

Coughing in pre-school children in general practice: When are RAST's for inhalation allergy indicated?

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To identify patterns of clinical history associated with extreme (high or low) probabilities of allergic sensitization in coughing children so as to restrict allergy testing to those with an intermediate probability of sensitization. A total of 752 children, aged 1–4, visiting their GPs for coughing (≥ 5 days), were tested for IgE-antibodies to house dust mite, cat and dog [RadioAllergoSorbent Test (RAST)]. Parents completed a questionnaire on family history of atopy, breastfeeding, smoking, pets, and floor covering. Data of 640 children could be analyzed, 83 (13%) were IgE-positive. In a logistic regression analysis, a scoring formula for the prediction of being IgE-positive was constructed using variables from the patient's history. Significant contributors for sensitization were: age (3–4 yr), infantile eczema, positive family history of mite-allergy, sibling(s) with pollen-allergy, and smoking by parents. If only one of these characteristics is present, the probability of sensitization is $< 25\%$. In such cases watchful waiting may be preferred over allergy testing. In other cases, a negative RAST may help to exclude sensitization, whereas a positive RAST helps to establish the diagnosis. Thus, acting on clinical history alone may save approximately 80% of RAST's. Patient history-derived information contributes to distinguishing children who are at low risk for sensitization to house dust mite, cat, and dog. The scoring formula may help GPs to identify children with a low probability of being sensitized. This may form the basis for watchful waiting. In others, allergy testing may be useful to gain more diagnostic certainty.

**Petra E. D. Eysink¹,
Ben J. A. M. Bottema²,
Gerben ter Riet^{1,3},
Rob C. Aalberse⁴, Steven O. Stapel⁵
and Patrick J. E. Bindels¹**

¹Department of General Practice, Division Clinical Methods and Public Health, Academic Medical Center - University of Amsterdam, Amsterdam, The Netherlands, ²Department of General Practice and Social Medicine, University of Nijmegen, Nijmegen, The Netherlands, ³Horten Zentrum, Zürich University, Zürich, Switzerland, ⁴Sanquin Research at CLB and Landsteiner Laboratory, Academic Medical Center - University of Amsterdam, Amsterdam, The Netherlands, ⁵Department of Allergy, Sanquin CLB, Academic Medical Center - University of Amsterdam, Amsterdam, The Netherlands

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Prof Dr Patrick J.E. Bindels, Department of General Practice, Academic Medical Center - University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands
Tel.: +31 20 566 4690
Fax: +31 20 566 9186
E-mail: p.j.bindels@amc.uva.nl

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Accounting for 12.9% of the reasons for encounter (1), coughing in children younger than 4 yr of age is the commonest problem in general practice. For GPs, it is difficult to identify among these children those who are at high risk of getting asthma and/or allergy. After all, not all children who cough will develop asthma or other allergy-related symptoms (2, 3). According to a morbidity registration in the Netherlands, about 20% of children with coughs in general practice are eventually diagnosed with asthma (1).

Furthermore, in coughing young children, sensitization to common allergens may influence

the choice of treatment (4). Before advising inconvenient treatments, such as avoidance measures or potentially disease-labeling drug therapy, most physicians (should) demand a high degree of certainty if a latent sensitization is present. If the diagnostic examination shows a low probability of sensitization, e.g., $< 25\%$, then a watchful waiting strategy may be considered.

In principle, a RadioAllergoSorbent Test (RAST) or a skin prick test may be used to establish sensitization. However, due to the inconvenience for the child and its parents and

the monetary costs of the test, it is not feasible in general practice to test *all* young children who present with coughing for allergen-specific IgE. Therefore, it would be attractive if those children who are very (un)likely to be allergic could be distinguished in a more convenient and inexpensive way.

We examined to which extent, in general practice, information from a child's clinical history only may be used to identify those persistently coughing pre-school children with extremely low or high probabilities to be allergic to inhalant allergens. We used the RAST as a reference standard for the diagnosis of allergy. We conducted a cross-sectional study among children who presented to their GP with complaints of coughing. In the Netherlands, the GP is the first physician to be contacted and the primary physician to identify children at risk of getting allergy.

