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Predictive value of MP4 (Milk Prick Four), a panel of skin prick test for the diagnosis of pediatric immediate cow's milk allergy

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Summary

Background. *Oral food challenge (OFC) is the gold standard for the diagnosis of food allergy (FA), but it is risky, expensive and time-consuming. Many studies aimed to avoid OFC by finding a cut off (CO) of skin prick test (SPT) to predict a positive outcome of OFC. Unfortunately the results of these studies are poorly reproducible for various reasons, including the absence of known protein concentration in the extracts. It has also been documented that some doctors mistakenly attributed some symptom/disease, for example recurrent respiratory infections of the upper airways, to the FA, expecially cow milk allergy (CMA). These doctors often performed SPT in their studies to confirm, if the result was positive, their diagnostic suspicion and prescribe an elimination diet without seeking the advice of allergy specialist (AS) and without making an OFC.* ***Objective.*** *To test the diagnostic performances of SPT with fresh cow's milk and commercial extracts of casein, beta-lactoglobulin, alpha-lactoalbumin at known protein concentrations (Milk Prick Four [MP4] test). To look for 2 clusters of SPT CO with positive predictive value (PPV) > 95%, one for AS, one for general practitioner (GP).* ***Methods.*** *A prospective study was carried out on 191 children referred by their GP to the allergy center for suspected immediate-type CMA (iCMA). Based on the history, the allergist has divided the children into two groups: a) group A, children with suspected (subgroup A1, 55 children) or known (subgroup A2, 27 children) diagnosis of iCMA; b) group B, 109 children with a clinical history incompatible with iCMA suspicion according to the AS (in this case the GP was wrong to send those patients to the allergy center). SPT with MP4 test was performed on all patients, and OFC was performed on all patients of group A. CO with PPV > 95% was calculated separately for the entire population of 191 children (CO for GP) and for the only group A (CO for AS).* ***Results.*** *Fresh cow's milk SPT was the most sensitive single prick test (sensitivity [SE] 94%, negative predictive value [NPV] 98%). The positivity to any of 3 SPT extracts (performed at the same time) had the same SE and NPV of the single fresh cow's milk SPT. Moreover, fresh cow's milk SPT or any of 3 SPT extract had 100% SE and 100% NPV, having excluded 2 children with Food Protein Induced Enterocolitis Syndorme from data analysis. MP4 CO for GP allow a total savings of 4% of OFC, a percentage that rises to 22% in the subgroup A2, and does not give false positives. MP4 CO for AS allow a total saving of*

33% of OFC, rising to 67% in the subgroup A2, but they give a 7/82 false positives in group A. SPT CO of alpha-lactoalbumin had the best performance in both settings. ***Conclusion.*** *MP4 is a safe and cheap test, easy to perform. All doctors may be confident in excluding iCMA if fresh cow's milk SPT is negative. GP could perform SPT to fresh milk at his own clinic, and safely diagnose iCMA by using our CO for GP, although this may happen only in a few cases. MP4 test performed by AS can help save a greater number of OFC, especially among children with known diagnosis of iCMA.*

Introduction

The gold standard for diagnosing food allergy (FA) is the oral food challenge (OFC) (1). However, it is risky, expensive and time-consuming (2). Therefore, many studies have investigated diagnostic tests in order to predict the results of OFC. Serum level of specific IgE antibodies to the offending food (3-10), patch tests response and the wheal diameter of skin prick test (SPT) (11-15) do not provide a definite mean to ascertain clinical food hypersensitivity. SPT remains the most common and easiest diagnostic test to use.

OFC is also subjected to misdiagnosis of food allergy: it has been documented (16) that some doctors, devoid of a specific allergy competence believe that certain symptoms (such as behavioral changes and, especially in children, recurrent respiratory infections of the upper airways), are due to FA, in particular immediate cow's milk allergy (iCMA). These doctors often performed SPT in their studies to confirm, their diagnostic suspicions and prescribe an elimination diet without making an OFC or at least seeking the advice of an allergy specialist (AS). Then, in general practitioner (GP) setting, it would be helpful to find SPT cut-off (CO) able to predict FA (especially iCMA) with PPV>95%, with little rate of false positive.

