

November 5, 2011

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Article Published in the Author Account of

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Peanut Allergy: An Evolving Clinical Challenge

Published on October 14, 2011

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Abstract: Peanut allergy is an IgE-mediated food allergy responsible for causing severe and occasionally fatal reactions in those sensitized to peanuts. The prevalence of peanut allergy appears to be on the rise worldwide, yet there are no therapeutics currently available that can alter the course of this condition. This article will review the epidemiology, pathogenesis, and clinical features of peanut allergy and discuss future possibilities in diagnostic and therapeutic modalities.

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Introduction

[Food allergy](#) refers to a condition in which individuals develop an aberrant immunologic reaction, characterized by [immunoglobulin E](#) (IgE) antibodies to food proteins. IgE antibodies bind avidly to high affinity IgE receptors on mast cells and basophils and, when exposed to the sensitizing proteins, activate these cells to release potent mediators that cause symptoms such as hives, swelling, wheezing, gastrointestinal involvement, and hypotension (shock) that are characteristic of allergic reactions (Boyce *et al.*, 2010).

Peanuts (*Arachis hypogaea*) are a major cause of severe IgE-mediated food [allergy](#) in both children and adults. Unlike allergies to cow's milk and egg and similar to allergies to [fish](#), shell fish, and tree nuts, allergy to peanuts resolves infrequently and remains a source of morbidity in approximately 80% of peanut allergic patients (Sampson, 2004). Compared to other food allergies, peanuts cause particularly severe reactions. Between 1994 and 1999, of the 32 food allergy related anaphylaxis fatalities that were reported to the Food Allergy and Anaphylaxis Network, 67% died of anaphylactic reactions to peanut (Bock *et al.*, 2001). Moreover, in some cases only a very minute dose (0.1-1 mg) is required to cause a systemic reaction (Hourihane *et al.*, 1997). For people who are sensitized to peanuts, avoidance currently remains the only viable option, although many promising therapeutic interventions are being investigated. Several reviews of this subject have been published recently (Finkelman, 2010; Hourihane, 2011; Pansare and Kamat, 2010).

[Epidemiology](#)

Allergy to peanuts is common and likely increasing in prevalence. There is variability in the age of onset to different groups of foods, with [peanut allergy](#) being most commonly diagnosed between 6-24 months of age. Sicherer and colleagues conducted a nationwide, cross-sectional, computer-assisted telephone interview with validated questions to survey participants regarding peanut allergy. In their first report, the prevalence of peanut allergy in children under 18 years of age increased from 0.4% in 1997 to 0.8% in 2002 (Sicherer *et al.*, 2003). This doubling of prevalence was also reported by Grundy and colleagues who showed that sensitization to peanut increased between 1989 and 1994-1996 from 0.5% to 1% in children 3-4 years of age living on the Isle of Wight, England (Grundy *et al.*, 2002). In an 11-year follow-up, Sicherer and colleagues further reported that the prevalence of peanut allergy in children under 18 years of age had increased to 2.1% in 2010 (Sicherer *et al.*, 2010).

Worldwide, the prevalence of peanut allergy is quite variable with the highest rates (1-2%) seen in westernized countries, most specifically the United States, United Kingdom, Canada, and Australia. However, the increase in these rates in the UK and Canada may have stabilized (Ben-Shoshan *et al.*, 2009; Venter *et al.*, 2010). Although still a significant medical problem, rates are lower in other westernized countries: France, 0.3-0.7% (Morisset *et al.*, 2005); Denmark, 0.2-0.6% (Osterballe *et al.*, 2009); and Israel, 0.04-0.17% (Du Toit *et al.*, 2008). This may reflect differences in the frequency of ingestion of peanuts as well as the method of preparation. For example, peanut allergy is rare in Asian countries even where peanuts are commonly part of the diet. The basis of this difference is not understood, although the most common method of preparation of peanuts, boiled in Asia versus roasted in the U.S., may be a contributor (Chung *et al.*, 2003).