Subjects and methods

Selection of the study population

Between February 1995 and January 1997, 72 Dutch GPs recruited children for a study on the development of inhalation allergy in pre-school children. Eligible were 1- to 4-yr-old children who presented to their GPs with complaints of coughing reported to have lasted more than five consecutive days and who were not known to have an allergy or to be IgE-positive. The parents and their child were invited by their GP to participate in the study and informed consent was obtained from the parents.

On entrance, the parents completed a questionnaire. They were asked for how long their child had been coughing and whether the child had seen a GP more than once during the last 12 months due to coughing. Other questions concerned history of infantile eczema, suffering from asthma, asthmatic bronchitis, allergy to house dust mite, to animals or to pollen by the child's parents and/or siblings, smoking at home, breastfeeding, pets at home, and floor covering.

At the same time, a blood sample was obtained from the children and total IgE and specific IgE for house dust mite, cat, and dog [being the most prevalent inhalant-allergens in this age-group in the Netherlands (5)] were determined.

The study was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam.

Laboratory methods

Total IgE and specific IgE to house dust mite, cat, and dog dander were determined as described by Stapel *et al.* (6). In brief blood, obtained by finger prick, was adsorbed on filter paper and eluted. Assays for measuring total serum IgE and specific IgE were adjusted for the application of small amounts of plasma. Total IgE was expressed in international units per millilitre (IU/ml), RAST results were expressed in RAST units per millilitre [U/ml, one RAST unit representing approximately 2.4 ng of specific IgE (7)]. All test results were corrected for actual amounts of plasma used in the tests, using serum albumin as a reference protein.

Statistics

Dependent variable. The results of the RAST were dichotomized as IgE-negative or IgE-positive. IgE-positivity to cat, dog and/or house dust mite was defined as a concentration ≥ 0.5 U/ml. A child was defined as sensitized if he or she was IgE-positive to any of the allergens.

Independent variables. The independent variables in the logistic regression analyses included age (1 and 2 yr vs. 3 and 4 yr), number of days of coughing before the current visit to the GP (6–14 days, more than 14 days and up to 3 months, and more than 3 months), earlier cough-related visits (yes/no), infantile eczema (yes/no), family history of allergy for house dust mites, pollen, animals (yes/no) and asthma (yes/no), breastfeeding (yes/no), presence of pets (yes/no), smoking by the parents at home (yes/no), and the kind of floor covering in the child's bedroom (smooth vs. non-smooth). A child was supposed to have a positive family history of allergy when either of the parents or one of the child's siblings had an allergy for house dust mite, pollen and/or animals. In the same way, the child had a positive family history of asthma when either of the parents or a sibling had been diagnosed with asthma. Floor covering was dichotomized in smooth (wooden floor, linoleum/floor-cloth and tiled floor) and non-smooth (wall-to-wall carpet, smooth floor with loose carpets or rugs).

Variable selection strategy. To select an efficient set of predictors for being sensitized, a forward stepwise logistic regression analysis was performed with IgE-status as the dependent variable (8). The p-values for entry into and removal of variables from the model were 0.10 and 0.15,

respectively. The stepwise selection algorithm used likelihood ratio statistics as a criterion for the selection of predictor variables in the regression model. We tested the interactions of age and family history with all other variables in the model. The regression coefficients were used to derive the probabilities of being sensitized. For each child profile the probability of being sensitized was computed, using the formula: $\text{probability} = 1/[1 + e^{-(\text{score} + \text{intercept})}]$. A receiver–operating characteristics (ROC) curve as a summary of predictive power was constructed using the best model. The final version of the regression model was fitted 10,000 times using bootstrap methodology and the 10,000 corresponding ROC curves were used to construct a more robust confidence interval (CI) around the area under the curve thus counteracting the influence of observations unique to our data set (9).

Statistical analyses were performed with SPSS 10.0.7 for Windows, except for the standard errors of the predicted probabilities and the bootstrapping procedure, which were calculated using STATA 7.0.

Results

During the inclusion period, the parents of 752 children consented to participate in the study. However, 98 children did not meet the inclusion criteria, because they were older than 5 yr of age ($n = 9$) or younger than 1 yr of age ($n = 31$) or their blood sample was too small for analysis ($<10 \mu\text{l}$ plasma-equivalent, $n = 58$). No questionnaire was received from 14 parents (2 IgE-positive and 12 IgE-negative children). Thus, complete data of 640 children were available.

