

The predictive value of specific immunoglobulin E levels for the first diagnosis of cow's milk allergy. A critical analysis of pediatric literature

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Investigators have tried to identify a level of seric specific immunoglobulin E (IgE) that had a sufficient predictive value to diagnose a food allergy without having will resort to the food challenge. To search in literature, all the studies that have estimated the possibility to identify a level of seric specific cow milk IgE with a positive predictive value (PPV) of 95% for the first diagnosis of cow's milk allergy (CMA) in pediatric age. We have identified six studies, nearly all studies suffer from relevant methodological bias. Proposed cut-off are all different. The studied pediatric populations were highly selected. Also neglecting the methodological bias of the studies and the great difference of value between the proposed cut-off, it always remains to consider that the pre-test probability of having a CMA between the children enrolled in the six studies included in this review is particularly high. The likelihood ratio helps to transfer the results of a study on a diagnostic test just to our population, and it is more realistic rather than to entrust itself to the PPV or the negative predictive value, that are much influenced from the prevalence of the disease in the studied population.

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The correct procedure for diagnosing any food allergy still today, with rare and well-codified exception, entails performing the food challenge (FC), a procedure that is without doubt a costly one (in terms of both time and money) and not immune from risk (1). Today, very often decisions are taken without following this correct procedure through to the end. One often makes do with a positive laboratory test, in particular specific serum immunoglobulin E (IgE) assay, in our case vs. cow's milk proteins. Many children are not allowed to eat milk as they have high specific IgEs and are kept on a diet while they remain high. But who says that this is correct? How much faith can we have in this?

The cut-off

Table 1, taken from an article by Sampson (2), shows the cut-off for the specific serum IgE levels for the more common of foodstuffs involved in allergic reactions. Above these levels, FC execution is not recommended as there is a >95% probability of a clinical reaction occurring. Sampson's recommendations are comforted by the European Academy of Allergy and Clinical Immunology (EAACI) which states that (3): 'FC may be avoided.....in selected cases where positive test results make challenge unnecessary as is the case in children with positive skin prick test to egg and specific

Table 1. Predictive value of food allergen-specific immunoglobulin E levels [from ref. (2), modified]

Allergen	95% Predictive level (kU/l)	Positive predictive value (%)
Egg	7	98
Infants <2 yr	2	95
Milk	15	95
Infants <2 yr	5	95
Peanut	14	100
Fish	20	100
Tree nuts	15	95
Soybean	30	73
Wheat	26	74

IgE (CAP) above a certain level from 0.35 to 17.5 KUA/l, in which the probability of a positive challenge outcome exceeds 95%.... At present, such a correlation has only been demonstrated in children with Atopic Eczema Dermatitis Syndrome and allergy to selected foods'.

Avoiding the FC is a desire shared by many, also by ourself. At the same time, however, we would like to be reasonably certain that, if we tell a child that he has to avoid a particular food, this recommendation has an adequate foundation. We briefly review the information available in the literature regarding the predictivity of the specific serum IgE assay with reference to food allergies. Furthermore, we shall limit ourselves to predicting cow's milk allergy (CMA) in children being diagnosed for the first time. We shall consider only those studies that claim to have obtained results able to ensure a positive predictive value (PPV) $\geq 95\%$, as less than this is of no use. However, let us briefly examine the criteria (at least the primary ones) that any study concerned with diagnosis should respect, as it is a matter of diagnosis. These criteria are taken from the Users' Guides to the Medical Literature (4, 5) and are set out in Box 1.

The first study at a pediatric age

This is by Sampson and Ho (6), and it is retrospective. It therefore could suffer from numerous biases (no standardization of diagnostic procedures, recall bias, etc.). Among others, the authors studied 109 subjects of pediatric age (average = 5.2 yr), all suffering from atopic dermatitis and suspected CMA. Fifty-four of the patients (50%) were declared allergic to cow's milk by means of FC (in 84% of them and in the majority of the latter by double-blind manner) or convincing history plus the presence of specific IgEs. In this population, a level of serum specific IgEs ≥ 32 kU/l, measured by the Pharmacia CAP-

System, had a sensitivity of 51% and a specificity of 98%, but above all a PPV $\geq 95\%$ vs. an adverse FC reaction to milk.

