

Ruling out food allergy in pediatrics and preventing the “march” of the allergic child

Alessandro Fiocchi, M.D., Gabriel R. Bouygue, M.Sc., Luigi Terracciano, M.D., Teresita Sarratud, M.D., and Alberto Martelli, M.D. (Italy)

ABSTRACT

When a child presents with an allergic symptom, the general pediatrician needs to discriminate which patient has to be sent to the specialist for an allergologic evaluation. If referred, the child will undergo not only skin-prick test, but also more complex specialistic evaluations that we define here as “the march of allergic children.” The objective of this article is to overview the clinical evidence about possible diagnostic interventions to avoid useless referrals of children reported with allergy from the general to the specialist level. Data sources include PubMed, using a search algorithm selecting for diagnostic studies of respiratory and food allergy in all children to August 2005. Also included are commentaries based on the authors’ clinical experience in the allergy unit of a University Hospital in Italy. No study prospectively assessed the rule-out efficacy of clinical history, physical evaluation, and skin-prick test panels on the allergic disease. Three prospective studies on in vitro panels of specific IgE sensitization matched entry criteria. Diverse trial designs and diagnostic criteria precluded meta-analytic methods. The use of in vitro panels proved effective in ruling out the allergic condition in children. The screening efficacy of panels of food and respiratory skin-prick tests remains to be evaluated. With sensitivities and negative predictive values exceeding 90%, in vitro panels can inform the decisions of pediatricians in their capacity as gateway to specialist care. Avoiding the march of allergic children from the GPs to the secondary level is a more realistic goal than preventing the allergic march.

(Allergy Asthma Proc 27:306–311, 2006; doi: 10.2500/aap.2006.27.2924)

Clinicians know that they have to “winnow out” far more patients presenting with “food allergy” symptoms than a rationale-based battery of tests is able to confirm.¹ The diagnosis of *allergy*, as intended by the nomenclature,² is complex because this manifestation of atopy is not easily phenotyped, even in an individual with adverse reactions to food(s). This may result in a child (who may or may not already be embarking on the so-called “allergic career”) and a family being subjected to a quasi routine through various specialists’ offices, depending on the target organ implicated or the clinical suspicion. The rote reaffirmation that “better tests are needed to identify food allergic children” is only a reflection of the secondary level of care problems confronting allergists. In this commentary, we argue that the ruling in or out of the food allergy diagnosis, in the final analysis, rests with the allergist.³ The differential diagnosis of food allergy is a decision process that may entail more than a calendar year of planned interventions. It is in this context that a distinction between tests that are “diagnostic,” i.e., “sen-

sitive,” with high positive predictive value (PPV) and “rule out” or “specific,” with high negative predictive value (NPV), becomes important. It is striking how often this decisional dichotomy between the utilities of tests has been overlooked in the literature. If the basic assumptions of high predictive values are met, the process is apparently quite straightforward: when a sign/test/symptom has a high specificity, a positive result rules in the diagnosis. Conversely, the diagnosis is ruled out when test sensitivity is high and the test outcome is negative.⁴ All too often, however, only the diagnostic utility of single⁵ or combined⁶ tests (i.e., their sensitivity) is emphasized. Proverbially, tossing a coin yields a random outcome if the coin is fair, but “heads” (or “tails”) are arbitrary values. However, the flipping itself is physically determined⁷ and may be biased to land the coin the same way it started out.⁸ Similarly, it is taken for granted that diagnostic tests will have substantial diagnostic (“heads”) and/or screening (“tails”) accuracy if their PPV and/or NPV are high, but the former appears to be deemed more “useful” than the latter (“better diagnostic tests are needed,” the literature claims). In this overview of literature on food allergy diagnosis, greater focus was given to studies that report NPV and on the use of NPV for the purpose of screening out food allergy in children. The reason for this is that food allergy presents a spectrum of disease that runs the whole phenotypical range, and identifying or excluding food allergy requires that tests be selected on their performance char-

From the Department of Child and Maternal Medicine, The Melloni University Hospital in Milan, Italy

A.F. and G.R.B. contributed equally to the conception and write-up of this article. L.T., T.S., and A.M. contributed to the literature overview and clinical background

Address correspondence and reprint requests to Alessandro Fiocchi, M.D., Department of Child and Maternal Medicine, University of Milan Medical School at the Melloni Hospital in Milan, 52 Via Melloni, 20129 Milan, Italy

E-mail address: allerg@tin.it

Copyright © 2006, OceanSide Publications, Inc., U.S.A.

acteristics, factoring the prevalence of the relevant food allergen and the post-test probability of disease to streamline the workup process.