We reported a prospective multicenter study aimed to assess the diagnostic value of MP4 (Milk Prick Four) test, a panel of SPT to fresh cow's milk and to commercial extracts at known concentration of casein, beta-lactoglobulin and alpha-lactoalbumin, according to the outcome of OFC in children with suspected iCMA referred by general practitioner (GP) to allergy pediatric centers. Furthermore, we hypothesized that the diameter of the wheal of SPT for predicting children who react to the OFC with a positive predictive value (PPV) > 95% (95% PPV CO) varies according the specific competence of the physicians who suspected iCMA. Therefore, the 95% PPV CO of MP4 test was determined both in a general population selected by the GP and in a population selected by the AS.

Methods

We enrolled children consecutively referred for suspected iCMA by their GP to the study centers.

After a careful anamnesis, the AS divided the children into the following groups:

Group A. Children for whom the suspicion of iCMA issued by the GP was confirmed by the AS. This group was divided into two subgroups: a) subgroup A1: children with suggestive history of iCMA (anaphylaxis, urticaria and/or angioedema, vomit and/or diarrhoea, rhino-conjunctivitis, asthma: all the above symptoms must have occurred within 2 hours from the beginning of ingestion of cow's milk proteins); b) subgroup A2: children with established diagnosis of iCMA (suggestive history, positive specific IgE and failed OFC), for these children AS evaluated the persistence of allergy or the achievement of tolerance.

Group B. Children for whom the suspicion of iCMA issued by the GP was not confirmed by the AS. These children did not have a suggestive history of iCMA, according to international criteria (17), i.e. they have recurring respiratory infections, failure to thrive, adenoid hypertrophy. These children were all consuming at least 100 ml of fresh cow's milk without presenting the known symptoms of the iCMA (such as those listed for the subgroup A1).

All patients who were eligible to participate took part to the study. The study was approved by Agostino Gemelli

Hospital' Ethics Committee. Oral informed consent was obtained from the study participants.

Skin prick test

SPT with fresh cow's milk (whole cow's milk, 3.6% fat) and commercial extracts of casein (Lofarma, Milan Italy, 0.207 mg/ml), beta-lactoglobulin (Lofarma, Milan Italy, 1.773 mg/ml), alpha-lactoalbumin (Lofarma, Milan Italy, 1.072 mg/ml) was performed on the volar surface of the forearm of all children. This panel was called Milk Prick Four (MP4). Histamine (Lofarma, Milan Italy, 10 mg/ml) was used as positive control. The solvent was used as negative control. SPT was performed according to international guidelines (18). A 1 mm tip metallic lancet was used (ALK Abellò, Hørsholm Denmark). Reactions were detected after 15 minutes and the SPT was considered positive if the mean diameter of the wheal was at least 3 mm larger than the negative control.

Oral Food Challenge

An open OFC was performed on all children of group A. OFC was performed in hospital setting by administering every 20 minutes 0.1, 0.5, 1, 2, 5, 10, 20, 50 and 100 ml of fresh cow's milk, 3.6% fat. Patients remained under clinical observation for 2 hours after last dose. OFC was stopped and considered positive in case of objective symptoms and/or serious and/or persistent and/or reproducible ones (19). OFC was performed within 2 weeks after SPT.

Statistical Analysis

Statistical analysis was performed by means of SPSS 15 for Windows, SPSS Inc, Chicago, Ill. To test the diagnostic accuracy of SPT with MP4 test we calculated, by mean of two by two tables, sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) for diagnosis of iCMA. Using logistic regression, we searched for two clusters of SPT CO with PPV ≥ 95% for iCMA diagnosis: a) one for AS, resulting from the analysis of group A (iCMA high-prevalence population); b) and one for GP, resulting from the analysis of groups A+B (iCMA low-prevalence population). We plotted receiver operating characteristic (ROC) curves for skin weal diameter of all children enrolled (group A + B): area under the curve (AUC) was calculated to quantify the accuracy of SPT results.

Results

Population

One hundred and ninety one patients were enrolled (100 males and 91 females). The median age was 2.74 years (range 1 month - 15 years), 31% had atopic dermatitis and 36% a positive family history for allergic diseases. Eighty-two children were included in group A (55 in subgroup A1 and 27 in subgroup A2) and 109 in group B. Table 1 describes the main characteristics of the study population.

Oral Food Challenge

All patients of group A underwent OFC except for two children with history of anaphylaxis, defined according to Sampson et al (20), in the previous 12 months. In the group A, 34 (41%) of 82 OFC gave positive results: 15 in subgroup A1 (13 OFC positive + 2 with history of anaphylaxis in the previous 12 month) and 19 in subgroup A2. Two children of subgroup A1 with negative

Table 1 - Main characteristics of the study population.

