

Current reviews of allergy and clinical immunology

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Section editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

Peanut allergy: Emerging concepts and approaches for an apparent epidemic

Scott H. Sicherer, MD, and Hugh A. Sampson, MD *New York, NY*

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Peanut allergy is typically lifelong, often severe, and potentially fatal. Because reactions can occur from small amounts, the allergy presents patients with significant obstacles to avoid allergic reactions. In North America and the United Kingdom, prevalence rates among schoolchildren are now in excess of 1%, framing an increasing public health concern and raising research questions about environmental, immunologic, and genetic factors that may influence outcomes of peanut allergy. This review focuses on recent observations that continue to question the influences of maternal and infant diet on outcomes of peanut allergy, and explore how peanut may be uniquely suited to induce an allergic response. We highlight studies that affect current diagnosis, management, and the nature of advice that can be provided to patients, including the utility of diagnostic tests, doses that elicit reactions, characteristics of reactions from exposure, issues of cross-reactivity, concerns about peanut contamination of manufactured goods, and the natural course of the allergy. Clinical, molecular, and immunologic advances are reviewed, highlighting research discoveries that influence strategies for improved diagnosis, prevention, and treatment. Among the therapeutic strategies reviewed are sublingual and oral immunotherapy, anti-IgE, Chinese herbal medicine, and vaccine strategies. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Food allergy, food hypersensitivity, peanut allergy, food allergens, anaphylaxis, treatment

Among food allergies, peanut, *Arachis hypogaea*, has attracted the most research attention because the allergy is relatively common, typically permanent, and often severe.

From the Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine.

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Reprint requests: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: scott.sicherer@mssm.edu.

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Abbreviations used

FDA: US Food and Drug Administration
HKE: Heat-killed *Escherichia coli*
ISS: Immunostimulatory sequence
mAra h 1-3: Modified Ara h 1-3
ODN: Oligodeoxynucleotide
OIT: Oral immunotherapy
OR: Odds ratio
SLIT: Sublingual immunotherapy
SPT: Skin prick test
UK: United Kingdom

Several recent studies from North America and the United Kingdom (UK) place peanut allergy rates among children near or slightly over 1%,¹⁻³ with a recent report of a cohort of children 4 to 5 years old from the UK born between 1999 and 2000 having a rate of peanut allergy of 1.8% (95% CI, 1.1% to 2.7%).⁴ Peanut allergy resolves for only ~20% of young children by school age.^{5,6} Food anaphylaxis fatality registries in the United States implicate peanut as a trigger in 59% of 63 deaths,^{7,8} though a report from the UK for a similar period implicated peanut as a less common cause, 19% of 48 fatalities.⁹ Fatality registries also indicate that adolescents and young adults are at greatest risk, with additional risk factors being asthma and delayed injection of epinephrine during anaphylaxis. Peanut is a ubiquitous food, and affected patients, who often react to small doses,¹⁰ are faced with numerous hurdles to avoid ingestion and experience an expected negative effect on quality of life.^{11,12} Unfortunately, accidental ingestion is common, with an annual incidence rate of 14.3% reported among schoolchildren in Montreal, Quebec, Canada.¹³

There appears to be an increase in peanut allergy. In population-based US studies using random calling, self-reported peanut allergy for children rose from 0.4% in 1997 to 0.8% in 2002 ($P = .05$).¹ Grundy et al² reported peanut sensitization and reactivity in a birth cohort of children 3 and 4 years old on the Isle of Wight, UK, born between 1994 and 1996 and compared the results with those of a cohort born in 1989, evaluated at age 4 years. They documented a 2-fold increase in reported peanut allergy

(0.5% to 1.0%; $P = .17$) and a 3-fold increase in sensitization (1.1% to 3.3%; $P < .001$). After analysis that included oral challenges, the total estimate for clinical peanut allergy was 1.5% among the 1994 to 1996 cohort.

The severity and persistence of peanut allergy and the apparent rise in prevalence raise important management and public health issues. In this review, we focus on advances published in the 5 years since our last reviews of this topic,^{14,15} emphasizing observations that affect current diagnosis and management primarily with regard to children, and we highlight clinical, molecular, and immunologic advances that may provide insights toward better prevention, diagnosis, and treatment in the future.

CLINICAL INSIGHTS REGARDING THE EPIDEMIC OF PEANUT ALLERGY

Peanut allergy is being described as “epidemic” only in certain countries, an observation that may provide clues toward etiology and prevention. When considering breathlessness as a reported symptom of a reaction to food from among 15 countries, peanut was identified as the most common food only for the United States.¹⁶ The estimated rate of peanut allergy in France is 0.3% to 0.75%¹⁷; in Denmark it is 0.2% to 0.4%¹⁸; and in a cross-sectional study from Israel, peanut allergy diagnosed by history and skin test was found in only 0.04%.¹⁹ In a review of food allergy in Asia, Shek and Lee²⁰ indicated a paucity of studies, but peanut allergy was considered uncommon, and a prevalence study of Thai children failed to disclose a significant rate of peanut allergy.²¹ The various international studies use diverse diagnostic criteria and age groups, precluding specific comparisons. Nonetheless, these observations raise the issue of whether international discrepancies and recent increases in peanut allergy prevalence reflect a peanut-specific phenomenon or are simply a reflection of the epidemiology of atopic disease in general, where westernization is associated with increased atopy, even within countries such as China (where atopy is higher in Hong Kong compared with less westernized regions).²² For example, serologic studies showing likely peanut and egg allergy²³ among 231 children with asthma (age ~9 years) in China (Hong Kong) were 0.9% and 1.3%, respectively,²⁴ whereas among 277 inner city US children²⁵ (age ~6 years), the rates were 5% and 3.6%, indicating a lower rate of both allergies in China (in a region with increased atopy) and just a slight preponderance of peanut compared with egg allergy in the United States. International differences in atopy rates and the rise of atopic disease in some regions have been attributed to differential exposure to infection, commonly termed the hygiene hypothesis, an albeit controversial notion that for peanut has been demonstrated in a murine model in which antibiotic treatment increased ease of peanut sensitization.²⁶ Additional global influences include the use of vitamins,²⁷ exposure to sunlight with regard to vitamin D,²⁸ maternal/infant diet,²⁹ and, for food allergy, anti-acid medications that may prevent destruction of potential allergens during digestion.³⁰