In sensitized individuals, re-exposure to a particular allergen causes allergic reactions. However, the mechanisms underlying the initial sensitization remain a great mystery. It appears that multiple factors including the dose and route of first exposure to peanut allergens are particularly important in the development of tolerance versus sensitization to

peanuts. In one example, the rate of peanut allergy in a school-aged cohort of Israeli Jewish children was 0.17% compared to 1.85% in Jewish children in the United Kingdom. The 10-fold difference between the children in the Israel versus U.K. may be explained by the fact that Israeli infants (8-14 months of age) routinely consume peanut protein (7.1 g) whereas the Jewish infants in U.K. homes do not (0 g) (Du Toit *et al.*, 2008). A case-control study conducted in the U.K. found that early oral exposure to peanut in infants with high environmental peanut exposure may contribute to a protective effect against the development of peanut allergy and that there was no effect of maternal peanut consumption during pregnancy or lactation with the development peanut allergy (Fox *et al.*, 2009). In both of these studies, the prevalence of peanut allergy correlated with the environment and not with genetic predilection.

Pathogenesis

Oral tolerance

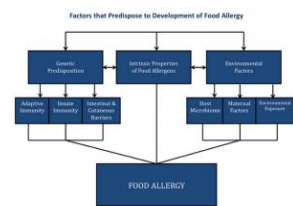


Figure 1. Predisposition to the development of food allergy is multifactorial and complex (adapted from Dreskin, 2006). Genetic predilection, environmental factors, and intrinsic properties of the [food allergen](#) all likely play a significant role in the development and potentiation of food allergy.

Peanut allergy, like most food allergies, has a complex pathogenesis that involves a perturbation in both physiologic and immunologic barriers in the context of [genetic predisposition](#), intrinsic properties of food allergens, and environmental factors such as the host microbiome (**Figure 1**). It is thought that IgE-mediated hypersensitivity reactions develop as food antigens are presented by antigen presenting cells (APCs) such as dendritic cells in the gut mucosa. Under normal circumstances the gut immune system is relatively tolerant to food antigens and this state of hyporesponsiveness (tolerance) is maintained by a number of mechanisms including the integrity of gut epithelium to minimize absorption of allergens and the presence of tolerogenic immune cells such as regulatory T cells (Tregs) (**Figure 2**). There is also evidence that dendritic cells and macrophages in the intestines play a pivotal role in mediating mucosal tolerance against commensal microorganisms and dietary allergens while mounting inflammatory responses against harmful pathogens (Manicassamy *et al.*, 2010). Therefore, a disruption to the [homeostasis](#) between gut antigens and the gut immune system can conceivably lead to either inflammation and/or the development of food allergies.

Physical barriers

Physical barriers in the gastrointestinal systems include intact columnar-epithelial cells in a single layer joined together by gap junctions. These cells act as a partition between the outside environment and the sterile internal environment. Their main function is to absorb nutrients from ingested foods while preventing pathogens from entering the circulation. A thick layer of mucus covers the gut epithelium and functions to trap foreign pathogens. The pH in the gut, enzymes, and bile acids all are part of the physiologic barriers that act to neutralize offending viruses and bacteria as well as to render allergens less immunogenic (Scurlock *et al.*, 2010). In a similar fashion, peanut allergy may develop due to alterations in another physical barrier, the skin. Cutaneous application of peanut proteins as occurs with exposure of inflamed skin to peanut-containing products has been implicated as a risk factor for development of peanut allergy (Strid *et al.*, 2005).

Immunological barriers

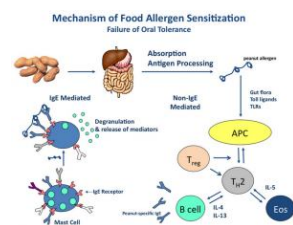


Figure 2. Mechanism of sensitization and reactivity to food allergens. Initial sensitization to foods is thought to be through the GI track. Food allergens are absorbed and taken up by dendritic cells or other antigen presenting cells (APCs). Peptides are then presented to T cells that are of the [Th2](#) variety, leading to activation of B cells that eventually mature into IgE-producing plasma cells. This IgE binds avidly to the high affinity receptor for IgE, FcεRI, on mast cells and basophils. When allergen is reintroduced, these IgE/FcεRI complexes are cross-linked, leading to cell activation and release of pro-inflammatory mediators (see text). Multiple layers of augmentation and control of this process have been described (Borish and Rosenwasser, 2009; Hsu and Boyce, 2009; Vercelli, 2009).