However, the prevalence of the disease in the population studied strongly affects the predictive value (both positive, PPV, and negative, NPV) of a test, with increasing prevalence the PPV increases and the NPV decreases. And in population of Sampson and Ho (6), the prevalence of CMA was very high (50% of the suspect cases). What would happen if we were dealing with a population with a decidedly lower prevalence? For instance, that attending the surgery of a general pediatrician? Can we always trust the PPV declared by Sampson for his population? To discover a little more, it is better to use not the predictive power but the likelihood ratio (LR). Unlike the PPV and the NPV, the latter is not affected by the prevalence of the disease in the population considered.

The LR and Sampson

The study by Sampson and Ho (6) shows us that a value ≥ 32 kU/l of serum specific IgEs vs. cow's milk has a sensitivity of 51% and a specificity of 98% vs. the diagnosis of CMA in children with atopic dermatitis. Sampson and Ho (6) also tell us that if a child displays this value of specific serum IgE vs. cow's milk (which we call a 'positive result') his probability of having an adverse reaction after ingesting cow's milk protein is $>95\%$: a diagnosis of CMA can then confidently be made without using FC.

The LR for a positive result (LR+) is computed using the simple formula 'sensitivity/1 - specificity'. Using the above values it comes to 25.5 [51% divided by (100% - 98%), i.e. 51/2]. Indeed if we transcribe on to Fagan's Nomogram (see Fig. 1) the pre-test probability of a CMA occurring in the population studied by Sampson and Ho (6) (which we assume to be equal to the prevalence they found, i.e. 50%), and the LR for a positive result (which we saw was equal to 25.5), we find that the post-test probability (i.e. after performing the CAP-System test to find specific serum IgEs vs. cow's milk) of a positive result actually rises to more than 95% (see the gray line in the Fig. 1).

However, if the pre-test probability of the patient we are dealing with is not as high as that of the population studied by Sampson and Ho (6), and is for example around 10%, we find (again in Fig. 1, see the black line) that the post-test probability is around 80%. And on the basis of the latter probability, we would have to tell our young patient to stop drinking cow's milk.

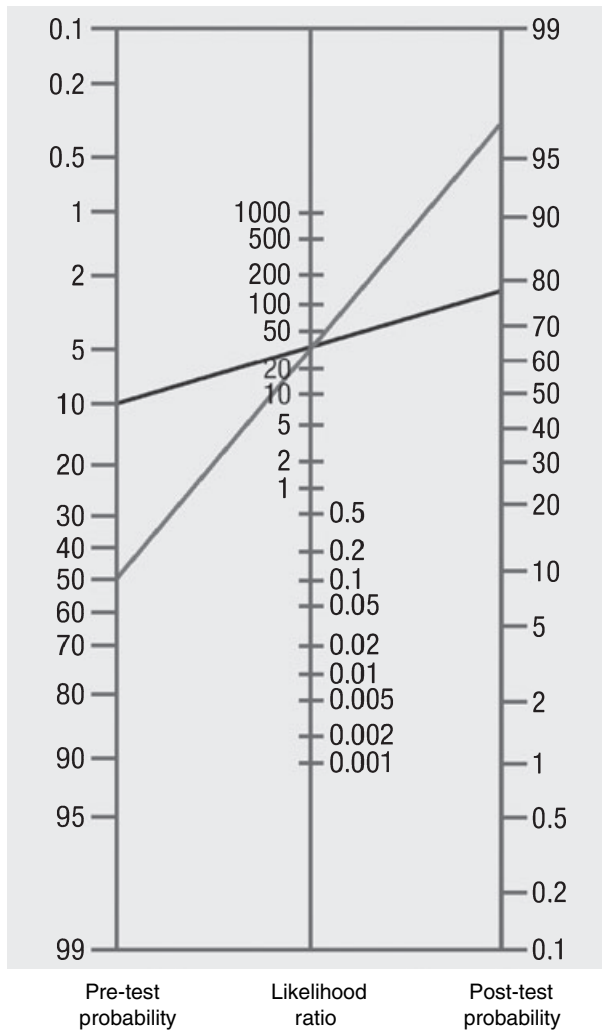


Fig. 1. Fagan's Nomogram for Sampson and Ho (6); explanations are given in the text.