Although genetic and environmental influences on atopy are undoubtedly partly responsible for the observed epidemiologic characteristics of peanut allergy, there are also genetic^{31,32} and environmental features that are specific to peanut allergy (Fig 1). Ostensibly, ingestion of peanut is the sensitizing route, which raises concerns about maternal ingestion of peanut during pregnancy and lactation and the timing of introduction of peanut to an infant or child. In the UK, the Department of Health, and in the United States, the American Academy of Pediatrics,³³ provided recommendations from 1998 to 2000 aimed toward women with infants at risk for atopy to avoid peanut during pregnancy and lactation, and to avoid feeding peanut to the child until age 3 years. It is potentially of concern that in these 2 regions, peanut allergy in children doubled since the advice was initiated, although this does not imply cause and effect. Interestingly, peanut was introduced to children in the UK at around 12.6 months for a cohort born in 1989 (peanut allergy rate, 0.5%)³⁴ and near 36 months for a cohort born between 1999 and 2000 (peanut allergy rate, 1.8%).⁴ Also of concern is that the rate of peanut allergy appears much lower in Israel, where the age of introduction is earlier (<12 months), although the preparation (boiled vs roasted) may differ, or the amount consumed may be less.^{19,35} Insights from studies about parents following the UK health department advice are emerging, so far without documenting a significant influence on outcomes for those following the advice.^{4,36} For example, Hourihane et al⁴ evaluated parent-child pairs of a school cohort born after the UK peanut avoidance advice (1072 children born 1999-2000) and showed no effect of atopy on following the advice and that only about 4% stopped all peanut during pregnancy and/or lactation, although nearly half reduced consumption. In evaluating the children with peanut allergy ($n = 20$), 8 had reduced and 1 stopped peanut during pregnancy, and peanut was introduced into the diet at 32 months among sensitized and 29 months among nonsensitized children ($P = .42$). The authors interpreted their findings as indicating that the avoidance advice had no discernible effect on the prevalence of peanut allergy. As indicated by studies in animal models, sensitization or tolerance depend on dosing amount and frequency,³⁷⁻³⁹ and human studies may not discern the influence of dosing on the basis of recall diets. Emerging studies question the sensitizing role of *in utero*^{40,41} or early oral exposures to allergen,⁴² but this area remains unresolved. Additional theories about the rise in peanut allergy implicate processing that could increase allergenicity such as roasting, emulsifying, and including additives⁴³⁻⁴⁸; these molecular and immunologic factors are described in more detail later in this review.

Theories to account for the increase in peanut allergy have also considered nonoral exposure as a risk,⁴⁹ which could include ambient environmental skin or respiratory exposure to peanut protein (although this has not been adequately studied). In a part prospective, part retrospective study of preschool children, Lack et al⁵⁰ found no evidence of increased risk from the maternal diet during

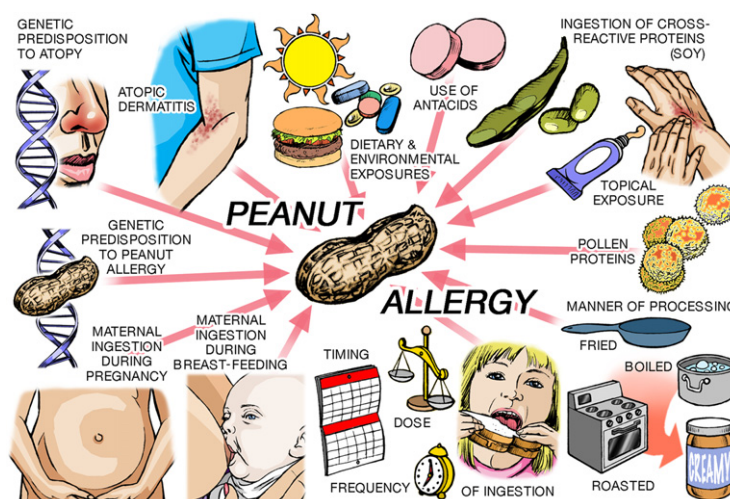


FIG 1. Possible genetic, immunologic, and environmental risk factors for food allergy.

pregnancy or lactation, but peanut allergy was independently associated with ingestion of soy (odds ratio [OR], 2.6), rash consistent with atopic dermatitis (OR, 5.2), and the use of skin preparations containing peanut oil (OR, 6.8). The several interesting observations from this study raise the concern that nonoral exposures to peanut, as opposed to oral ones, may be a primary risk factor, especially for an atopy-prone infant with a damaged skin barrier that may allow increased absorption and sensitization to topical allergen exposure (perhaps at additional risk if they have not yet developed tolerance through oral exposure). Although oral ingestion of soy was implicated as a risk factor in the study, in 1 randomized trial, ingestion of soy formula was not associated with an increased risk for peanut allergy.⁵¹ In addition, a murine model of peanut allergy suggested that treatment with soy protein decreased the response to peanut.⁵² Murine models of cutaneous food sensitization leading to reactions after oral exposure also support the possibility of cutaneous sensitization.⁵³ Exposure to homologous proteins in pollens may be another nonoral sensitizing route,^{54,55} although this has not been explored with regard to childhood peanut allergy. Although the jury is still out on the relative benefit of avoidance strategies for the prevention of peanut allergy, our patients will be increasingly concerned that strategies for treatment increasingly emphasize oral exposure (as described in this review). Although we currently lack evidence-based advice to present to atopy-prone parents who want to avoid having a child with peanut allergy, it is also apparent that we can reassure families with a child with peanut allergy that they need not feel guilty that they caused the allergy by following, or not following, the advice of various agencies or medical societies.

PRESENT AND FUTURE DIAGNOSTIC STRATEGIES/NATURAL COURSE

The clinician may be faced with diagnosing peanut allergy in several diverse circumstances: a patient who had

an apparent reaction to peanut (clinical history), a child who has not ingested peanut but was tested for peanut IgE because of other food allergies or atopic disease (no ingestion history), or a previously diagnosed child who may have outgrown the allergy. Serum peanut-specific IgE or skin prick tests (SPTs) are primary modalities to determine sensitization and have a major role in diagnosis. However, merely detecting sensitization is not necessarily diagnostic of clinical allergy.⁵⁶ A population-based US study⁵⁷ using SPTs showed a peanut sensitization rate of 8.6%, and although that study deferred the test for persons with known peanut allergy, assuming roughly 0.5% of the population has peanut allergy, the result would indicate that for an unselected group in the United States, about 95% of sensitized individuals are not clinically allergic. This observation underscores the importance of the clinical history. The prior probability of a true peanut allergy is obviously higher in patients presenting for an allergy evaluation compared with unselected individuals. Studies are continually emerging that correlate clinical reactions/food challenge outcomes to test results, and examples are shown in this article's Table E1 in the Online Repository at www.jacionline.org.⁵⁸⁻⁶⁷ Most of the studies focused on children, and it must be appreciated that skin test sizes may be affected by variables such as technique, probe type, extract, modality of measuring/reporting, age, and so forth. Discrepancies among studies can also be attributed to variables such as the procedures that define a positive food challenge, inclusion/exclusion from food challenges, and subtleties of regional differences in practice. Overall, the results clearly show that likelihood of a true allergy increases as skin test size or peanut-specific IgE increases. However, the studies also generally point out that age, disease (atopic dermatitis), and, importantly, past history of reactions may influence the relationships. Except at extremes of high test results reflecting higher peanut-specific IgE antibody concentrations, the history must be considered in deciding on likelihood of current allergy and deciding to proceed to

an oral food challenge, an approach that can make use of probability nomograms.⁶² Concern must remain when a test is negative and a history presents a high prior probability of allergy; performing additional tests, such as using whole food for prick testing, and performing a physician supervised challenge are reasonable approaches.⁶⁸ Methods to mask peanut for use in double-blind, placebo-controlled food challenge have been described.⁶⁹