	Subgroup A1	Subgroup A2	Group B	p
	(N. 55)	(N. 27)	(N. 109)	
Age				
1m - 2y	28	2	45	0.56
2y-5y	18	18	31	
5y-10y	6	3	28	
10y-15y	3	4	5	
M/F	30/25	20/7	50/59	0.87
Atopic dermatitis	17 (31%)	7 (26%)	35 (32%)	0.24
Family history for atopy	21 (38%)	6 (22%)	42 (38%)	0.36

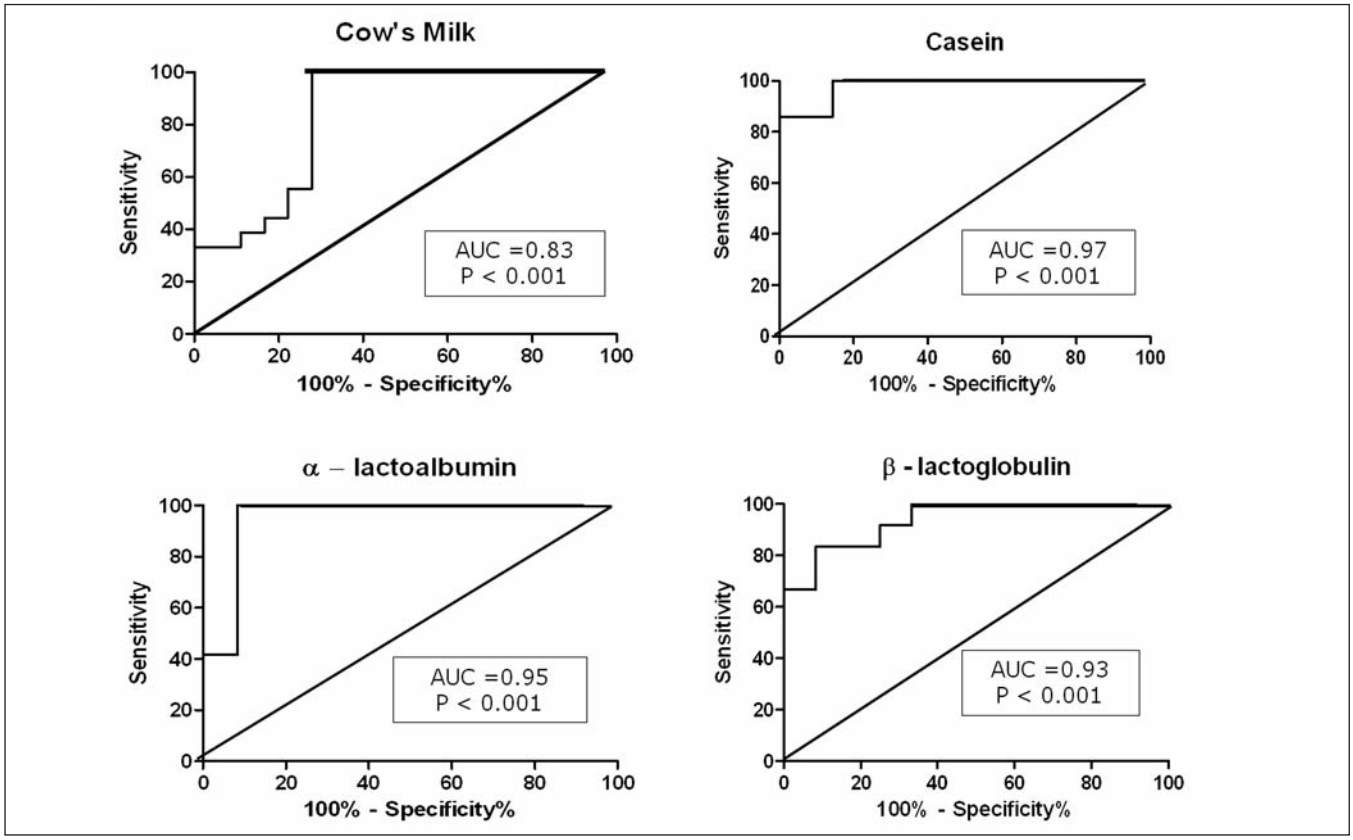
SPT who failed OFC received the diagnosis of Food Protein Induced Enterocolitis Syndrome (FPIES).
OFC Symptoms were anaphylaxis, urticaria and/or angioedema, asthma, rhinoconjunctivitis, repeated vomiting, diarrhoea: all of the above symptoms were of immediate type, appeared within 2 hours from last ingestion of cow's milk.