For our, 'only' 80% likelihood of having a CMA is not enough to deprive the child of the pleasure of drinking cow's milk.

And yet, the authors of this study themselves, because of its retrospective nature (i.e. weak from the methodological standpoint and unsuitable to support any management change) felt the need to confirm the results of a prospective study ('...although future prospective studies are necessary to confirm this') which was published in 2001 (7).

The prospective study of Sampson (7)

The population of this second study was, however, selected, 61% of the children had atopic dermatitis, half had asthma and 90% an atopic familiarity. Above all, the vast majority (82%) was allergic to two or more foods, which is certainly not something you encounter every day.

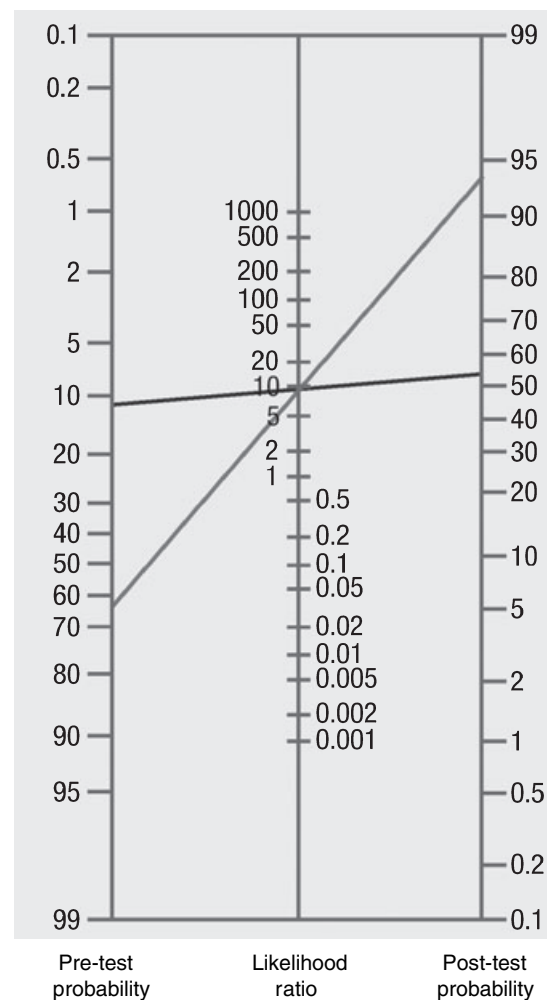


Fig. 2. Fagan's Nomogram for Sampson (7); explanations are given in the text.

Out of the 100 children included, 62 received a diagnosis of CMA (i.e. 62%) and this time Sampson pointed out that he had applied a corrective to take account of the high prevalence of the disease in question in the population he studied. As a result of using this corrective, we are told that this time the cut-off for predicting a CMA with a 95% probability of being right is ≥ 15 kU/l (sensitivity = 57%, specificity = 94% and $LR+ = 9.5$). However, if we compute the LR and once again take into account a pre-test probability of having a CMA of 10% (which may be assumed as the case in a general pediatrician's surgery for children he is treating, for example, for atopic dermatitis), we get a post-test probability that is much lower than 95% (see the black line in Fig. 2).