It is evident that approximately 20% of young children with peanut allergy will tolerate peanut by school age, so repeated evaluations are needed.^{5,6} Fleischer et al⁷⁰ evaluated their approach to young patients with the possibility of resolved peanut allergy. Eighty children (median age, 6 years) with peanut-IgE concentrations of 5 kIU/L or less were evaluated, and 55% overall and 63% of those with levels of 2 kIU/L or less passed challenges. Previous studies (see review¹⁴) suggest in addition that persons with smaller SPT results, less certain clinical history, mild reactions, and fewer additional allergies are more likely to experience resolution. Unfortunately, peanut allergy proven to be resolved by oral food challenge can recur.⁷¹ Fleischer et al⁷² followed patients with resolved peanut allergy and found 8% experienced recurrence. Children with recurrent peanut allergy generally avoided peanut after tolerating it during a food challenge.^{71,72} The important clinical point is that children with resolved peanut allergy should be instructed to eat peanut regularly and have epinephrine available until it is certain they are tolerating the food. The intriguing corollary is that avoidance of a food to which there is potential allergy (eg, food-specific IgE antibody) may have adverse immune consequences^{68,73} presumably because of loss of tolerance or loss of a desensitized state. Information on the natural history of peanut allergy among adults is limited. Adults with late-onset disease (after age 10 years) compared with adults with early childhood onset have milder symptoms, smaller peanut SPT wheals, and lower peanut IgE levels, possibly because late-onset disease is related to sensitization to cross-reactive pollen allergens.⁶⁸

Patients are often under the impression that test results reflect the severity of their allergy. Several studies suggest that the severity of a clinical reaction to peanut does not correlate well with the IgE test results.^{58,66} Hourihane et al,⁷⁴ however, showed a modest association ($r = 0.6$; $p = .001$) of supervised food challenge outcome severity with serum peanut-specific IgE concentrations (although correlation to community reactions was not apparent). Perry et al⁷⁵ noted that reaction severity did not correlate positively with dose during food challenges; severe reactions were common in persons reacting at lower doses. Presumably, the severity of a reaction in the community in addition is affected by factors such as the amount consumed, underlying disease and state of health (asthma), and food matrix,⁷⁶ but better means to predict the potential for anaphylaxis are needed.⁷⁷

Several studies have evaluated additional immunologic parameters that may correlate with clinical severity of peanut allergy and may provide a means to predict severity. Peeters et al⁷⁸ used purified peanut proteins (Ara h 1-3, Ara h 6) and found a correlation of clinical severity with

recognition of Ara h 2 and 6 at low concentrations, and Ara h 1 and 3 at higher concentrations, indicating apparent increased potency of Ara h 2, also noted by Palmer et al.⁷⁹ Astier et al⁸⁰ used recombinant peanut proteins, recombinant Ara h 1-3, and found binding was dominant to recombinant Ara h 2, but severity correlated with polysensitization. Indeed, a positive correlation of reaction severity with increased diversity of binding, whether to the allergens^{78,81} or epitopes,⁸² is a common theme that may translate to future diagnostic tests that can predict severity, likelihood of current allergy, and resolution.

CLINICAL OBSERVATIONS THAT AFFECT MANAGEMENT

The general treatment for a patient diagnosed with peanut allergy is to avoid the food and have an emergency plan in place to treat an allergic reaction/anaphylaxis. The plan typically includes prescription of self-injectable epinephrine⁸³; resources for families are available through the Food Allergy & Anaphylaxis Network (www.foodallergy.org) and similar organizations in several other countries. However, the noted severity of peanut allergy, the young age of children affected, and the ubiquity of the food requires consideration of many factors for daily management. In addition, particularly for young children with peanut allergy, concerns arise about allergies to related foods.

Allergies to related foods

Peanut is a legume, but its proteins share homology not only with other beans (soy, pea, and so forth) but also with other foods such as tree nuts and seeds (eg, sesame).⁸⁴⁻⁸⁶ There are limited studies on the rates of confirmed clinical reactions on the basis of immune responses to shared allergens among these foods. That is, detection of similar proteins (positive tests to related foods) does not imply there would be clinical reactions to the food groups. Coallergy is another factor with regard to questions of allergy to various food groups; for example, allergy is commonly reported to unrelated foods such as egg and milk in persons with peanut allergy. In previous reviews,^{14,87} we summarized that for an individual with a peanut allergy, (1) allergy to beans such as soy, green beans, and pea is generally 5% or less, and most children should be evaluated with the expectation that most beans will be tolerated; and (2) in referral populations, coallergy to at least 1 type of tree nut was ~25% to 50%, and although decisions could be individualized to allow, for example, isolated ingestion of tolerated tree nuts, we and others have typically recommended avoidance of tree nuts for concerns of cross-contact with peanut in processed foods. Lupine is a bean that may prove to have higher clinical cross-reactivity with peanut than documented for other beans. Lupine is often processed into flour and is accounting for increasing reports of severe reactions and reactions to small exposures, often among persons with peanut allergy (~50%), although there remains controversy whether the reactions are a result of primary allergy to peanut

or lupine proteins.⁸⁸⁻⁹⁰ With regard to tree nuts, Clark and Ewan⁹¹ reported an observational, cross-sectional study of 784 children presenting to their allergy clinic at various ages with peanut and/or tree nut allergy. They reported that the rate of sensitization to multiple nuts increased with age from at least 19% in the infant age group to >72% from age 4 years onward, and the rate of reported reactions to multiple nuts also increased from 2% at age 0 to 2 years to 47% at 14 years (although many had not ingested multiple nuts). The study was neither longitudinal nor interventional, so it is difficult to assess influence of exposure, but the study result presents a caution that an individual with peanut allergy may need repeated evaluations if ingesting nuts is planned.