THE EXTENT OF THE PROBLEM

Whether worldwide prevalence is on the rise,^{9–14} has peaked after decades of steady increase,^{15–17} or reflects a peak-and-plateau cycle in the societal expression of allergy will affect how we apply epidemiological findings clinically. Moreover, prevalence (as prior probability) affects decision models and test accuracy analyses. However, the medicalization of atopy in our societies is labor and resource intensive. Allergic rhinitis is estimated to cost billions annually in direct and indirect costs in the European Union¹⁸ and in the United States,¹⁹ where the annual health care costs of asthma have been estimated to approach \$10 billion.²⁰ In a large European regional political unit, such as Lombardy in northern Italy (population 9,000,000), one of every 100 inhabitants requires an evaluation for allergy on a yearly basis and 40% of visits involve children.²¹ Early intervention is an increasing clinical challenge for general practitioners (GPs) as well as a burden for health authorities the world over.²² Early intervention implies early diagnosis,²³ which, under the present “epidemic” conditions of perceived allergy, requires integration and synergy between stakeholders at all levels of the medicalization process of allergic disease (Fig. 1). There is also a medical education effort to be made as how diagnostic test properties relate to the individual patient. This is not always appreciated equally by all the practitioners who may be involved in caring for a child presenting with suspected food allergy. The methodological quality and adherence to standards of reporting²⁴ by test evaluation studies often also demands study time and commitment incompatible with all medical settings.

OBJECTIVES AND METHODS OF THIS OVERVIEW

We retrieved studies from the National Center for Biotechnology Information (NCBI) PubMed database running the following search algorithm: [screening AND “respiratory allergy” AND “food allergy”/OR asthma/OR rhinitis/OR anaphylaxis/OR eczema/AND history/AND “skin-prick test”/OR “specific IgE”] and setting the following limits: 0–18 years, English, January 1975–August 2005 to assess the ruling out efficacy of tests, the inclusion criterion was the reporting of NPV assessed against the clinical diagnosis of allergy as reference standard. In this overview, the diagnostic interventions considered were clinical history and physical evaluation, skin-prick test (SPT), food allergen-specific IgE determinations, and allergen panels. Their utility to rule out food allergy in children

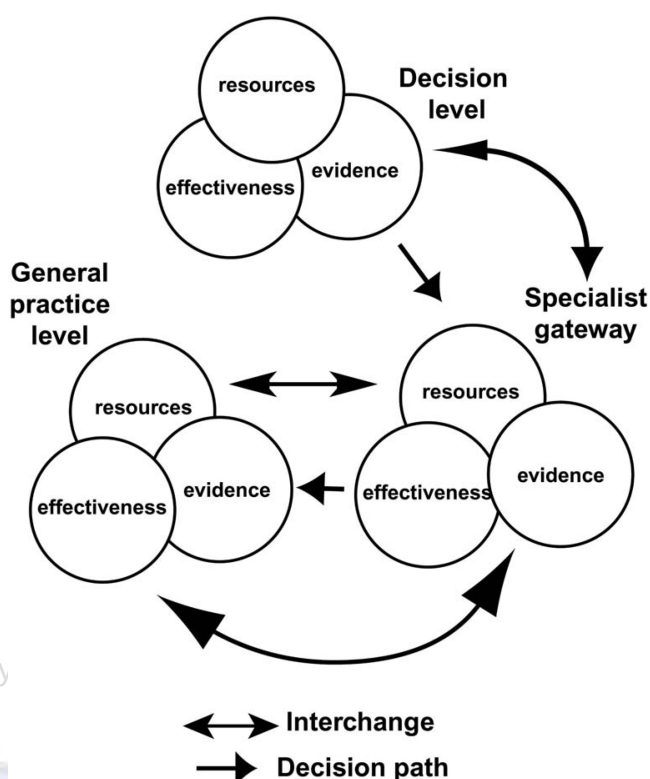


Figure 1. Interactions and competences of the three levels of care involved in the allocation of medical resources available for clinical diagnostic tests in allergy medicine in Lombardy, Italy. The medical networks summarized here show how diagnostic/screening tests are assigned on the basis of e SpPin/SnNout utilities for testing method positioning.²² The priorities and requisites of the three levels of care are represented symbolically as a pile of three coins that may be flipped at need. The relative importance of each item is represented by the position of the coin in the pile. “Resources” are actually at the disposal of all levels and thus uppermost in the decision level pile. “Evidence” represents the performance characteristics of the tests. “Effectiveness” represents their screening NPV. It should be noted that evidence and effectiveness as defined hold different meanings to different stakeholders in the network. The interchange arrows connote interactions between levels and single items, whereas “decision path” arrows show their impact as a result of policy implementation. The figure of the “general pediatrician” is unique to Italy and Spain but this level of care corresponds to the GP and primary care elsewhere.