Furthermore, the criteria used in diagnosing the food allergy in this study are not wholly satisfactory. Indeed the authors: 'For ethical

reasons,..., all parents were informed of the previous study, which suggested that high levels of food-specific IgE antibodies correlated with clinical reactivity to a food, and the results of their child's food-specific IgE antibody concentrations... Consequently, many parents of children with suggestive histories of food allergies and high levels of food-specific IgE antibodies refused to have their children undergo double-blind placebo controlled food challenges (DBPCFCs),..., in the present study only 33% of the diagnoses of egg or milk allergy, 2% of the diagnoses for peanut allergy, and none of the diagnoses of fish allergy was based on DBPCFC results..., the paucity of DBPCFCs clearly impaired our ability to validate the 95% diagnostic decision points for egg, milk, peanut and fish generated in the previous study'. In other words, he notified the parents of the results of the 1997 study (6) and they, if the IgEs were higher than the cut-off established at the time, refused to allow an FC to be carried out on their child. In a 67% of cases, the diagnosis of CMA was made without using the acknowledged 'gold standard', thus failing to observe the most important of the primary criteria laid down by evidence-based medicine (EBM) (4, 5).

Lastly, Sampson (7) concludes his article as follows: 'The final proof of using food allergen-specific IgE levels for the diagnosis of symptomatic food allergy awaits confirmation by other investigators'.

What else have we got?

The problem is of such great clinical importance (the FC, as we have seen, is a risky procedure, costly in terms of both time and financial resources) that has been addressed in at least four other studies. And, on this occasion, we shall consider only those concerned with CMA and children receiving the diagnosis for the first time.

Roehr et al. (8)

The authors enrolled 71 children (average age = 13 months, range = 2 months – 11 yr), all suffering from atopic dermatitis (more than half in a light form, SCORAD < 25) and a clinical history indicative of CMA. They were all assayed for specific serum IgEs using the CAP-System and all underwent a DBPCFC, we do not know whether the DBPCFC executor was aware of the results of the specific IgE assay or not. Forty-five children (63%) had a positive DBPCFC (which would be the CMA prevalence in this popula-

tion). A specific IgE level >0.35 kU/l had a sensitivity of 84%, a specificity of 38% and a PPV of 70%, not enough for our purpose (which is to avoid the FC). With a cut-off of 3.5 kU/l the PPV already increases to 83% (still not enough for our). However, if we push as far as a specific IgE level ≥ 50 kU/l, the sensitivity decreases enormously (up to 6.6%), while the specificity rises to 100% and so the PPV soars to 100%. With a specificity of 100%, the LR+ becomes 'infinite' (see Fig. 3) and the diagnosis becomes certain. This study is methodologically sound. At worst one may not be certain that the FC was carried out without the operator knowing the result of the IgE assay (which is one of the primary criteria for a good study performed on a diagnostic test) and the children are in any case all suffering from atopic dermatitis, an element of population selection and a limit to the

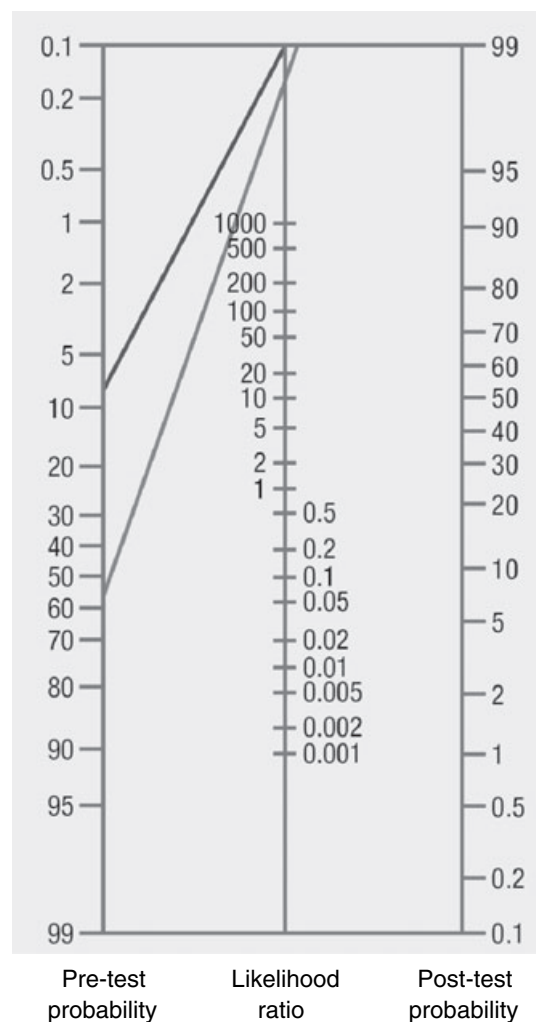


Fig. 3. Fagan's Nomogram for Roher et al. (8); explanations are given in the text.

transferability of the results to children with other manifestations of CMA.