Amount that triggers a reaction, avoidance instructions, and concerns about casual exposure

An element of concern about peanut allergy is that a small amount ingested can trigger a reaction. Threshold studies are influenced by patient selection, the form of peanut used for testing, and study procedures. Past reviews⁹² have placed lowest doses to provoke symptoms primarily in the ranges of 1.25 to 2.5 mg protein. A study in adults⁹³ noted mild reactions at as low as 0.1 mg peanut protein by using a partially defatted, roasted peanut meal (~25% protein). Among 22 children undergoing a positive double-blind, placebo-controlled food challenge, none reacted to 1 mg peanut flour (defatted, light roasted, 50% protein), subjective symptoms developed at 10 mg to 3 g, and objective symptoms developed at 100 mg to 3 g.¹⁰ Using the same material in 22 adults with a positive challenge,⁷⁸ none reacted to 0.01 mg, the eliciting dose for subjective symptoms was 0.1 mg to 300 mg, and for objective symptoms the eliciting dose was 10 to 3000 mg. Considering the 26 adults and children^{10,78} challenged until they experienced objective symptoms, 77% reacted at a dose at or above 1 g peanut flour (the most serious reaction at the lowest dose was dyspnea in a child at 100 mg). Systemic reactions have been described in challenge studies to amounts as low as 5 mg protein.⁹⁴ In a multicenter treatment study of 82 persons age 13 to 59 years (mean, 32 years) who reacted to at least 2 g peanut flour (~50% protein), the mean threshold was 331 mg (range, 1-2000 mg).⁹⁵ Although the distribution and concentration of relevant peanut proteins may vary in the materials used for oral challenge studies, a peanut is roughly equivalent to 325 mg peanut flour. It therefore appears, within the limitations of the aforementioned studies that may have excluded the most exquisitely sensitive persons, that objective symptoms for many individuals occur from ingestion of visible amounts on the order of about 1 to 3 peanut kernels.

Still, it is not easy to predict how sensitive an individual may be, and strict avoidance is the general advice. Labeling laws in the United States now require declaration of peanut proteins, but manufacturers may voluntarily present precautionary labels such as "may contain." A recent study⁹⁶ indicated that individuals are increasingly not heeding the advice of the precautionary labels, and

also differentiate their willingness to ingest products with warnings according to their perception of risk on the basis of the label terminology; for example, consumers with allergy are more likely to avoid "may contain peanut" compared with "made in a factory that processes peanut." However, assays of the products reveal that label terms may not discriminate risks because some products labeled "shared facility" had the highest levels of contamination—for instance, 4000 ppm.⁹⁶ It remains prudent to advise patient to avoid products that have provisional labeling.

Although not reviewed here, school and community management of food allergy often focuses on concerns of casual contact through touch or inhalation. Simonte et al⁹⁷ exposed children highly allergic to peanut to inhalation of peanut butter for 10 minutes and to skin contact with a small amount of peanut butter for 1 minute and found no reactions aside from local ones from contact. They concluded with 96% confidence that 90% of children highly allergic to peanut would not have a reaction from similar contact with peanut butter, cautioning the situation would likely be different for powdery forms of peanut that can become airborne (eg, flour). In an effort to evaluate a diagnostic modality, Wainstein et al⁶⁵ applied 1 g of peanut butter for 15 minutes to children (n = 52) who had a positive oral challenge to peanut for evaluation of a diagnostic test, and although the test did not perform as well as a standard SPT, no significant or systemic adverse reactions developed, further showing no systemic reactions from casual skin contact. Perry et al⁹⁸ used an assay to detect the major peanut allergen, Ara h 1, to evaluate environmental exposures to peanut and efficacy of cleaning methods. They found that after purposeful hand exposure to peanut (adult volunteers), no Ara h 1 was detectable when soap and water or commercial wipes were used for cleaning (plain water or sanitizer was not efficient). They also found that tables that were purposefully peanut-contaminated could be cleaned efficiently with common agents such as water or household cleaners, but not dishwashing liquid. In a survey of several schools (1 peanut-free), Ara h 1 was undetectable on numerous desks and tables and was detected only in very low amounts unlikely to induce a reaction on 1 of 13 water fountains. Last, they could not detect peanut in the air near peanut butter or peanuts. These results should help allay some of the concerns families may have about inadvertent casual exposure to peanut, particularly when no peanut is visible on surfaces, but the results do not indicate a change in approach to management of peanut allergy in schools with regard to care about transfer of peanut to the mouth in young children. In addition, inadvertent exposure can occur from innocent oral exposure such as through shared utensils, straws, or kissing. Maloney et al⁹⁹ evaluated the time course of the peanut protein Ara h 1 in saliva and determined with 95% confidence that 90% of persons who ingested peanut butter would have no detectable Ara h 1 in their saliva after a peanut-free meal along with a period of several hours. Even so, the authors suggest that a partner of a person with peanut allergy generally refrain from the food. Further studies of management plans¹⁰⁰ for

TABLE I. Selected clinical pearls and observations about managing peanut allergy

Observations	Implications	Cautions
PNA may resolve (~20% young children)	Repeat evaluations periodically	Base decisions for medically supervised food challenges on history, age, and test results
Most (95%) persons with PNA tolerate other legumes	If not already a part of the diet, may individualize evaluations to include beans in the diet	Lupine may present increased risks
About 7% of younger siblings of a child with PNA will also have PNA	Evaluate before introduction	May need supervised food challenge if tests are indeterminate
In the context of a strong history, reactions may rarely occur despite negative IgE test results	Consider retesting; skin tests with whole food	Perform medically supervised challenge if suspicion is high despite negative tests
Peanut allergy may recur following a passed oral food challenge (~8%)	Subjects experiencing a recurrence so far have typically not incorporated the food into the diet	Before oral challenge, discuss that the food should be incorporated in the regular diet if tolerated; maintain an emergency plan until the food is a proven tolerated part of the diet (consider 1-2 y)
Children with peanut allergy have an increased rate of tree nut allergy (~25% to 50%)	For issues of allergy and cross-contact with peanut, recommend avoidance or individualize (testing as indicated) if ingestion planned	Need to present risks of cross-contact, potential to develop a tree nut allergy over time
Reactions can occur to trace amounts (~0.1 to 10 mg), though a more typical amount to trigger an objective reaction is about 1 peanut kernel	Significant caution with regard to ensuring foods are peanut-free	Simple IgE tests do not determine level of sensitivity; caution patients about cross-contact in food preparation, sharing utensils, kissing, and so forth
Significant peanut contamination is sometimes found in products with provisional labeling	Advise to avoid the products	Proliferation of such labeling could result in increased risk-taking
Modest skin or inhalational exposure to peanut butter is not likely to trigger systemic reactions	Patients can be counseled about reasonable precautions to avoid ingestion without fear of a reaction from minor skin exposure or being near peanut butter	Aerosolized peanut (eg, flour) presumed more likely to elicit a reaction; skin contact could be problematic if there is transfer to ingestion (hand to mouth)
PNA potentially severe: adolescents, persons with asthma at special risk	Education about avoidance, use of self-injectable epinephrine, anaphylaxis action plans, asthma control, acknowledge that PN-IgE level/skin test size does not indicate severity	Teenagers may take risks: discuss avoidance issues and prompt treatment with epinephrine, and involve teen peers
PNA is an immunologic disease	Passive transient transfer of PNA from an allergic person to a recipient of plasma has been reported; loss of PNA through bone marrow transplant has been reported; transfer of peanut allergy through liver transplantation has been reported.	Screening is prudent with regard to peanut allergy when blood and tissue products are given