(expressed as NPV) was analyzed instead of their diagnostic efficacy.

RESULTS OF THE LITERATURE OVERVIEW SEARCH

Three hundred five studies fulfilled the inclusion criteria and were analyzed. Expert clinical literature readers from our research team rejected articles ($n = 180$) on the grounds of relevance, *i.e.*, for not reporting NPV/screening utility or for considering only patients with a positive history. Many studies were excluded

because intervention (diagnosis or nonpharmacologic therapy) was not consistent with controlled trial design. Test blindness was not among inclusion criteria but would have excluded more studies. Reviews ($n = 44$) and irretrievable full-text items ($n = 42$) were not considered. The remaining 39 articles differed so markedly in study populations, types of diagnostic intervention, study design, and outcome assessment methods to preclude attempts at systematization.

CLINICAL HISTORY

A study of children and adolescents seeking an allergist's help reported that clinical history and physical examination together generate a low 1.6% false negative rate.²⁵ History of food allergy identified 35% of 124 adults and only 3 of 30 children in a study appraising the diagnosis of natural rubber latex allergy.²⁶ For comparison outside the food allergy context, in a population of children with spina bifida who underwent direct challenge, history of previous reactions to natural rubber latex generated a 75.6% NPV.²⁷ Thus, in this population, the NPV of history in the diagnostic pathway was far lower than the NPV of SPT (98.3%), CAP technology (Pharmacia Diagnostics, Uppsala, Sweden) determination (96.6%), and immunoblotting (96.2%). Therefore, in the context of allergy to natural rubber latex, the rule-out utility of allergy history was clearly arguing in favor of a screening positioning. This is less striking in the wider context of food and respiratory allergy. In a recent study of 139 children under the age of 4 years referred for allergy evaluation by their primary care physicians, case history (*i.e.*, symptom duration and severity, triggering factors, and a family history of IgE-mediated allergy) and physical examination were able to anticipate only 71/147 diagnoses (31 children were diagnosed with IgE-mediated allergy and 40 children were diagnosed with IgE-mediated food allergy). A full diagnostic evaluation, including SPT, specific IgE determination, and—if appropriate—oral food challenges classified 73 children as “with an inconclusive preliminary diagnosis.” As an effect of the specialist's evaluation, 11/71 of the preliminary evaluations were modified and 2.7% were found to be false negative.²⁸ Therefore, given the high rate of “inconclusive” histories, history and physical examination are far from being up to the task of identifying candidates unlikely to benefit from referral to an allergist.

SKIN PRICK TESTS

It has been noted that negative SPT results can be useful in ruling out allergic sensitization and therefore immediate reactions to cow's milk hydrolysates,^{29,30} but no study retrieved investigated the screening value of SPT in pediatric allergy prospectively. There is also double-blind, placebo-controlled food challenge evi-

dence that a negative SPT outcome can not rule out allergy to the often implicated hazelnut,³¹ fruits and vegetables,³² egg,³³ and cereal³³ allergens. In a 1997 study, the performance characteristics of SPT were calculated using a 3-mm wheal diameter as positivity threshold against double-blind, placebo-controlled food challenge outcome. The NPV of SPT with different food allergens varied between 80 and 94%.³³ Sensitivity and specificity were high, but the question of positioning of tests was not discussed. Since then, a number of studies have specifically addressed the relevance of SPT with commercial extracts and fresh foods in diagnosing and excluding food allergy in a pediatric setting.^{33–38} However, because of evidence of epitope and allergen characterization in the test material, standardization of SPT material remains elusive in commercially available reagents.³⁹