The median number of days of coughing before the current visit to the GP was 14 days (IQR = 7–34.8 days). The majority of the children (83.2%) had seen a physician more than once during the past 12 months.

Table 1 shows their general characteristics. Eighty-three (13.0%) were IgE-positive for at least one allergen at the time of inclusion.

Eighteen of the 234 children were 1-yr-old (7.7%) and IgE-positive, 27 of the 186 were 2-yr-old (14.5%), 22 of the 125 were 3-yr-old (17.6%) and 16 of the 95 were 4-yr-old (16.8%). The 1-yr-old children were mostly positive for dog (11/18). The older children were predominantly IgE-positive for mites (14 out of 27 IgE-positive 2-yr-old, 19 out of 22 IgE-positive 3-yr-old and 14 out of 16 IgE-positive 4-yr-old) (Fig. 1).

Table 1. General characteristics of the children in the study population ($n = 640$)

	Total
Total (n)	640 (100)
Gender	
Boys	339 (53.0)
Girls	301 (47.0)
Age at time of RAST (years)	
1	234 (36.6)
2	186 (29.1)
3	125 (19.5)
4	95 (14.8)
Number of positive RAST scores	
0	557 (87.0)
1	64 (10.0)
2	15 (2.3)
3	4 (0.6)
Total IgE (95% CI) (IU/ml)	19.4 (0.7–503.7)

Data expressed as numbers (percentages) or geometric means (95% CI).

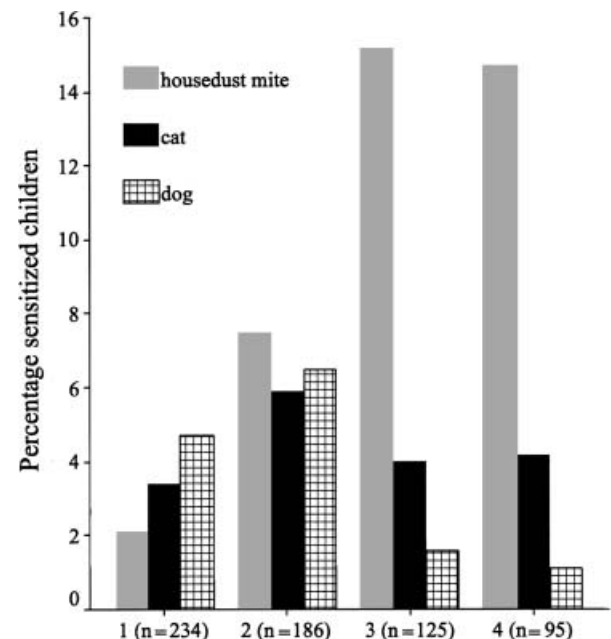


Fig. 1. Percentage of house dust mite, cat, and dog-positive children per age category ($n = 640$).

All variables of the questionnaire were used to construct a model. Age (cut of point at 3 yr), history of infantile eczema, mite-allergy in the family, allergy for pollen in siblings, and smoking by the parents at home contributed importantly to the prediction of sensitization (Table 2). The 'effect' of infantile eczema turned out to be different for the two age-categories. For each child profile, the products of the regression coefficients and their corresponding variable

Table 2. Results from logistic regression analyses [odds ratios (OR) (with 95% CI) and regression coefficients] for sensitization in relation to easily obtainable characteristics of the children in the study population (n = 640). All variables included in the model were present (=1) or absent (=0). Dependent variable is sensitization, non-sensitized children used as references

	OR*	Regression coefficient β
Age (years)		
1–2	1	0
3–4	2.6 (1.4–4.8)	0.9
Infantile eczema	5.4 (2.8–10.5)	1.7
Positive family history of mite-allergy	2.2 (1.3–3.7)	0.8
Pollen-allergy sibling(s)	5.5 (2.1–14.7)	1.7
Smoking by parents	1.8 (1.1–3.0)	0.6
Eczema $\times$ age	0.3 (0.1–0.9)	–1.2

*e ^{β} = OR, intercept of the model: –3.3.