PNA, Peanut allergy/allergic.

peanut and food allergy are needed to determine best practices. Table I summarizes clinical issues and pearls in managing peanut allergy.^{14,15,101,102}

INSIGHTS FROM MOLECULAR AND IMMUNOLOGIC CHARACTERIZATION

As noted in this article's Table E2 in the Online Repository at www.jacionline.org, the International Union of Immunological Societies Nomenclature Subcommittee recognizes 8 allergenic proteins in peanuts,

although Ara h 3 and Ara h 4 are nearly identical isoforms and Ara h 6 is highly homologous to Ara h 2.^{103,104} The 3 major allergens, Ara h 1-3, are comprised of a vicilin, conglutin, and glycinin seed storage proteins, respectively.¹⁰⁴ Two of the 8 identified peanut allergens are not storage proteins but proteins associated with pollen-associated food allergy; Ara h 5 is a profilin and Ara h 8 is a Bet v 1-like protein.⁵⁵ In a study of 20 patients with birch pollen allergy with histories of reactivity to peanut, 60% of patients tested developed symptoms of oral allergy syndrome, and the remaining patients developed more

systemic symptoms consisting of stomach pain and nausea, urticaria, flushing, or throat tightness after double-blind challenge.⁵⁵ In 1/2 of these patients, peanut allergy began after the age of 8 years, which is in contrast with most patients with peanut allergy, in whom allergy is typically noted in the first 2 years of life. As anticipated, Ara h 8 was found to be poorly stable to heat and essentially unstable to gastric digestion. More than 90% of patients with peanut allergy have IgE antibodies to Ara h 1 and 2 in most studies, whereas the percentage with IgE antibodies to Ara h 3 varies between 45% and 95%.^{105,106}

One question that is constantly posed is why peanuts are so allergenic compared with other legumes. Ara h 1 and 2 have been studied extensively, and several physicochemical properties make them particularly resistant to heat and digestive enzymes, properties consistently found in major food allergens. In a number of countries, such as China and countries in southeast Asia, the consumption of peanuts is comparable to that in the United States and other westernized countries on a *per capita* basis, yet the prevalence of peanut allergy is significantly less.⁴⁵ The protein composition of various peanut species from around the world have been studied and found to be fairly consistent,¹⁰⁷ but a number of factors related to the harvesting and processing of peanuts may have a significant effect on the allergenic properties of various peanut products. For example, studies investigating the effects of maturation, drying, and roasting have shown a major effect on the quantity of extractable Ara h 1 in peanuts.¹⁰⁸ More mature, larger peanut kernels contain a greater percentage of Ara h 1 protein than small kernels, and drying or curing at higher temperatures also leads to increased extractable Ara h 1 compared with kernels dried at <35°C. Processing can also have a major effect on the amount of extractable protein. A number of investigators have shown that the high heat of roasting peanuts increases their allergenicity compared with boiled or fried peanuts.^{43,45} The roasting process (~180°C) leads to a Maillard reaction, which is a nonenzymatic reaction resulting in glycosylation of amino groups to form stable advanced glycation end-products.¹⁰⁹ In addition, both drying at high temperature and roasting lead to increased levels of stress proteins, which also leads to higher levels of advanced glycation end-products.¹⁰⁸ Extractable Ara h 1 was found to be 22-fold higher in peanuts roasted 10 to 15 minutes compared with raw peanuts (emulates conventional oven roasting or parching), whereas further prolonging the roasting time leads to decreased solubility of the proteins.⁴⁴ In another study, 2-fold less extractable peanut protein was obtained from boiled peanuts, primarily because of loss of water-soluble proteins in the water.¹¹⁰ In addition, Maleki et al¹¹¹ reported that whole roasted peanut proteins inhibited IgE binding to raw peanut proteins 90-fold more effectively than raw peanut protein. In countries where peanut butter is popular, such as the United States, Canada, and the UK, the popularity of whipped or emulsified peanut butter in the past few decades also may have contributed to increased allergenicity. To prevent the oil from layering out of the solid fraction, as seen with peanut

butter purchased in most health food stores, manufacturers now whip or emulsify peanut butter, which disperses the water-soluble protein in the oil, forming an emulsion, not unlike incomplete Freund's adjuvant. Metabolizable vegetable oils, such as peanut oil, have been shown to increase the immune response to antigens¹¹² and may serve to increase the immunogenicity of peanut proteins when ingested in this manner.

Another question frequently raised is why peanuts are so allergenic compared with other food proteins. A recent study by Shreffler et al¹¹³ provides some insight. These investigators found that glycosylated Ara h 1, but not the deglycosylated form, acted as a T_H2 adjuvant by activating dendritic cells to drive the maturation of T_H2 cells, as demonstrated by the increased T-cell production of IL-4 and IL-13. Ara h 1 acts as a ligand for dendritic cell-specific ICAM-grabbing nonintegrin (DC-SIGN) (CD209), an immunoreceptor tyrosine-based activation motif (ITAM)-containing type II member of the C-type lectin family that also has been shown to interact with schistosome glycoproteins and induce T_H2 responses.¹¹⁴ The roasting process, with the formation of stable trimers, may further enhance the valency of this glycan-lectin interaction, increasing the allergenicity of peanut protein in this form.

Although this study provided some insight into why peanuts may be more allergenic than many other foods lacking the specific glycans found in peanuts, it could not explain why certain individuals develop an allergic response whereas the majority does not. In an effort to understand better the immune response in subjects with peanut allergy compared with normal controls, Turcanu et al¹¹⁵ expanded peanut-specific T cells from the peripheral blood with peanut antigen *in vitro* and then stimulated cells with phorbol 12-myristate 13-acetate and ionomycin to maximize cytokine secretion. Expanded T cells from 9 subjects with peanut allergy were interpreted to be T_H2-biased with IFN- γ /IL-4 and IFN- γ /IL-13 ratios of 1:1 and 30:1, respectively, compared with ratios of 40:1 and 80:1 in the controls without peanut allergy. The authors concluded that the T_H1-biased response in controls without allergy was at least in part responsible for oral tolerance. However, by using a short-term culture system, Thottingal et al¹¹⁶ demonstrated that normal adults who were ingesting peanuts regardless of SPT positivity to peanut extract could mount a T_H2 response to peanut antigen *in vitro*, as demonstrated by the secretion of IL-5, IL-13, and CCL22, but failed to mount a significant T_H1 response, as demonstrated by lack of IFN- γ or CXCL10 in the cell supernatant. These investigators concluded that T_H1 responsiveness did not protect against clinical reactivity to peanut, but rather the degree of T_H2 cytokine production and peanut-specific IgE was responsible for clinical reactivity. Although it is apparent that both peanut-specific IgE and T_H2 responsiveness are necessary for clinical reactivity to peanut, neither appears sufficient for clinical reactivity.