SPECIFIC IgE DETERMINATIONS

Specific IgE determinations are accepted predictors of allergy in pediatrics.⁴⁰ Their rule-out performance depends on the allergen being tested and on the cutoff thresholds considered the best discriminant in the interpretation, but many studies fail to report their respective predictive values for specific IgE determinations. A receiver-operating characteristic curve can be used to analyze IgE levels to find the cutoff point that yields the highest combined sensitivity and specificity to predict the outcome of IgE level determinations tests or technology. In a sample of 34 atopic children, a specificity of no more than 57.1% (PPV = 93.15) and 90% sensitivity, negative CAP technology outcome did not rule out beef allergy but had good diagnostic performance (NPV = 65.2%) with a 1.8 kUI/L cutoff.⁴¹ In the same series, IgE levels below 0.35 kUI/L were not found in children who did not respond at oral challenge with beef. Thresholds were so low for beef that a negative CAP test with beef can be considered an almost-perfect rule-out test.

ALLERGEN PANELS

In IgE-mediated allergic disease the use of allergen panels is now routine. Although no studies have specifically addressed the screening utility of composite SPT panels, panels for *in vitro*-specific IgE determinations are used widely. These panels are set at a low cutoff level and have been in use as qualitative serologic tests since the 1980s.⁴² Their performance against RAST has been ascertained in adults⁴³ and in children and are consistent and reproducible.^{44,45} With a clinical sensitivity invariably higher than their specificity (*e.g.*, 93% versus 89%⁴⁶), in young adults with respiratory allergy, the rule-out utility of a panel of inhalant allergens is impressive (NPV of up to 99.8%⁴⁷). In pediatrics, presently, there are only two studies directly com-

paring the accuracy of specific IgE panels against the standard allergy workup, using the clinician diagnosis as a reference test to calculate test sensitivity and specificity. Williams and colleagues²⁵ assessed 145 children and adolescents for suspected respiratory allergic disease and compared the allergist's conclusion based on history, physical examination, SPT, and specific IgE determinations by UniCAP Phadiatop. All patients with a positive diagnosis of allergy and all those diagnosed as nonallergic were identified correctly by the test, with a sensitivity and a specificity of 100%, with consequent near-perfect NPV. In a recent assessment of a qualitative test to detect IgE antibody to common food and inhalant allergens, using a physician diagnosis as reference standard, generated a sensitivity and specificity of 92% (PPV = 80%) and 82% (NPV = 93%), respectively. Stratification on age (0–2 years and 2–4 years) or symptoms did not show large differences in performance characteristics.²⁸ Another pediatric evaluation of the performance characteristics of two allergen panels (respiratory and food allergens) was aimed at investigating their sensitivity and specificity against the suspicion of allergic disease.⁴⁸ This study confirms that a high NPV suggests the use of these panels as a first approach to rule out negative patients. A similar lesson may be drawn from a recent study performed in a primary care setting.⁴⁹ However, because this study aimed at evaluating the impact of tests on practical management more than on diagnosis, true and false negative rates are not reported. Therefore, the design of the study does not allow us to calculate the rule-out value of the allergen panel used.

RULE-OUT TEST NPV AND LEVELS OF CARE

In pediatric allergy, a streamlined, patient-oriented, efficiency-based model of the management process does not exist and the rule-out utility of common diagnostic interventions is not widely considered in the literature. The retrieved studies deal with questions of management without considering the objective positioning of the available tests as so many screening instruments, *i.e.*, ideally requiring no further medical act. Instead, we advocate choosing rule-out tests on the basis of (1) the performance characteristics of the test, (2) the prevalence (or its estimation) of the condition being tested, and (3) the availability of additional resources. However, the lesson from the current literature is not only that tests are not selected based on their performance characteristics, but that their rule-out utility is ignored in its preventive possibilities regarding referrals. SPT research in particular is hampered by the fact that test materials from different manufacturers and even different batches may differ, processing can influence the performance of an allergen as an in-office procedure,^{50,51} and native allergen extracts and differ-

ent preparations of the same foods defy standardization if not reproducibility. Thus, it is not surprising that the performance characteristics of SPTs with food allergens may vary. This should not detract from the general opinion, borne out by the present overview, that a negative SPT can be considered a good rule-out instrument.¹ The only tests that were extensive enough to describe the performance characteristics were the *in vitro* determinations measurements of allergen panels, which can even be proposed as a useful tool at the general level of care in the context of screening. Additional research is needed to confirm that the use of an allergen panel may halve the number of allergic referrals, as has been claimed. However, it is sobering from an economical point of view that many referrals from the primary care setting to the specialist level might have been prevented if a clear-cut diagnostic decision of “nonatopy” had been made on the most appropriate test(s) selected on their proper positioning.