Model: Score = 0.9 $\times$ age + 1.7 $\times$ eczema + 0.8 $\times$ family history mite-allergy + 1.7 $\times$ pollen-allergy sibling + 0.6 $\times$ smoking – 1.2 $\times$ eczema $\times$ age

The corresponding probabilities of being sensitized can be calculated from $Pr = 1/[1 + e^{-(\text{score} + \text{intercept})}]$. For example, a 3-yr-old boy with infantile eczema, a positive family history of mite-allergy, no siblings with pollen-allergy and non-smoking parents has a score of 2.2, which means that he has a probability of being sensitized of 25.0%, using $Pr = 1/[1 + e^{-(\text{score} + \text{intercept})}]$. This can also be found in Table 3.

values can be summed and used to predict the probability of sensitization. The variables are absent (=0) or present (=1) for each child. For example, a 3-yr-old, who 'tested' negative on all questions (i.e. all variable values = 0), has a score of 0.9, which is associated with a probability of being sensitized of 0.083 (8.3%, 95% CI: 4.9–13.8).

The logistic regression analysis was used to estimate the probabilities for sensitization for all the available child profiles (Table 3). For example, the combination of higher age (3–4 as compared to 1–2-yr-old), a positive family history of mite-allergy, infantile eczema, having a sibling with a pollen-allergy and a smoking parent at home corresponded with the highest probability of being IgE-positive (76.9%, 95% CI: 50.3–91.6). Table 3 also shows that our study population contained 28 of the 32 theoretically possible diagnostic child profiles. There were no 1–2-yr-old children presenting with cough who had had infantile eczema, positive family histories, and parents who smoked at home.

For the 1–2-yr-old children, with a prior probability of 10.7% being sensitized, combinations of at least two positive characteristics increased the posterior probability considerably, except for one pattern with two characteristics in which the posterior probability was 13.0%. There were six diagnostic profiles in which the

probability was very small (cells with bold numbers in Table 3). These six profiles include 85% (n = 355) of the 1–2-yr-old children. The other profiles, with two or more characteristics present, are associated with a probability of sensitization of at least 25%. Similar results can be found for the 3–4-yr-old children. Testing when two or more characteristics are present increases the probability of being sensitized from 17.3% (prior probability) to at least 25.0%, with the exception of one profile in which the probability is almost unchanged (21.4%).

Our model is associated with an area under the ROC curve of 0.73 (0.69–0.78) (Fig. 2).

Discussion

In a primary care setting, we examined the extent to which sensitized pre-school children presenting with complaints of coughing, can be distinguished from their non-sensitized counterparts using information from their medical history only. The aim was to learn in which children allergy testing (RAST or skin prick test) might be (un)necessary to establish sensitization or the absence of it with a sufficiently high degree of certainty. Therefore, we developed a model based on multivariable logistic regression analysis of data obtained from coughing pre-school children in general practice. This model is based on information readily available at the time of presentation.

In our study population of pre-school coughing children, the prevalence of sensitization to house dust mite, cat or dog was 13% using a RAST cut-off value of 0.5 U/ml. The best model showed a patient history containing age of 3–4, infantile eczema, a family history of mite-allergy, having a sibling with pollen-allergy and smoking of the parents at home and was associated with the probability of sensitization of 77% or at least 50% (=if one takes the lower limit of the 95% CI). In the absence of any of these characteristics the probability of being sensitized is small (8.3%) and testing for an allergy may not be useful.

It is of clinical importance for a GP to know in which coughing children the likelihood of sensitization is high enough to do an allergy test without having to test all coughing children, and thus, how testing can be made more efficiently. When a coughing child meets two or more characteristics in our model, the GP has to consider or to exclude a diagnosis of allergy and to decide whether or not to do an allergy test. If these characteristics are absent or only one is present, there is no need for a GP to have an allergy test performed because of the low prob-

Table 3. Estimated probability (with 95% CI)* of being sensitized in relation to characteristics of the children in the study population (n = 640)