The major peanut allergens, Ara h 1-3, have been well characterized and the sequential allergenic (IgE-binding) epitopes mapped.^{105,117,118} In comparing the binding of

IgE antibodies from large numbers of patients with peanut allergy, it became apparent that there was great heterogeneity in individual responses to peanut proteins.^{82,119,120} Diversity, maturation, and class switching are highly regulated processes that may provide insight into the host's immune response to an antigen and may have potential as diagnostic and prognostic markers. In a study by Beyer et al,¹¹⁹ it was found that patients with peanut allergy bound specific allergenic (IgE-binding) epitopes, labeled "informative" epitopes, which were not recognized by those who outgrew their peanut allergy or those who were sensitized but tolerated peanut ingestion. Patients with low levels of peanut-specific IgE antibodies, who could not easily be classified as reactors or nonreactors on the basis of these levels, were able to be differentiated on the basis of their binding to these informative epitopes. In further studies using a peptide microarray assay,⁸² it was found that patients reacting to greater numbers of allergenic epitopes—that is, those with greater epitope diversity recognition—experienced more severe allergic reactions after ingestion and tended to react to smaller doses. The development of epitope-specific assays may offer more specific markers of clinical reactivity and provide insight into the prognosis and severity of a patient's peanut sensitivity.

FUTURE THERAPEUTIC OPTIONS

Currently, the only proven therapy for the treatment of peanut allergy, and food allergy in general, is strict avoidance of the peanut-containing foods and education of patients to recognize and treat allergic reactions caused by accidental exposure.²³ Attempts at standard subcutaneous immunotherapy have been abandoned because of overwhelming adverse reactions and marginal efficacy.¹²¹ As indicated in Table II, immunotherapeutic approaches have more recently focused on 2 main strategies: allergen-specific and allergen-nonspecific.

Sublingual and oral immunotherapy

Two old allergen-specific therapeutic immunomodulatory approaches have been revived and are under investigation in a number of centers, although only 1 has been investigated in a rigorous controlled fashion. Sublingual immunotherapy (SLIT) and oral immunotherapy (OIT) are based on the concept that contact of an antigen with the oral mucosa/gut-associated lymphoid system leads to the induction of oral tolerance.¹²² In both approaches, patients are started on minute amounts of allergen orally and over time are given increasing quantities of allergen in an attempt to develop generalized tolerance. To date, only a few uncontrolled trials, mostly case reports, have been reported using OIT or SLIT in patients with peanut allergy.¹²³⁻¹²⁶ However, Enrique et al¹²⁷ performed a double-blind placebo-controlled trial of SLIT in patients with hazelnut allergy. Twenty-three adults underwent a double-blind placebo-controlled hazelnut challenge to establish their threshold of reactivity and then were divided into 2 groups (12 received hazelnut SLIT and 11 placebo

TABLE II. Potential immunotherapeutic approaches to treat food allergy

Allergen-nonspecific
Anti-IgE administration
Chinese herbal medicines
Allergen-specific
OIT and SLIT
Engineered (mutated) recombinant protein
Peptide immunotherapy
ISS-conjugated protein immunotherapy
Plasmid DNA immunotherapy

SLIT). After a 4-day escalation phase in a clinic setting, study subjects continued daily maintenance SLIT for 3 months using the sublingual-discharge (spit) technique. A double-blind hazelnut challenge was then repeated, and those receiving the hazelnut extract tolerated a larger quantity of hazelnut (increased from 2.29 g to 11.56 g; $P = .02$), whereas subjects receiving placebo experienced no increase in their hazelnut threshold of reactivity (3.49 to 4.14 g; $P = \text{NS}$). A slight but significant increase in hazelnut-specific IgG₄ was observed in the actively treated group. Although OIT and SLIT for egg, milk, and hazelnut allergy appear to provide desensitization for the majority of subjects while on therapy,^{123,127,128} thus allowing them to ingest small amounts of the allergen without allergic reactivity, there is no evidence to date of long-term tolerance induction. In fact, authors caution that significant allergic reactions are likely if the patient stops therapy for 1 to 3 weeks and then resumes therapy at the same dose or accidentally ingests the food allergen.¹²⁹ Until appropriate safety, dosing, and efficacy studies are completed, we advise against routine treatment with these methods.

Anti-IgE therapy

A nonspecific immunomodulatory approach, anti-IgE therapy has been investigated for the treatment of peanut allergy in human beings and showed great promise. A double-blind placebo-controlled dose-ranging clinical trial of anti-IgE therapy (TNX-901) was performed in 84 volunteers with a history of immediate hypersensitivity to peanut.⁹⁵ The research subjects each underwent a double-blind, placebo-controlled oral peanut challenge at initial screening to establish their threshold of reactivity. Subjects were randomly assigned to receive either TNX-901 (150, 300, or 450 mg anti-IgE antibodies) or placebo subcutaneously every 4 weeks for 4 doses, after which they underwent a second oral peanut challenge. The 450-mg dose of TNX-901 significantly ($P < .001$) increased the threshold of reactivity to peanut by oral food challenge from 178 mg (equivalent to approximately ½ a peanut) to 2.8 g (equivalent to almost 9 peanuts), an effect that should provide protection against most accidental ingestions of peanut. However, the response to therapy was not uniform; about 25% of those subjects in the

450-mg dose group tolerated the entire peanut challenge (~10 g peanut protein or >20 peanuts), whereas another 25% experienced no change in their threshold of reactivity. The reason for this disparate outcome is not clear, but it did not correlate with the subject's peanut-specific or total serum IgE concentration. Although anti-IgE therapy is not a cure for food allergy and protection would require monthly or biweekly injections indefinitely, it could be useful for the majority of patients with potential food-induced anaphylaxis regardless of the causative food allergen. However, drug development of TNX-901 was discontinued. Subsequently, a controlled trial with a different anti-IgE antibody preparation (omalizumab; Xolair, Genentech, San Francisco, Calif) was initiated but was discontinued before significant results could be obtained.¹³⁰

A number of other immunotherapeutic strategies are under investigation in preclinical trials, with some entering clinical trials in the next year. Much of this work has been aided by the development of a murine model of food-induced anaphylaxis. Using the Toll-like receptor 4-deficient C3H/HeJ mouse strain, Li et al^{131,132} demonstrated that oral administration of milk or peanut in combination with cholera toxin generated a highly allergic mouse that would develop symptoms of anaphylaxis after the feeding of the sensitizing food allergen. After sensitization with whole peanut, mice develop markedly elevated peanut-specific IgE levels, and splenocytes incubated in the presence of peanut protein *in vitro* undergo significant proliferation and produce high levels of T_H2 cytokines IL-4, IL-5, and IL-13 compared with nonsensitized mice.