Immunological barriers include aspects of both the innate and the adaptive immune system. The innate immune system includes cells (macrophages, neutrophils, and dendritic cells) that ingest foreign antigens and receptors (e.g., toll-like receptors, TLRs) that are activated by bacterial products (e.g., from microorganisms in the gut) and modulate cellular function. The adaptive immune system includes cells (T and B lymphocytes) along with circulating antibodies such as IgG and IgE that specifically recognize foreign molecules. Specific cytokines (e.g., [IL-4](#) and [IL-13](#)) produced by immune cells direct the adaptive immune system to generate T cells called T helper 2 (Th2) cells that mount an IgE response (Nakanishi, 2010). Each aspect of the immune system is very complex and, adding to this complexity, there is interplay among these elements and newly appreciated plasticity (O'Shea and Paul, 2010). For example, dendritic cells in the intestinal mucosal expressing low levels of costimulatory molecules such as B7 required for T-cell activation become activated by increased exposure to bacterial toxins and enable activation of food antigen-specific T cells in the mesenteric lymph nodes. Activation of B lymphocytes and their maturation into plasma cells leads to increased levels of [peanut allergen](#)-specific IgG and IgE that characterize peanut allergy. An IgG response is evidence of loss of tolerance to

peanut allergens and an IgE response is pathophysiologic as discussed above (Martucci and Dreskin, 2011). The factors involved in the activation of Th2 cells and the development of peanut allergy still remains unclear.

In addition to primary sensitization, secondary sensitization to peanut allergens can occur as a result of exposure to cross-reactive allergens. For example, the birch pollen allergen, Bet v 1, is a homologue to [Ara h 8](#), and the peach allergen, Pru p 3, is a homologue to Ara h 9. In this scenario, patients primarily affected with birch pollen allergy or allergy to peaches can develop a secondary allergy to peanuts (Mittag *et al.*, 2004).

Physical properties of food allergens

The major food allergens are varied but do have a number of similar physical properties. For example, allergenic molecules tend to be small, water-soluble glycoproteins derived from animal or plant sources and are resistant to heat, acidic environments and proteases (Hoffmann-Sommergruber and Mills, 2009).

Peanut allergens

Eleven peanut allergens (Ara h 1-11) are currently subject to the extensive biochemical and immunological studies (Krause *et al.*, 2010). Three of the 11 peanut allergens, Ara h 1, Ara h 2, and Ara h 3, have been called the major peanut allergens, but this is not universally accepted and there is evolving evidence that Ara h 2 and Ara h 6 are the most important peanut allergens (Porterfield *et al.*, 2009).

Several reasons have been given as to why peanuts are more allergenic than other foods. Seed storage proteins are extremely stable against denaturation from heat, acidity, and proteolytic activities (Koppelman *et al.*, 2010). Moreover, factors associated in the manner in which peanuts are processed can also lead to higher allergenicity. It has been suggested that roasting peanuts in high temperatures can cause increase in allergenicity versus boiling or frying, with the latter methods of preparation being found in cultures with a lower incidence of peanut allergy (Chung *et al.*, 2003; Maleki *et al.*, 2003).

Personal and familial risk factors

A personal history of atopic disease as well as a family history of peanut allergy can increase an individual's risk of developing peanut allergy. Studies in twins have demonstrated that there is strong heritability of risk for peanut allergy. Given a sibling with peanut allergy, the concordance for a second sibling is 64% for [monozygotic twins](#) and 7% for both dizygotic twins and for other siblings compared to the background rate of approximately 1% (Hourihane *et al.*, 1996; Sicherer *et al.*, 2000).

Genetic risk factors

Howell *et al.* (1998) examined [HLA](#) genes in peanut allergic patients, non-peanut allergic siblings, and unrelated controls. Although there were no significant differences between the peanut-allergic subjects and their peanut-tolerant siblings, they found significant differences between peanut-allergic subjects and unrelated controls for the presence of DRB1*08 suggesting that this HLA allele is a risk factor. Two more recent studies also did not find any significant differences between peanut-allergic and peanut-tolerant siblings even when HLA class II genes were analyzed at the DNA level (Dreskin *et al.*, 2010; Shreffler *et al.*, 2006). However, the HLA locus DRB1*0803 was identified as a likely risk factor for those families with a predisposition for peanut allergy (Dreskin *et al.*, 2010). Results from genome wide screens for peanut allergy should be available within a few years.

Filaggrin is a protein that is thought to play a key role in epithelial barrier function (Sandilands, 2009). Loss of function mutations within the filaggrin gene are strong and significant risk factors for [atopic dermatitis](#) (Rodriguez *et al.*, 2009) as well as for developing allergic disorders such as [allergic rhinitis](#) and [asthma](#) (van den Oord and Sheikh, 2009). Brown *et al.* (2011) recently reported that loss of function variants in the filaggrin gene are also strongly associated with peanut allergy suggesting that filaggrin mutations are a novel risk factor for IgE-mediated peanut allergy and that epithelial barrier dysfunction is important in the pathogenesis of this disease.