Characteristics			1- and 2-yr-old				3- and 4-yr-old			
Eczema	Pollen†	Smoking	n‡	Positive family history§	n‡	Negative family history§	n‡	Positive family history§	n‡	Negative family history§
Yes	Yes	Yes	–	81.8¶	–	66.8¶	1	76.9 (50.3–91.6)	1	59.9 (31.6–82.8)
Yes	Yes	No	3	71.9 (45.5–87.9)	–	52.5¶	1	64.6 (37.6–84.6)	2	45.0 (21.0–71.6)
Yes	No	Yes	7	45.0 (30.1–60.9)	32	26.9 (17.3–39.3)	4	37.8 (21.0–58.1)	10	21.4 (11.0–37.4)**
No	Yes	Yes	–	45.0¶	1	26.9 (10.9–52.5)	1	66.8 (40.6–85.6)	2	47.5 (24.1–72.1)
Yes	No	No	21	31.0 (19.9–44.9)	33	16.8 (10.2–26.3)	13	25.0 (13.3–41.9)	16	13.0 (6.4–24.6)††
No	Yes	No	1	31.0 (13.3–56.8)	3	16.8 (6.4–37.4)	3	52.5 (28.4–75.5)	2	33.2 (15.1–58.1)‡‡
No	No	Yes	36	13.0 (7.6–21.5)	111	6.3 (3.8–10.3)	18	26.9 (16.7–40.3)	54	14.2 (9.0–21.7)
No	No	No	49	7.6 (4.3–13.0)	123	3.6 (2.0–6.3)	23	16.8 (10.1–26.7)	69	8.3 (4.9–13.8)

*95% CI = $1/1 + e^{-[\text{score} + \text{intercept} \pm (1.96 \times \text{standard error})]}$

†Allergy for pollen in sibling(s).

‡Number of children with covariate pattern.

§Family history of mite-allergy.

¶Not possible to calculate 95% CI because there are no children with this covariate pattern.

Cells with bold numbers correspond with covariate patterns associated with a posterior probability <25% and no or one positive variable. However, there are three exceptions: two bold number patterns (** and ††) with probabilities of 13.0%, and 21.4%, respectively but with two positive variables and one pattern (‡‡) with one positive variable and a posterior probability of 33.2%.

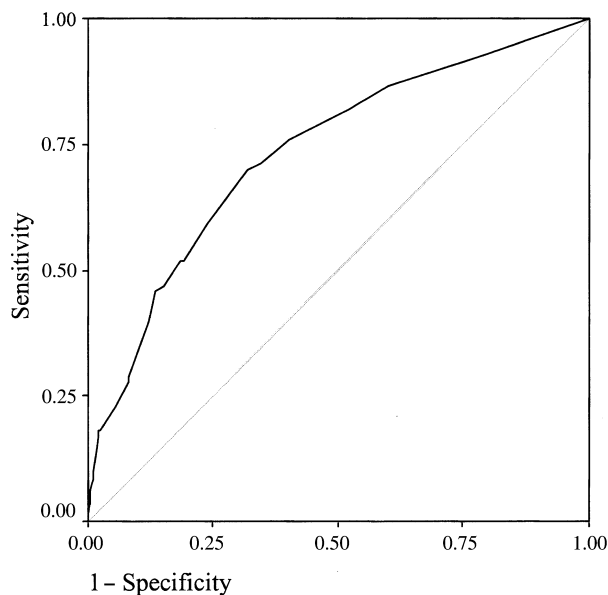


Fig. 2. Receiver-operating characteristics (ROC) curve for the model with sensitization as the dependent variable. The model contains age, infantile eczema, family history of mite-allergy, pollen-allergy sibling(s), smoking by parents, and interaction between eczema and age. ROC area under the curve = 0.73, 95% CI: 0.69–0.78.

ability of sensitization and the RAST might be omitted in about 80% of the 1- to 4-yr-old children. Thus, performing an allergy test only in a subgroup of coughing children for whom the probability of sensitization is high according to the clinical history increases the probability to detect a sensitized child and substantially reduces the number of children that need to be tested in order to know their IgE-status.

Of course, not all GPs share the same cut-points for drug treatment or avoidance advice. The question is when a probability is sufficiently high to base subsequent treatment activities upon. Our study cannot answer the question of how much certainty different GPs demand or should demand before embarking on a drug treatment or allergen-avoidance advice. The decision problem(s) GPs face in persistently coughing children can only be solved by a formal decision analysis including all relevant effects on the (human) cost side and (side-)effectiveness side of the equation.