Chinese herbal medicine

Although food allergy is not described in traditional Chinese literature, Li and colleagues have developed a 9-herb preparation, designated Food Allergy Herbal Formula (FAHF)-2, which completely blocks anaphylactic symptoms in the peanut-sensitized murine model.¹³³⁻¹³⁵ After the daily administration of FAHF-2 or placebo to peanut-sensitized mice for 6 weeks, mice were challenged monthly to determine the extent of protection. The investigators found that placebo-treated mice developed anaphylactic symptoms with each peanut challenge, whereas the FAHF-2-treated mice were fully protected until the sixth month (or about one fourth the lifespan of the mouse), when some mice experienced mild allergic symptoms (X.-M. Li et al, unpublished data, December 2006). Mice were retreated with FAHF-2 and full protection to peanut challenge returned. In addition, the investigators found that FAHF-2-treated mice had significantly less plasma peanut-specific IgE than placebo-treated mice, and splenocytes cultured *in vitro* with peanut protein produced less IL-4, IL-5, and IL-13 than placebo-treated mice and more IFN- γ . The US Food and Drug Administration (FDA) recently approved a botanical Investigational New Drug (IND) application for FAHF-2, and a phase I clinical trial in human beings will soon be underway. Whether FAHF-2 will prove as effective in human beings, and if so, how long the protection will last, remains to be established.

Engineered (mutated) recombinant protein

As noted, standard immunotherapy for peanut allergy was abandoned largely because of the adverse allergic reactions provoked by the vaccine. In an attempt to circumvent this problem, the 3 major allergenic proteins in peanut, Ara h 1, 2, and 3, were isolated, sequenced, and mapped to identify the allergenic epitopes (IgE-binding sites).¹³⁶ Using site-directed mutagenesis, critical amino acids within the IgE binding sites—that is, those necessary for IgE binding—were altered to produce modified Ara h 1-3 (mAra h 1-3) that had minimal binding to IgE but induced T-cell proliferation similar to native Ara h 1, 2, and 3. Because the modified peanut proteins are produced in *Escherichia coli*, and because bacterial products are known to generate a more potent immune response through concomitant activation of the innate immune signaling, it was decided to generate a vaccine in which the modified proteins were delivered within the *E coli*. In initial studies, peanut-sensitized mice were treated with heat-killed *E coli* (HKE) containing mAra h 1-3, mAra h 1-3 alone, HKE with plasmid vector alone, or placebo given by the oral, intranasal, rectal, or subcutaneous route.^{137,138} The HKE-mAra h 1-3 was significantly more effective at blocking symptoms of anaphylaxis than the mAra h 1-3 alone, and both were more effective than HKE vector alone and placebo. Mice treated with HKE-mAra h 1-3 delivered by the rectal or subcutaneous routes had the lowest symptom scores, least decrease in body temperature, and least rise in plasma histamine compared with other groups. Splenocytes from HKE-mAra h 1-3-treated mice cultured *in vitro* in the presence of peanut protein produced significantly less IL-4, IL-5, and IL-13 than placebo-treated mice, and significantly more IFN- γ and TGF- β .¹³⁷ In pre-IND discussions, the FDA indicated that it would not approve a whole cell vaccine for subcutaneous administration. However, because the HKE-mAra h 1-3 was most effective when administered into the rectal vault, an environment replete with *E coli* and other bacteria, there was minimal concern about the safety of administering such a vaccine rectally. The HKE-mAra h 1-3 has been manufactured in a GMP facility (EMP-123) for use in human beings and is undergoing final toxicology studies before an IND application is submitted to the FDA.

Peptide immunotherapy

One strategy for immunotherapy is to create a vaccine with specific T-cell epitopes, but in an attempt to circumvent the need for identifying all relevant peanut T-cell epitopes, a vaccine was generated composed of small peptides (10-20-mers) that overlap and represent the entire amino acid sequence. For example, with Ara h 2, thirty 20-mers that overlapped by 15 amino acids were generated.¹³⁸ In this way, antigen presenting cells are provided with all potential T-cell binding epitopes, but mast cells are not activated because these peptides are unable to cross-link IgE. Preliminary studies in the C3H/HeJ murine model of peanut anaphylaxis showed that subcutaneous or intranasal administration of a vaccine containing the 30

overlapping Ara h 2 20-mers (3 doses/wk for 4 weeks) markedly reduced serum Ara h 2-specific IgE, significantly lowered plasma histamine levels and anaphylaxis symptoms scores after challenge, and increased IFN- γ production by splenocytes cultured with Ara h 2 *in vitro* compared with controls (X.-M. Li et al, unpublished data, April 2002). Although this method shows promise, validating the stability and uniformity of peptide mixtures for use in human beings is a major technical challenge.

Plasmid DNA-based immunotherapy

More than 10 years ago, Raz et al demonstrated that the intramuscular injection of a bacterial plasmid DNA encoding a specific antigen could induce a T_H1 response and inhibit IgE production.¹³⁹ These investigators demonstrated that the T_H1-skewed response was a result of immunostimulatory sequences (ISSs) consisting of unmethylated cytosine and guanine motifs in the plasmid DNA backbone. A later study found that the intramuscular immunization of naive AKR/J and C3H/HeJ mice with plasmid DNA encoding Ara h 2 before intraperitoneal sensitization with peanut had a protective effect in AKR/J mice but resulted in slightly worse anaphylactic reactions in C3H/HeJ mice after peanut challenge.¹⁴⁰ In another study, chitosan-embedded pAra h 2 administered orally to AKR/J mice also had a protective effect.¹⁴¹ However, the strain specificity of plasmid DNA in the prevention of peanut sensitization suggests that it is unlikely to provide uniform protective in human beings. Although the prophylactic effect of plasmid DNA may be useful in high-risk populations, there have been no published reports of successful plasmid DNA-based immunotherapy reversing established peanut or other food allergy. In an unpublished study, we were unable to block anaphylaxis in Ara h 2-sensitized C3H/HeJ mice with the pAra h 2 used in the prophylactic study.