Garcia-Ara et al. (9)

The authors conclude: 'If these values are 2.5 kU/l or greater, the challenge test should not be performed because of its high PPV (90%)'. One-hundred and seventy children are enrolled in a prospective study spanning a period of 4 yr, all aged less than one (median age 4.8 months) and having a suspect immediate reaction to the ingestion of cow's milk. The children were given the prick test, specific serum IgE assay for cow's milk proteins using the CAP-System, FC in an open form (which is not the gold standard of scientific works). Forty-four per cent were declared to have IgE-mediated CMA (which is thus the prevalence of the disease studied in the population in question, and may be likened to their pre-test probability of having an IgE-mediated CMA). Considering solely the most powerful of the results reported by them (the one obtainable using a cut-off ≥ 5 kU/l, which gives a sensitivity of 30% and a specificity of 99%) a LR + of 30 is obtained. Which leads us to post-test probabilities of the order of those shown in Fig. 4.

Saarinen et al. (10)

The authors enrolled 239 Finnish children having an average age of about 7 months and a history indicative of CMA (with reactions that may be classified as being of either of the immediate or the non-immediate type), who had displayed remission of the symptoms on eliminating cow's milk proteins from their diet (therefore, already a first diagnostic step forward had been taken; the starting population, with the indicative case history alone, was numerically about three times larger). There was thus already a population with a greater probability of having a CMA than the general population and also than a population composed of children for whom the suspicion of CMA has just been established. Indeed as many as 118 of them (48%) displayed a clinical reaction to FC, which was however performed in its open form. The authors suggest a cut-off of 3.5 kU/ml, measured using the Pharmacia CAP system, which has a PPV of 94%, a sensitivity of 25% and a specificity of 98%; these values refer to a population with a pre-test probability of having CMA of 48%. If we then decided to transfer their results to our outpatients population, assuming the customary pre-test probability of 10% and taking into account that with the cut-off proposed by Saarinen et al. (10), the

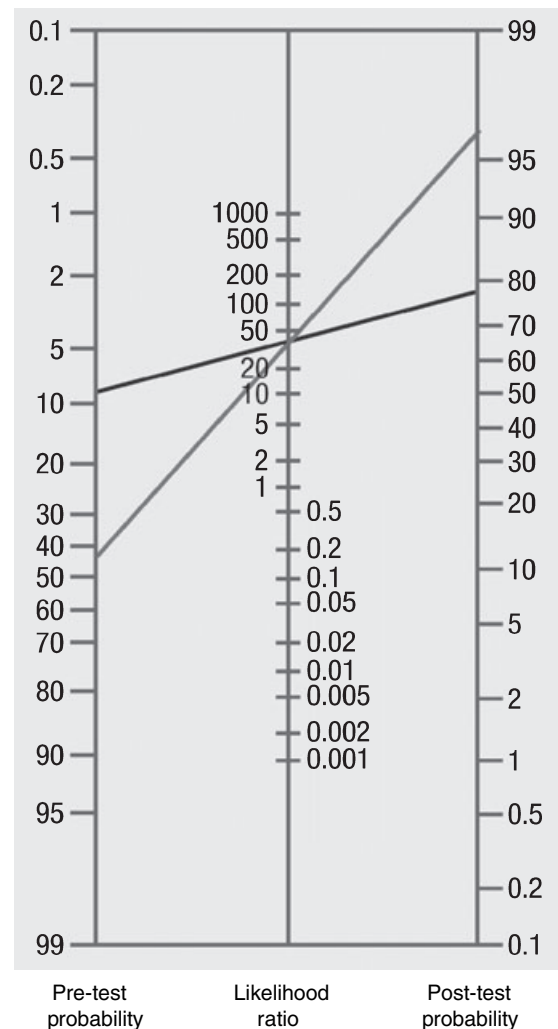


Fig. 4. Fagan's Nomogram for Garcia-Ara et al. (9); explanations are given in the text.