[Toll-like receptor 4 \(TLR4\)](#), the receptor for [lipopolysaccharide](#) (LPS), and its co-receptor, CD14, are critical parts of the innate immune system and contribute to the ability of the host to respond to gut flora. Mice that are deficient in TLR4 are particularly prone to peanut allergy and a [single nucleotide polymorphism](#) in CD14 has been shown to be associated with peanut allergy in humans (Bashir *et al.*, 2004; Dreskin *et al.*, 2011). The mechanisms whereby bacteria (part of the host microbiome) in the gut interact with the host and contribute to the risk of peanut allergy are far from being understood.

Clinical Features

Systemic IgE mediated reactions

Severe allergic reactions to peanuts are type I hypersensitivity reactions mediated by IgE antibody. When these sensitized individuals who have peanut-specific IgE are exposed to peanut proteins, there is cross-linking of IgE antibodies bound to the high affinity receptor for IgE, FcεRI, on cell surfaces of mast cells and basophils, sending a downstream signal to release preformed and newly synthesized mediators such as histamine, tryptase, [prostaglandin D₂](#), leukotrienes B₄, platelet activating factor, the cysteinyl leukotrienes, and cytokines such as IL-4.

Symptoms of food-induced allergic reactions derive directly from these mediators and can range from cutaneous signs (hives, angioedema, flushing) to life-threatening anaphylaxis, characterized by involvement of at least 2 organ systems. Multiple organ systems are commonly involved, yielding a wide-range of reactions. For example, involvement of the gastrointestinal tract can cause vomiting, abdominal pain cramping, and [diarrhea](#), and respiratory tract involvement can be upper (laryngeal edema, stridor, sneezing, nasal pruritis, rhinorrhea) and/or lower (wheezing, chest tightness, dyspnea, cough, intercostal retractions). Ocular symptoms can cause conjunctival erythema, tearing, and pruritis, and cardiovascular involvement can cause tachycardia, bradycardia, hypotension, dizziness, and syncope.

Localized reactions

Localized cutaneous reactions can also occur at the site of contact with a food allergen. These reactions are usually mild and rarely progress into systemic reactions (Simonte, 2003). Food allergens introduced into the eye can cause periorbital swelling, erythema, pruritis, and tearing. Airborne or aerosolized food allergens can cause allergic reactions in those who are sensitized. This can be due to exposure to a large quantity of allergens such as in occupational exposure (Crespo *et al.*, 2001). Isolated oral allergy symptoms can occur, mostly in individuals with concomitant sensitization to other cross-reactive, homologous allergens (see below).

Non-IgE mediated reactions

Non-IgE mediated reactions have been known to occur with exposure to peanuts. For example, peanut proteins can contribute to anaphylaxis by activating the complement system and generating biologically active complement fragments. Non-anaphylactic disorders such as [eosinophilic esophagitis](#) can occur, as well as worsening of atopic dermatitis. Removal of offending allergen in both of these situations can lead to resolution of symptoms. Delayed contact hypersensitivity can also occur after cutaneous exposure. Food aversion as well as other alterations in behavior or mood can be seen especially in young children with peanut allergy.

Diagnosis

Recently, the National Institutes of Allergy and [Infectious Diseases](#) (NIAID)-sponsored expert panel put forth guidelines for management of food allergy in the United States (Boyce *et al.*, 2010). In the context of typical allergic reactions (as determined by taking a careful history), serum measurements of food-specific IgE antibody levels and percutaneous skin prick tests with saline extracts of suspect foods can support the presence of specific food allergy. Very high levels of IgE for specific foods or very large percutaneous skin tests to specific foods can often give the practitioner 95% confidence that a clinically important food allergy is present (Celik-Bilgili *et al.*, 2005). Skin prick testing is useful for its negative predictive value (>90%) to support the absence of IgE-mediated allergic reactivity but is not absolute. Likewise, positive tests do not conclusively prove that a particular food is causative (Chapman *et al.*, 2006). The effect of eliminating the potentially offending food items (food elimination diets) may be a useful diagnostic test, but the gold standard for the diagnosis of food allergy remains double-blind, placebo-controlled oral food challenges (DBPCFC).