DISCUSSION

Allergic disease is more frequent in childhood and rule-out tests with high discriminating potential have an important gateway function to fulfill for screening children among whom allergic symptoms may be difficult to distinguish from, *e.g.*, respiratory infections. Genetics also is in the wings, but here too, in the absence of markers identifying patients at risk, in order to plan for early intervention to slow down or interfere with atopic disease progression is the main clinical challenge.^{22,52–59} Children undergoing assessment should not be put through the double jeopardy of not only experiencing the full sequence of the “allergic march,” but also of being “marched” from the GP's office to specialist clinics (and, sometimes, through several subspecialties: ear, nose, and throat; dermatology; ophthalmology; pulmonology; various pediatricians, etc.) before completing the workup in a hospital allergy department under a pediatrician allergist. We argue that to prevent this, second-tier pediatricians and allergists who are able to identify appropriate diagnostics (a SnNout-type test⁴) within their local area of competence and epidemiological context work out a screening instrument for food allergy.

Literature on the performance characteristics of diagnostic tests teaches us how performance characteristics are useful to validate the selection process we make among available tests for acute patients and referrals. In practice, however, this decision process does not occur in a medical vacuum, but is socialized as “allergy medicine.” The importance assumed by managed care and health maintenance organizations in this respect argues in favor of rationalizing the process of test selection to make the best use of the resources that diagnostics represent. Al-

though a “unified theory” of positioning tests lies beyond the scope of the present commentary, as an illustration, we provide a sketch of how positioning food allergy tests is organized within the remit of a regional health authority. Figure 1 shows real-life conditions in Northern Italy (described elsewhere⁶⁰) and illustrates the context into which rule-out test performance characteristics are inserted and ultimately should be made use of and the difficulty of interpreting negative test results in the public health context in which allergy tests are used. In the literature we searched, none of the evaluated items have NPV sufficiently relevant for use as an all-round rule-out test for atopic disease. The utility of both SPT and specific IgE as SnNout tests is overlooked by most studies. None has been specifically designed to evaluate the performance characteristics of the clinical history and the physical exam, *e.g.*, and the literature we examined confirms that—except for latex allergy—history alone is uninformative for the purpose.⁶¹ Low NPV is found when history and physical evaluation are performed by a secondary level caregiver to whom children have been sent based on a GP/pediatrician’s suspicion, but the percentage of negative clinical histories is expected to be low²¹ and one can assume that at the GP starting level the percentage of false negative histories should be far higher. From this review of the rule-out ability of tests in the pediatric literature we conclude that the burden represented by indiscriminate testing may be avoided. SPTs are good rule-out tests for single allergens, but studies using standardized reagents could be designed to indicate the screening value of SPT panels. Specific IgE determinations also have high screening value for individual allergens, but the studies we reviewed positioning panels of specific IgE as screening tests is difficult because of the heterogeneity of populations and diagnostic end points studied. Nevertheless, in the present epidemiological situation, *preventing the march of allergic children* is an inescapable task for the GP, and, probably, it is a more realistic objective than preventing the *allergic march*.