ISS-oligodeoxynucleotide-based immunotherapy

There has been a growing interest in the use of synthetic immunostimulatory oligodeoxynucleotides (ODNs) containing unmethylated cytosine and guanine motifs (ISS) for prevention or treatment of allergic disorders such as allergic asthma.¹⁴² In one study, C3H/HeJ mice were immunized intradermally with ISS-linked Ara h 2 or ISS-linked Amb a 1 as control. Four weeks after initial immunization, mice were intragastrically sensitized with peanut and then challenged with Ara h 2 five weeks later. ISS-Ara h 2-treated mice did not develop obvious symptoms after oral challenge with Ara h 2, whereas ISS-Amb a 1-treated mice did. Plasma histamine levels were also significantly lower in the ISS-Ara h 2-treated group than in the ISS-Amb a 1-treated group (X.-M. Li, unpublished data, April 2002). These findings suggest that ISS-linked Ara h 2 immunization had some preventive effect on peanut-induced allergic response in an antigen-specific manner. In a similar study, Nguyen et al¹⁴³ found that intradermal immunization with a mixture of ISS-ODN and β -gal, but not with either ISS-ODN or β -gal alone,

provided significant protection against fatal anaphylactic shock induced by β -gal intraperitoneal sensitization and challenge. Taken together, these data suggest that anti-gen-ISS-ODN immunization may be able to prevent food allergy in high-risk individuals, but whether it will be capable of desensitizing someone with established food allergy remains to be determined.

CONCLUSION

Peanut allergy appears to be increasing, and we are just beginning to recognize potential genetic, environmental, and immunologic influences on the development and progression of the disease. Recent studies have refined our understanding of the natural course of peanut allergy and have provided insights for improved diagnosis, management, and patient education. Molecular characterization and clinical-epidemiologic studies continue to increase our understanding of risk factors and present insights toward improved diagnosis and prevention. Yet numerous open questions in these areas await further research. A number of promising immunotherapeutic approaches to treat peanut allergy are now being investigated or will soon be investigated in clinical trials, such as SLIT, OIT, anti-IgE, OIT plus anti-IgE, Chinese herbal medicine, and engineered recombinant proteins. In addition, a number of other novel approaches to treat peanut allergy are still in the preclinical stage, such as ISS-ODN, cytokines (for example, IL-12 liposomes), chimeric antibodies (for example, peanut-IgG Fc chimera), and various probiotic agents. Although much remains to be learned about the underlying immunologic effects of these various therapeutic approaches, it is likely that at least 1 will provide the means to treat peanut allergy, a goal that has eluded allergists for decades.

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TABLE E1. Examples of outcomes of peanut food challenge (or convincing clinical reactions) against SPT and serum test results

Age	No. in study	Serum specific IgE (kIU/L)	Skin test wheal (mm)	Probability of reaction/reaction rates	Comments	Reference
Mean, 5 y	41		3 mm	PPV, 0.55 NPV, 0.75	US study, ~age 5 y, retrospective, all AD, not all OFC	Sampson 1997 ^{E1}
	196	0.35		PPV, 0.78 NPV, 0.85		
		15		95%		
Median, 4 y	68	14 <0.35		95% ~20%	US study, ~age 5 y, prospective, ~50% AD, 2% challenged (remainder by history)	Sampson 2001 ^{E2}
Median, 5 y	173	2 (history of past reaction) 5 (no significant history)		~50% ~50%	US, included 8 adults, OFC if suspected tolerance (no recent reaction, IgE ~25% of 95% values)	Perry 2004 ^{E3}
Median, 3 y <2 y	95		8 mm 4 mm	~100% ~100%	Australia, referred for suspected allergy, lancet technique, commercial extracts, wheal diameter, open OFC	Sporik 2000 ^{E4}
Mean, 7 y	157	<0.35 15	8 mm 3 mm 0 mm	~95% ~50% ~13%	UK, mixed suspected allergy, ages 1-16 y, lancet technique, extract, longest diameter, open or double-blind OFC	Roberts 2005 ^{E5}
				~28% ~92%		
Median, 5 y	140		<3 mm 3-8 mm 9 to >12 mm	0/76 (0%) 9/46 (20%) 9/18 (50%)	Canada referral practice, commercial extract, wheal diameter, open or single-blind challenge	Pucar 2001 ^{E6}
Age >2 y	551		0 mm ≥3 mm ≥6 mm ≥8 mm	PPV, NC NPV, 0.9 PPV, 0.64 NPV, 0.92 PPV, 0.87 NPV, 0.76 PPV, 0.96 NPV, 0.63	Australia, allergy center, lancet, mean diameter, commercial extract, open or blind OFC	Ho 2006 ^{E7}
Age ≤2 y	48		0 mm ≥3 mm ≥4 mm	PPV, NC NPV, 0.92 PPV, 0.67 NPV, 0.90 PPV, 1.0 NPV, 0.85		
Mean, 4.5 y	84		≥8 mm ≥15 mm	PPV, 0.78 NPV, 0.63 PPV, 1.0 NPV, 0.40 PPV, 0.70 NPV, 0.92	Australia, referral center, children with positive skin test to peanut, commercial extract, mean wheal, open OFC	Wainstein 2007 ^{E8}
		0.37		PPV, 1.0 NPV, 0.58		
		10				
Median, 4 y	363		≥3 mm ≥16 mm	PPV, 0.74 NPV, 1.0 PPV, 1.0 NPV, 0.55 PPV, 0.71 NPV, 0.95	France, referral center, double-blind OFC, raw peanut, lancet, largest wheal diameter	Rance 2002 ^{E9}
		≥0.35		PPV, 1.0 NPV, 0.55		
		≥57				

TABLE E1. Examples of outcomes of peanut food challenge (or convincing clinical reactions) against SPT and serum test results (*continued*)

Age	No. in study	Serum specific IgE (kIU/L)	Skin test wheal (mm)	Probability of reaction/reaction rates	Comments	Reference
Median, 6 y	51		≥6 mm	PPV, 0.89 NPV, 0.93	Australia, referral, focused to additional prediction from SPT if sIgE-PN < 10 kIU/L, commercial extract, largest diameter, 3 challenges not done for large SPT, 5 challenges indeterminate	Nolan 2007 ^{E10}

PPV, Positive predictive value; NPV, negative predictive value; AD, atopic dermatitis; OFC, oral food challenge; NC, not calculated.

TABLE E2. Peanut allergenic proteins

Allergenic protein	Plant family	Amino acids
Ara h 1	Vicilin (7S globulin)	>600
Ara h 2	Conglutin (2S globulin)	156
Ara h 3/4	Glycinin (11S globulin)	507/530
Ara h 5	Profilin (Bet v 2–like)	131
Ara h 6	Conglutin (Ara h 2 homolog)	129
Ara h 7	Conglutin	160
Ara h 8	Bet v 1–like (PR-10)	157