Skin prick tests
Table 2 summarizes the performance of SPT, in all children enrolled (group A + B), according to the diagnosis of iCMA when it is considered to be positive even although minimal (mean wheal diameter ≥ 3 mm). The positivity to all three extracts (casein, alpha-lactoalbumin and beta-lactoglobulin) at the same time had the best SP (97%) and a PPV of 74%. Casein SPT was the most specific single prick test (SP 95%, PPV 72%). Fresh cow's milk SPT was the most sensitive single prick test (SE 94%, NPV 98%), the SPT positivity to any of 3 extracts (performed at the same time) had the same SE and NPV of fresh cow's milk SPT. Moreover, fresh cow's milk SPT or any of 3 extract SPT had 100% SE and 100% NPV, excluding 2 children with FPIES from data analysis (data not showed in the table). In short, making a single SPT with fresh cow's milk or make 3 SPT with extracts of casein, alpha-lactoglobulin and beta-lactoglobulin has the same diagnostic accuracy against the iCMA diagnosis when considering a mean wheal diameter ≥ 3 mm positive.
SPT results were positive (mean wheal diameter ≥ 3 mm) in 17.4% of children of group B (19/109 children, false positives), who were eating cow's milk without clinical problems suggestive of iCMA.
A graphic presentation of the correlation between SE and SP can be obtained by calculating ROC curves for skin weal diameter all children enrolled (group A + B) as shown in figure 1. AUC for weal size showed acceptable values for fresh cow's milk (0.82) and better values for the extracts (0.93 - 0.97).
The results of MP4 SPT CO with 95% PPV calculated on entire enrolled population (group A + B, iCMA low-prevalence population) were: fresh cow's milk = 13.6 mm, alpha-lactoalbumin = 8.8 mm, beta-lactoglobulin = 9.1 mm, casein = 6.2 mm (table 3). Since all of these children were sent to specialist centers by their GP with suspected iCMA, we believe that these 95% PPV CO may be useful just in the setting of the GP. In fact, it should be empha-

Table 2 - MP4 test Sensitivity (SE), Specificity (SP), Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Confidence Intervals (CI) for a cut-off > 3 mm. The results regard all the children studied (group A)

Allergen	SE (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Fresh cow's milk	0.94 (0.86 - 1)	0.78 (0.71 - 0.84)	0.48 (0.40 - 0.55)	0.98 (1 - 0.94)
Alpha-lactoalbumin	0.73 (0.58 - 0.89)	0.94 (0.90 - 0.97)	0.71 (0.57 - 0.82)	0.94 (0.97 - 0.90)
Beta-lactoglobulin	0.82 (0.69 - 0.95)	0.87 (0.82 - 0.92)	0.58 (0.47 - 0.68)	0.96 (0.98 - 0.92)
Casein	0.53 (0.36 - 0.70)	0.95 (0.92 - 0.99)	0.72 (0.54 - 0.85)	0.90 (0.93 - 0.87)
1 of 4 SPT	0.94 (0.86 - 1)	0.76 (0.70 - 0.83)	0.46 (0.39 - 0.54)	0.98 (1 - 0.94)
All 4 SPT	0.41 (0.24 - 0.58)	0.97 (0.94 - 1)	0.74 (0.52 - 0.88)	0.88 (0.91 - 0.85)
1 of 3 extracts	0.94 (0.86 - 1)	0.85 (0.80 - 0.91)	0.58 (0.49 - 0.67)	0.98 (1 - 0.94)
All 3 extracts	0.41 (0.24 - 0.58)	0.97 (0.94 - 1)	0.74 (0.52 - 0.88)	0.88 (0.91 - 0.85)

Figure 1 - ROC curves for raw cow's milk and alpha-lattoalbumin, beta-lattoglobulin and casein extracts for the weal size of SPT



sized that with these 95% PPV CO has not been possible to issue any definitive diagnosis of iCMA in group B (children with wrong suspicion of iCMA): that is, MP4 SPT CO for GP had no false positives (table 3). Moreover, these CO could have prevented 7 OFC in group A, the vast majority in the subgroup A2 (6/27, 22%). Analyzing single SPT CO performance, alpha-lactoalbumin CO was the best in this setting.

Table 3 - Diagnosis of iCMA with MP4 cut off (CO) with 95% PPV for General Practitioner. The numbers in column indicate the avoidable OFC through the use of CO in question.