In diagnostic cohort studies, in contrast to etiologic studies, the emphasis is not on some exposure of interest whose influence is to be quantified and adjusted for confounding factors. Rather, the contrasts in patients' test results (where 'tests' include clinical history items) are used to predict the likelihood of allergy. This also implies that the analysis is centered on efficiency, that is, optimal prediction using information that becomes available early in the diagnostic work-up and often virtually for free (clinical history). So, the issue of confounding in etiologic cohorts changes into an issue of redundancy of diagnostic information in studies such as the current one (10).

The selection of the pre-school children in this study was based on their presentation at the GP's surgery with complaints of coughing for 5 days or more. This means that the parents had to take the decision to contact the GP. This implies that the formula we constructed is likely to be valid for coughing children who present at GP's

surgeries, and not necessarily for children in the open population. In our population of pre-school children, distinct positive IgE-levels (≥ 0.5 U/ml) to mites and animal dander were seen in children as young as 1-yr-old. Although the frequency of inhalation allergy for the 1-yr-old was low (7.7%), it was higher than found in other (population-based) studies, with percentages of 1.5–4.0 (11–13). Coughing for 5 days or more seems to be a relevant first selection criterion to identify sensitization among these children.

In general practice children present with a different distribution of symptoms than in a clinical/specialist setting because of the GP filter and its influence on the frequency of clinical presentations. In allergic diseases many of the symptoms are quite common, which can make it difficult to diagnose allergy with certainty and to sort out specific causes entirely by looking at the clinical history only. As expected, clinical history only does not fully predict which children are sensitized (14). Therefore, it is important to test children in whom an allergy is suspected with a high enough certainty based on clinical history. If this certainty is taken to be 25%, based on our formula the RAST can be omitted in 80% of the children and for 20% of the children testing might be useful.

In the questionnaire for medical history for this study, no attention was paid to wheezing or other symptoms. Therefore, these variables could not be included in the logistic regression model to predict sensitization. We cannot completely exclude that the model is different in situations where patient history is more extensive. However, the value of wheezing in the model could also be limited in these young children, as the majority of children who wheeze do not develop an allergy or asthma and parents' report of wheeze and clinicians' findings differ (15).

Ideally a prediction rule should be derived, and then validated prospectively on a separate population. The results are usually less robust when applied to a separate population (16). A limitation in this study is the current lack of such a validation. Another drawback in the application of the model is that the number of cases in the separate classes of specific allergens was insufficient to allow for a more detailed analysis. Most of the sensitized children in our study population were sensitized to mites and analyses for this mite-positive group gave the same results as for the entire sensitized group. Avoidance measures depend on the type of allergy present. The avoidance advice should be as specific as possible, but our data set was not sufficient for these analyses. Future research should be done to explore this.

To avoid over-fitting, we used the rule that the number of predictors was not allowed to be more than $m/10$ (17), in which m refers to the number of outcome events. In this study, 83 IgE-positive children were available, which meant eight predictors were allowed in the model. The number of predictors was six and did not exceed the $m/10$ -limit. Nevertheless, the CIs around the probability estimates reflect the sometimes limited number of observations for a particular diagnostic profile (Table 3). For example, there were no 1–2-yr-old children who had had infantile eczema, positive family histories, and parents who smoked at home. Our population contained 28 out of the 32 theoretically possible profiles.

The results show that it is possible for the GP to identify coughing children with a high probability of being IgE-positive or IgE-negative to house dust mite, cat and dog by using information readily available at the time of presentation (age, infantile eczema, family history of mite-allergy, sibling with pollen-allergy and smoking of the parents). Nevertheless, for some children it remains uncertain whether they are sensitized or not. Testing for an allergy could be useful for them. When the GP only tests coughing children if the probability of being sensitized is at least 25%, i.e., when they meet two or more characteristics in our formula, the RAST can be omitted in 80% of the 1- to 4-yr-old children. At what point a GP considers the probability high enough to test, depends on the degree of uncertainty and on the number of unnecessarily tested children the GP is willing to accept. More elaborate decision-analytic studies are needed to determine appropriate cut-points of the probability of sensitization at which allergy testing is (un)necessary in order to choose a correct treatment strategy.

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