LR + would be 12.5, we would have a post-test probability indicated by the black line in Fig. 5.

Celik-Bilgili et al. (11)

This is the most recent study that has faced the thematic one in object. However, it does not lend itself to the analysis made for the previous ones. The authors indicate a cut-off equal to 88.8 kU/l of specific serum IgE against cow milk proteins: this level has a PPV of 90% vs. the CMA diagnosis. But they do not supply the sensitivity and specificity of this cut-off and, therefore, it is not possible to gain of correspondent LR.

What cut-off ?

In addition to the doubts we have expressed so far, there is another one that we would say is

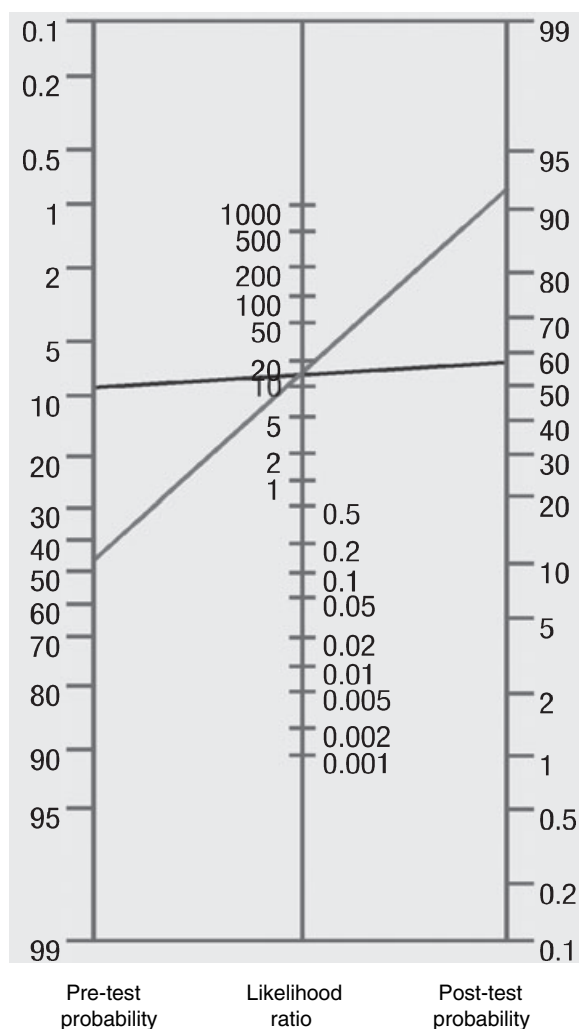


Fig. 5. Fagan's Nomogram for Saarinen et al. (10); explanations are given in the text.

even more elementary. For the specific problem, we examined several cut-offs had been proposed, we shall list them briefly:

- Sampson and Ho (6), 32 kU/l.
- Sampson (7), 15 kU/l.
- Roehr et al. (8), 50 kU/l.
- Garcia-Ara et al. (9), 5 kU/l.
- Saarinen et al. (10), 3.5 kU/l.
- Celik-Bilgili et al. (11), 88.8 kU/l.

Which is the most credible? And on what basis?

Without overlooking the above-mentioned methodological problems, which are also summarized in the following:

- Sampson and Ho (6), retrospective.
- Sampson (7), gold standard not applied in 67% of cases.

- Roehr et al. (8), gold standard perhaps not applied blind.
- Garcia-Ara et al. (9), FC in open form, perhaps non blind comparison between test being experimented and FC.
- Saarinen et al. (10), FC in open form, perhaps non blind comparison between test being experimented and FC.
- Celik-Bilgili et al. (11), do not supplied the sensibility and specificity.