	Group A (N. 82)	Subgroup A1 (N. 55)	Subgroup A2 (N. 27)	Group B (N. 109)
Children with definitive iCMA diagnosis and with MP4 CO positives	7	1	6	0
CO fresh cow's milk = 13.6 mm	2	0	2	0
CO alpha-lactoalbumin = 8.8 mm	6	1	5	0
CO beta-lactoglobulin = 9.1 mm	3	1	2	0
CO casein = 6.2 mm	0	0	0	0
Children without definitive iCMA diagnosis and with MP4 CO positives	0	0	0	0

The results of MP4 SPT CO with 95% PPV calculated only on children of group A (subgroup A1 + A2, iCMA high-prevalence population) were: fresh cow's milk = 9.3 mm, alpha-lactoalbumin = 4.9 mm, beta-lactoglobulin = 5.6 mm, casein = 4.3 mm (table 4). This 95% PPV should be considered a useful result for AS. In this setting MP4 95% PPV CO give a better result: as many as 27/82 (33%) OFC would be avoidable, also in this case especially in the subgroup A2 (18/27, 67%). Unfortunately, with these CO there is a certain risk of false positives: 7/82 in group A, and in particular 3/27 in subgroup A2. Also in the AS setting, alpha-lactoalbumin was the best single SPT CO.

Discussion

With this study we pursued two objectives: a) to provide a tool to GP to eliminate the suspicion of iCMA and not to issue misdiagnosis of iCMA; b) to provide a tool to AS to try to avoid, at least in part, the OFC for the definitive diagnosis of iCMA.

In our data, fresh cow's milk SPT or any of 3 extract SPT (casein, alpha-lactoalbumin, beta-lactoglobulin) performed at the same time, had 98% NPV for iCMA diagnosis (100% if FPIES was ruled out). This result is completely in line with the systematic review carried out during the drafting of the WAO DRACMA guidelines (17). These guidelines (17) state that in patients with low pretest probability of CMA (about 10%), based on history and presenting symptoms, it may happen that about 2% children older than 12 months with a negative result of skin prick test (ie, diameter <3 mm) can be misclassified as not having CMA while they actually would be allergic to cow' s milk (false negative results). We have not excluded the two cases of FPIES from this calculation because the onset of the symptoms of this syndrome is usually within the definition of "immediate", ie within 2 hours from beginning of ingestion of guilty food.

MP4 95% PPV CO for GP allow a total savings of 4% of OFC, rising to 22% in the subgroup of children with a previous diagnosis of iCMA (subgroup A2), and, above all, do not give false positives. MP4 95% PPV CO for AS allow a total saving of 33% of OFC, rising to 67% in the subgroup of children with a previous diagnosis of iCMA (subgroup A2), but they give a 9% false positives, and in particular 11% in subgroup A2. 95% PPV CO of alpha-lactoalbumin SPT had the best performance in both setting, and, more generally, all three 95% PPV CO of the extracts, considered individually, were found to have better performances than those of fresh cow's milk, particularly in subgroup A2. Therefore, fresh milk is best suited for the exclusion of the suspicious diagnosis of iCMA, while the extracts are best suited for its confirmation.

Over the past 15 years, many authors tried to correlate

Table 4 - Diagnosis of iCMA with MP4 cut off (CO) with 95% PPV for allergy specialist. The numbers in column indicate the avoidable OFC through the use of CO in question.

	Group A (N. 82)	Subgroup A1 (N. 55)	Subgroup A2 (N. 27)	Group B (N. 109)
Children with definitive iCMA diagnosis and with MP4 CO positives	27	9	18	0
CO fresh cow's milk = 9.3 mm	10	3	7	0
CO alpha-lactoalbumin = 4.9 mm	23	8	15	0
CO beta-lactoglobulin = 5.6 mm	12	5	7	0
CO casein = 4.3 mm	11	1	10	0
Children without definitive iCMA diagnosis and with MP4 CO positives	7	4	3	2
CO fresh cow's milk = 9.3 mm	5	2	3	0
CO alpha-lactoalbumin = 4.9 mm	4	3	1	2
CO beta-lactoglobulin = 5.6 mm	3	2	1	0
CO casein = 4.3 mm	2	1	1	1

SPT results to OFC outcome (6, 11-15) in order to find a cheap and safe test with a good prediction for the diagnosis of iCMA.