REFERENCES

- Fiocchi A, Bouygue GR, Restani P, et al. Accuracy of skin prick tests in bovine protein allergy (BPA). *Ann Allergy Asthma Immunol* 89(suppl 1):26–32, 2002.
- Johansson SG, Hourihane JO, Bousquet J, et al. and the European Academy of Allergology and Clinical Immunology (EAACI) nomenclature task force. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 56:813–824, 2001.
- Zeiger RS, and Schatz M. Effect of allergist intervention on patient-centred and societal outcomes: Allergists as leaders, innovators, and educators. *J Allergy Clin Immunol* 106:995–1018, 2000.
- Straus SE, Richardson WS, Glasziou P, and Haynes RB. Evidence-based Medicine. In *How to Practice and Teach EBM*, 3rd ed. Edinburgh: Churchill Livingstone, 2005, 67–93.
- Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 107:891–896, 2001.
- Roehr CC, Reibel S, Ziegert M, et al. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 107:548–553, 2001.
- Vulovic VZ, and Prange RE. Randomness of a true coin toss. *Phys Rev A* 33:576–582, 1986.
- Diaconis P. The search for randomness. In *Proc. of the American Association for the Advancement of Science Annual Meeting*, Seattle, WA, February 14, 2004.
- Burr ML, Butland BK, King S, and Vaughan-Williams E. Changes in asthma prevalence: Two surveys 15 years apart. *Arch Dis Child* 64:1452–1456, 1989.
- Aberg N, Hesselmar B, Aberg B, and Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 25:815–819, 1995.
- Kalyoncu AF, Selcuk ZT, Enunlu T, et al. Prevalence of asthma and allergic diseases in primary school children in Ankara, Turkey: Two cross-sectional studies, five years apart. *Pediatr Allergy Immunol* 10:261–265, 1999.
- Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 8:161–176, 1997.
- Latvala J, von Hertzen L, Lindholm H, and Haahtela T. Trends in prevalence of asthma and allergy in Finnish young men: Nation-wide study, 1966–2003. *BMJ* 330:1186–1187, 2005.
- The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 351:1225–1232, 1998.
- Nickel R, Lau S, Niggemann B, et al. Messages from the German Multicentre Allergy Study. *Pediatr Allergy Immunol* 13(suppl 15):7–10, 2002.
- Kurukulaaratchy RJ, Fenn M, Twiselton R, et al. The prevalence of asthma and wheezing illnesses amongst 10-year-old school-children. *Respir Med* 96:163–169, 2002.
- Zollner IK, Weiland SK, Piechotowski I, et al. No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992–2001. *Thorax* 60:545–548, 2005.
- Van Cauwenberge P. Advances in allergy management. *Allergy* 57(suppl 75):29–36, 2002.
- Blais MS. Important aspects in management of allergic rhinitis: Compliance, cost, and quality of life. *Allergy Asthma Proc* 24:231–238, 2003.
- O’Connell EJ. The burden of atopy and asthma in children. *Allergy* 59(suppl 78):7–11, 2004.
- Lombardy Regional Health Authority Public Hygiene Service. Regional Handbook for the Prevention, Diagnosis, and Treatment of Allergic Diseases, Milan, Italy: Lombardy Regional Council, 1999 [in Italian].
- Wahn U, and Von Mutius E. Childhood risk factors for atopy and the importance of early intervention. *J Allergy Clin Immunol* 107:567–574, 2001.
- Host A, Andrae S, Charkin S, et al. Allergy testing in children: Why, who, when, and how? *Allergy* 58:559–569, 2003.
- Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. *BMJ* 326:41–44, 2003.
- Williams PB, Siegel C, and Portnoy J. Efficacy of a single diagnostic test for sensitization to common inhalant allergens. *Ann Allergy Asthma Immunol* 86:196–202, 2001.