None of them respected the two primary criteria required by the Users' Guide to the Medical Literature (4, 5). The best is that of Roher et al. (8), which nevertheless has one small flaw. And in any case, the results are valid only with the Pharmacia CAP-System method, result transferability is by no means automatic if the specific serum IgE assay is performed using another method. Even if all of this is not taken into consideration, let us take into account the fact that the proposed cut-offs are almost always distinctly high (and so very few children would benefit) and the population to which they refer is prevalently that of atopic dermatitis (in four studies out of six).

Individualization of clinical decision

But above all, it is in any case necessary to remember that (and this is true also in other similar situations), in our daily practice, we must transfer the results of these studies in the populations of which the prevalence of CMA was high (40–60%) to populations with a much lower prevalence (in all likelihood those we customarily have to deal with). And, as we have seen, it is possible to do this using the LR and seeking, or at least imagining, the pre-test probability of there being a CMA that is precisely that of the child we are assessing.

In this way, we are already implementing an 'individualization' of the clinical decision and we do so precisely by virtue of the use of EBM, which has had the merit of disseminating the LR. And we 'individualize' the clinical decision even more when we have draw on our own personal experience and on the needs of that individual patient to establish whether the post-test probability of having a CMA determined by using the LR is enough to eliminate cow's milk from his diet. Or else whether we consider it essential to proceed to the FC, which is a time-consuming, costly and above all risky procedure, as we have already said. But also the elimination diet has been shown to have sometimes adverse and socioeconomic difficulties effects.

The FC

However, is the FC really so risky? Perhaps less than we fear, if Perry et al. (12) saw fit to write: 'Given the benefits that result from a negative challenge, these risks are reasonable when challenges are performed under the guidance of an experienced practitioner in a properly equipped setting'.

And thus, for the time being, we prefer to issue a diagnosis of CMA and recommend a diet free of this food only after performing an FC. One possible exception is perhaps children with atopic dermatitis and a level of specific serum IgE vs. cow's milk (and measured with the CAP-System) that is ≥ 50 kU/l [and we would like to receive confirmation of this from groups other than that of Roher et al. (8)], and certainly in cases of anaphylaxis (occurring within a certain time span after the diagnostic stage) with positive specific IgEs vs. the suspected food.

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BOX 1 – The primary criteria that a study concerned with diagnosis should respect (and some mention of the LR)

Are the study results valid?

Has an independent, blind comparison been made with a standard comparative test?

This means that two criteria must be satisfied:

- The patients studied must be subjected 'both' to the diagnostic test 'and' the reference gold standard.
- The results of one of the two tests must not be communicated to those who are applying and interpreting the other one.

Thanks to this second characteristic, researchers can avoid the conscious or unconscious distortion that might otherwise lead to the reference standard being 'overinterpreted' when the diagnostic test being experimented is positive, and 'underinterpreted' when it is negative. This primary criterion is not placed ahead of all the others by chance. It really is the most important and is not always rigorously observed.

Were the diagnostic tests considered test applied to the sample representative of the patients?

The diagnostic test must be evaluated in a suitable group of patients similar in type to the population treated in which the test may be used. The population must be varied, with different levels of seriousness of the disorder (both in its mild and its severe form, both at an early and an advanced stage, both in treated and untreated patients). Furthermore, a feature of not secondary importance, the test must be administered to patients that 'certainly' do not have the disease (or complication) to be diagnosed and to patients that have disorders that are often confused with the one being studied but who actually do not have the disease in question.

What are the results of the study?

Are the LRs of the test results provided or else the data required to compute them?

The clinical usefulness of a diagnostic test is largely determined by the degree of validity with which it identifies the disease that forms the object of the test. We are accustomed to finding indications of sensitivity and specificity and

occasionally of PPV and NPV. However, the latter suffer from the prevalence of the disease in the sample studied: with increasing prevalence the PPV increases and the NPV decreases.

The LR is better, as it can easily be calculated from the sensitivity and specificity and indicates the extent to which a diagnostic test will increase or decrease the pre-test prob-

ability (of that particular patient) having a given disease (or complication).

It is thus necessary to know the pre-test probability, the LR (for a positive or negative result) and have a Fagan's Nomogram available. This can thus lead to the much desired post-test probability precisely for that particular patient.