6.0	91.7	75.8	80.0	89.4	80.4
PGD ₂	6.0	100	89.7	91.1	95.6	100

Abbreviations: NPV, negative predictive value; PGD₂, prostaglandin D₂; PPV, positive predictive value.

Table 5. Skin Prick Test Diameters to Cat Dander Yielding PPVs and NPVs of 95%

Standard	95% PPV			95% NPV		
	Cutoff, mm	Sensitivity, %	Specificity, %	Cutoff, mm	Sensitivity, %	Specificity, %
History	5.5	81	92		Best NPV = 77% at 2.5 mm	
Symptom score	5.5	89	89	4.5	100	89
Specific IgE	6.0	93	87		Best NPV = 85% at 6.0 mm	
Tryptase	7.5	42	91		Best NPV = 80% at 5.5 mm	
PGD ₂	5.5	100	90	5.5	100	90

Abbreviations: NPV, negative predictive value; PGD₂, prostaglandin D₂; PPV, positive predictive value.

Table 6. Wheal Diameter Cutoffs for a Positive Skin Prick Test Result to Cat*

Method	Cutoff, mm	Sensitivity, %	Specificity, %	Efficiency, %
Traditional	3.0	100	81	96.8
ROC	6.0	100	100	100
95% PPV	6.0	100	100	100
95% NPV	6.0	100	100	100

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

* Results are based on the following composite criteria: history, symptom score, cat specific IgE level by CAP FEIA, postnasal challenge prostaglandin D₂ level, and mast cell tryptase level.

Cutoff values for a positive skin test result to cat based on 95% PPV are given in Table 5. Using history, symptom score, or PGD₂ level, the skin prick wheal diameter that would predict a positive clinical response in more than 95% of individuals exposed to cats is approximately 5.5 mm. Using a specific IgE result of 0.35 KU_A/L or more, the skin prick wheal diameter producing more than 95% PPV was 6.0 mm. Using a positive postnasal challenge mast cell tryptase result as a marker of cat allergy, the skin prick wheal diameter producing more than 95% PPV was 7.5 mm. Skin prick wheal diameters yielding 95% NPV were not attainable using specific IgE level, mast cell tryptase level, or clinical history as markers of cat allergy.

Table 6 depicts the performance characteristics of the traditional 3-mm skin prick wheal diameter and optimal cutoffs obtained from ROC curves and 95% PPV and NPV from the 32 patients with either all positive (11 patients) or all negative (21 patients) clinical histories, specific IgE levels, and challenge results. The 3-mm cutoff yields a sensitivity of 100% but a specificity of 81% and an efficiency of 96.8%. Thus, a skin prick wheal diameter of less than 3 mm definitely rules out cat allergy but does not necessarily predict cat

allergy if 3 mm or greater. Using ROC analysis to obtain optimal decision points based on sensitivity and specificity, a 6-mm cutoff has a specificity and sensitivity of 100%. The skin prick wheal diameter to cat extract resulting in 95% PPV and 95% NPV is likewise 6 mm with a specificity and sensitivity of 100%. Thus, a skin prick wheal diameter of 6 mm or greater will accurately predict cat allergy in at least 95% of cases and a skin prick wheal diameter less than 6 mm will rule out cat allergy in 95% of cases.

DISCUSSION

The clinical potential of skin tests was first realized when von Pirquet introduced cutaneous testing for the diagnosis of tuberculosis.³² Despite the widespread use of skin testing for allergy diagnosis, there is little available information regarding what constitutes a positive test result. This situation is particularly true for environmental allergies due to the lack of a generally acceptable gold standard analogous to the oral, double-blind, placebo-controlled challenge for food allergies.

To determine the validity of a 3-mm wheal diameter to predict inhalant allergy, one can define the allergic state in terms of the clinical history, another test for allergen specific

IgE such as the radioallergosorbent test (RAST), and direct inhalant challenge with allergen. In a recent review of skin tests compared with other diagnostic modalities for allergy, including history, RAST, and nasal and bronchial challenge, Ownby³³ concluded, based on several published studies, that all of these methods correlate well with skin prick tests when potent, well characterized allergens are used. Our results indicate that a 3-mm cutoff for a positive skin test result to cat dander will overestimate cat allergy using history, specific IgE level, or postchallenge symptom score and mediator release as a reference for the allergic state. Using ROC analysis to obtain the optimal decision point for a positive skin test result, we found the cutoff to be approximately 6 mm. A PPV of 95% for an allergy test is indicative of a high degree of certainty for the development of symptoms following allergen exposure. On the other hand, an NPV of 95% indicates the likeliness of not developing symptoms on exposure to the allergen is high. We used a direct nasal challenge model in this study, which may not be representative of natural exposure. Comparisons between direct nasal challenge and the natural exposure model for cat challenge have not been reported. The cutoff for a positive skin test result to cat dander producing a 95% PPV was also close to 6 mm. Cutoffs for a negative skin test result to cat dander producing a 95% NPV were not attainable using specific IgE level, postchallenge tryptase level, or history as standards for cat allergy. Using symptom score or postchallenge PGD₂ levels as standards for cat allergy, the cutoff for a negative skin test result at 95% NPV was approximately 4.5 to 5.5 mm, which is indicative of the uncertainty of interpreting skin test results to cat dander between 4.5 and 6 mm.

Individually, clinical history, postchallenge symptom score, measurement of mediators in postchallenge secretions, and in vitro determination of antigen-specific IgE are not considered gold standards for diagnosis of allergy. We thought that if all of these markers were positive in an individual, a closer realization of true cat allergy would be achieved. We thus examined separately the 32 patients who tested either all positive or all negative for the above parameters. Our results confirm that a 3-mm wheal cutoff for a positive skin test result to cat dander will overestimate clinical allergy because of only fair specificity (81%). The optimal cutoff value for distinguishing between a positive and a negative skin test result to cat dander based on ROC analysis and 95% PPV and NPV using this very conservative definition of true cat allergy would appear to be 6.0 mm.

A limitation of this study is the known variability of skin testing that has previously been reported.^{34–36} Thus, a 6-mm wheal should not be construed as an absolute cutoff for a positive skin test result to cat. There may be individuals with strong clinical histories for cat allergy who react at wheal diameters less than 6 mm who may be truly cat allergic. Our data indicate that in a population of cat allergic individuals, wheal diameters of 6 mm correlate better with multiple parameters of potential clinical sensitivity than the widely accepted 3-mm cutoff for a positive skin test result. It should

also be emphasized that different wheal sizes may be obtained with different skin test devices.^{11–13} In a limited study with 3 different commercial skin test devices, including the Greer Dermapik, we have shown there is a statistical difference between this device and the 2 others.³⁷ In addition, based on previous work on establishing clinical cutoffs for CAP FEIA for food allergies, the allergen, geographic location, and patient age may affect the level of specific IgE necessary to produce symptoms.³⁸ Thus, the data reported in this study should not be extrapolated to other skin test devices or allergens.

In conclusion, in a preselected allergic population undergoing skin prick testing using standardized cat extract, a 3-mm wheal will overestimate the presence of allergy in a population, leading to potentially inappropriate and costly treatment. A more realistic cutoff to diagnose or exclude clinically relevant allergy cat dander using the Dermapik appears to be closer to 6 mm.

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