26. Hamilton RG, and Adkinson NF Jr. Diagnosis of natural rubber latex allergy: Multicenter latex skin testing efficacy study. Multicenter Latex Skin Testing Study Task Force. *J Allergy Clin Immunol* 102:482–490, 1998.
27. Gruber C, Buck D, Wahn U, and Niggemann B. Is there a role for immunoblots in the diagnosis of latex allergy? Internethod comparison of in vitro and in vivo IgE assays in spina bifida patients. *Allergy* 55:476–483, 2000.
28. Fiocchi A, Besana R, Ryden AC, et al. Differential diagnosis of IgE-mediated allergy in young children with wheezing or eczema symptoms using a single blood test. *Ann Allergy Asthma Immunol* 93:328–333, 2004.
29. Sampson HA, Bernishel-Broadbent J, Yang E, and Scanlon SM. Safety of casein hydrolysate formula in children with cow's milk allergy. *Pediatrics* 90:463, 1992.
30. Rance F, Brondeau V, and Abbal M. Use of prick-tests in the screening of immediate allergy to protein: 16 cases. *Allerg Immunol (Paris)* 34:71–76, 2002.
31. Ortolani C, Ballmer-Weber BK, Hansen KS, et al. Hazelnut allergy: A double-blind, placebo-controlled food challenge multicenter study. *J Allergy Clin Immunol* 105:577–581, 2000.
32. Ortolani C, Pastorello E, Farioli L, et al. IgE-mediated allergy from vegetable allergens. *Ann Allergy* 71:470–476, 1993.
33. Rancé F, Juchet A, Brémont F, and Dutau G. Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges. *Allergy* 52:1031–1035, 1997.
34. Eigenmann PA, and Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 9:186–191, 1998.
35. Saarinen KM, Suomalainen H, and Savilahti E. Diagnostic value of skin-prick and patch tests and serum eosinophil cationic protein and cow's milk specific IgE in infants with cow's milk allergy. *Clin Exp Allergy* 31:423–429, 2001.
36. Majamaa H, Moisio P, Holm K, et al. Cow's milk allergy: Diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 54:346–351, 1999.
37. Eigenmann PA, and Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. *Pediatr Allergy Immunol* 11:95–100, 2000.
38. Hill DJ, Heine RG, and Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol* 15:435–441, 2004.
39. Bernishel-Broadbent J. Allergenic cross-reactivity of food and characterization of food allergens and extracts. *Ann Allergy Asthma Immunol* 75:295–303, 1995.
40. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 107:891–896, 2001.
41. Fiocchi A, Travaini M, and Decet E. Optimisation of RAST for beef allergy using a cut-off point calculated by ROC analysis. *Ann Allergy Asthma Immunol* 84:168, 2000.
42. Merrett J, and Merrett TG. Phadiatop—A novel IgE antibody screening test. *Clin Allergy* 17:409–416, 1987.
43. Wever AM, Wever-Hess J, van Schayck CP, and van Weel C. Evaluation of the Phadiatop test in an epidemiological study. *Allergy* 45:92–97, 1990.
44. De Amici M, Colivicchi M, and Monafó V. Phadiatop-Paediatric, a new screening test for atopy: A comparison with RAST results. *Pediatr Med Chir* 15:189–191, 1993.
45. Naspitiz CK, Sole D, Aguiar MC, et al. Phadiatop in the diagnosis of respiratory allergy in children. *J Pediatr (Rio J)* 80:217–222, 2004.
46. Paganelli R, Ansotegui IJ, Sastre J, et al. Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new in-vitro test system, uniCAP, in six European allergy clinics. *Allergy* 53:763–768, 1998.
47. Matricardi PM, Nisini N, Pizzolo JG, and D'Amelio R. The use of Phadiatop in mass-screening programmes of inhalant allergies: Advantages and limitations. *Clin Exp Allergy* 20:151–155, 1990.
48. Altrineti V, Salmaso C, Montagna P, et al. Sensitization to food or inhalant allergens in pediatric patients. Clinical usefulness of first-level panel tests for specific IgE. *J Investig Allergol Clin Immunol* 13:286–289, 2003.
49. Duran-Tauleria E, Vignati G, Guedan MJ, and Petersson CJ. The utility of specific immunoglobulin E measurements in primary care. *Allergy* 59(suppl 78):35–41, 2004.
50. Martínez San Ireneo M, Ibanez Sandin MD, Fernandez-Caldas E, et al. The diagnostic value of crude or boiled extracts to identify tolerant versus non tolerant lentil-sensitive children. *Ann Allergy Asthma Immunol* 86:686–690, 2001.
51. Fiocchi A, Restani P, Riva E, et al. Heat treatment modifies the allergenicity of beef and bovine serum albumin. *Allergy* 53:798–802, 1998.
52. Bergmann RL, Wahn R, and Bergmann KE. The allergy march from food to pollen. *Environ Toxicol Pharmacol* 4:79–83, 1997.
53. Wahn U, Bergmann R, Kulig M, et al. The natural course of sensitization and atopic disease in infancy and childhood. *Pediatr Allergy Immunol* 8:16–20, 1997.
54. Nickel R, Kulig M, Forster J, et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 99:613–617, 1997.
55. Kulig M, Bergmann R, Klette U, et al. Long-lasting sensitization to food during the first two years precedes allergic airway disease. *Pediatr Allergy Immunol* 9:61–67, 1998.
56. ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: First results of ETAC. *Pediatr Allergy Immunol* 9:116–124, 1998.
57. Kulig M, Bergmann R, Klettke U, et al. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 103:1173–1179, 1999.
58. Wickman M. When allergies complicate allergies. *Allergy* 60(suppl 79):14–18, 2005.
59. Sampson HA. Can we diagnose atopy with a laboratory test? *Ann Allergy Asthma Immunol* 93:307–308, 2004.
60. Fiocchi A, Qualizza R, Martelli A, et al. Local feedback from food allergy prevention guidelines. *Int J Pediatr* 29:130–136, 2003.
61. Bahna SL. Diagnosis of food allergy. *Ann Allergy Asthma Immunol* 90(suppl 3):77–80, 2003. □