Eingemann et al (11) proposed 5 mm SPT CO for extract of whole milk, Sporik et al (12) 6 mm SPT CO for children < 2 years and 8 mm SPT CO for children > 2 years. Verstege et al (13) found 12.5 mm SPT CO for fresh cow's milk in a retrospective study, Mehl et al (14) 13.8 mm SPT CO for fresh cow's milk in a prospective study and Calvani et al (15) 15 mm SPT CO for fresh cow's milk in a retrospective study. It is worth to stress that the CO for fresh cow milk obtained in the last 3 studies (13-15) are very close to our 95% CO GP for fresh cow milk, that refers to a population similar to that of the studies of Verstege et al (13), Mehl et al (14) and Calvani et al (15). This reproducibility reinforces the value of this CO, since we believe that a value of 13 mm for the mean wheal diameter of SPT with fresh cow milk can be adopted with confidence as 95% PPV CO for the diagnosis of iCMA. The topic was also recently discussed. Calvani et al (21) analyzed the PPV of SPT to cow's milk in relation to the diagnosis of CMA, performed by OFC. The transferability and generalizability of the data from this study are partly compromised by the retrospective collection of data and by the great heterogeneity of practice of the enrolled centers. Mehl et al (22) evaluated the concordance between SPT and serum specific IgE levels, the authors didn't provide informations about the PPV or NPV of these tests or about the CO values.

The combination of 4 SPT (whole cow's milk plus 3 extracts of casein, alpha-lactoalbumin and beta-lactoglobulin) has also been studied in the past. Calvani et al (15) retrospectively compared the diagnostic accuracy of SPT with the three extracts with that of SPT with fresh cow's milk in children with immediate and delayed symptoms of CMA. They showed that positive SPT with fresh cow's milk had 98% NPV and that positive SPT to all three cow's milk proteins extracts had 92% PPV. They tried to determine SPT CO to discriminate between allergic and tolerant children and found that the positivity of SPT to all three cow's milk proteins was clinically more useful than any CO. Our results do not allow us to confirm the latter observation. SPT combination to perform iCMA diagnosis has been already studied by Garcia Ara et al (6). The authors prospectively assessed the performance of the 4 SPT (extracts of whole cow's milk, casein, beta-lactoglobulin,alpha-lactoalbumin) and reported high SE (99%) if at least 1 of 4 SPT was positive. They didn't research a CO, but found 97% NPV with mean average weal of ≥ 3 mm. These data were confirmed by ours. We found that fresh cow's milk SPT (or any of 3 extract SPT) had 94% SE and 98% NPV, and that the SE and NPV reach 100% if the 2 children with FPIES are excluded from data analysis. According to our study (100% NPV) and to Calvani et al (98% NPV) SPT with fresh cow's milk can be performed even by a GP who can exclude iCMA if the test is negative and the history is not compatible with FPIES suspect.

In our study we used, for the first time in literature, commercial extracts at known concentration in order to facilitate the reproducibility and transferability of our results. The other novel aspect of our study is the use of a group of children without symptoms suggestive of iCMA (group B).

This was implemented for the following reasons:

- some doctors believe erroneously that the symptoms exhibited by children in group B (i.e., recurrent respiratory infections) are caused by iCMA,
- the same doctors performed the SPT in their office to confirm their suspicion,
- SPT can give false positive result.

We then decided to create two types of CO with 95% PPV, one resulting from the analysis of a high iCMA prevalence population (34/82 [41%] children with diagnosis of iCMA, group A), and the other from the analysis of a low iCMA prevalence population (34/191 [18%] children with diagnosis of iCMA, group A+B), respectively named AS CO and GP CO. It is true that the prevalence of iCMA in the general pediatric population is much lower than 18%, and is about 2% -3% but we wanted to refer to the symptomatic pediatric population for which the GP may suspect iCMA and for which may require either an advice of an allergist or can do the diagnostic and therapeutic process independently. In fact the children of group B were sent by their GP to allergy centers participating in this study with this specific suspect. This behavior is certainly wrong but not unusual: Cruz et al (16) found that doctors sometimes reported neurobehavioral manifestations, musculoskeletal symptoms, and upper airway symptoms to be common in FA. Therefore we included in group B children with such symptoms and found that CO for GP had no false positive and we concluded that, even when iCMA is wrongly suspected, it is never wrongly definitely diagnosed with our CO for GP. We would suggest that a GP could perform MP4 test at its own office, and safely diagnose iCMA by using it, although this is seldom occurred in practice.

The benefit of the CO use of MP4 is most evident in the setting of AS, in this case the savings of OFC is conside-

rably greater, but it pays a price in terms of false positives. The decision whether to accept the risk of unnecessarily go on a diet will be the result of a careful discussion between AS and the child's family.

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