Newly available commercial assays looking at IgE binding to recombinant Ara h 1, 2, and 8 (rather than to a crude extract of peanuts) show promise, and measuring IgE binding to Ara h 2 appears to be useful (Nicolau *et al.*, 2011; Lin *et al.*, 2009). Developing methodology for measurement of IgE binding to linear epitopes of allergens by microarray may soon become an important tool for understanding food allergies as patients with more severe clinical histories for peanut, milk, and egg allergies have IgE that recognize a greater number of epitopes (Lin *et al.*, 2009).

Therapeutics

Treatment of acute reactions

The current standard of care for individuals affected with peanut allergy is limited to making a correct diagnosis, prevention of accidental exposures, and prompt, effective treatment

of allergic reactions. Patients are advised to practice strict avoidance of peanuts and to carry both autoinjectable epinephrine (for intramuscular injection) and diphenhydramine (an antihistamine) even for highly sensitized patients who have never been exposed to peanuts. Of note, successful recovery from anaphylaxis is directly correlated to how soon intramuscular epinephrine is given following the onset of an allergic reaction (Boyce *et al.*, 2010).

Prevention of sensitization

The current NIAID Guideline and Management of Food Allergy (Boyce *et al.*, 2010) also provides recommendations for the prevention of food allergy. These guidelines do not advocate maternal diet restriction during pregnancy or lactation and state that there is insufficient evidence that maternal diet affects the development or the course of food allergy. The current recommendations are that all infants be exclusively breast-fed for 4-6 months and that the introduction of solid foods (including potential allergens) should not be delayed beyond 4-6 months.

Therapies to modify sensitization

Unfortunately, accidental exposures leading to fatalities still occur with 90% of such cases attributed to peanuts and tree nuts (Bock *et al.*, 2001; Bock *et al.*, 2007). For this reason, there are efforts to develop approaches that can reduce the level of sensitization and thus the risk of food related IgE-mediated reactions. Current approaches include the use of [oral immunotherapy](#) (OIT), [sublingual immunotherapy](#) (SLIT), and [epicutaneous immunotherapy](#) (ECIT). Each of these three methods is allergen-specific and is in various stages of clinical trials.

Oral immunotherapy (OIT)

A recent open labeled uncontrolled study of OIT to peanut proteins enrolled 39 children between the ages of 12-111 months for a 36-month trial in a gradual build-up phase followed by a maintenance phase (Jones *et al.*, 2009). Despite adverse reactions (92% in build-up phase), almost all subjects completed the study and were able to ingest 3.9 g of peanut protein without adverse reactions. This is a sufficient level to protect subjects from accidental exposure. Blumchen and co-workers (Blumchen *et al.*, 2010) recently studied rush OIT in 23 children in Germany after peanut allergy severity was confirmed with DBPCFC. Escalating doses of roasted peanuts were given 2-4 times daily for up to 7 days. Therapy was discontinued after 8 weeks of maintenance therapy (at least 500 mg) and two weeks after therapy was discontinued, the patients underwent another DBPCFC. Fourteen of 23 children reached maintenance dose after a median of 7 months. At the final DBPCFC the subjects were able to tolerate a median of 1,000 mg (250-4,000 mg) compared to a median of 190 mg (20-1,000 mg) prior to the OIT. It has been reported that, of all the patients treated to date with OIT, 10-20% of subjects failed the initial escalation phase; another 10-20% failed to reach full maintenance dose, and another 10-20% failed during tolerance food challenge, leaving 40-60% of the patients achieving tolerance after oral desensitization (Nowak-Wegrzyn and Sampson, 2011). The mechanisms whereby OIT is effective and factors that may be responsible for the inability to achieve complete desensitization are under intense investigation.

Sublingual immunotherapy (SLIT)

The efficacy of SLIT with peanuts has been studied in 18 children who then were tested with a DBPCFC (Kim *et al.*, 2011). In this procedure, placebo or crude peanut extract (CPE) is held under the tongue for two minutes prior to swallowing. After 12 months of therapy, the active group was able to tolerate a dose 20 fold higher (1,710 mg versus 85 mg) than the placebo group. Skin prick test wheal size and [basophil](#) responsiveness also were lower in the active group following SLIT. Unlike OIT where systemic adverse effects were common, individuals undergoing SLIT experienced predominantly localized oropharyngeal symptoms, with only 0.3% of the active doses requiring oral antihistamine.

Epicutaneous immunotherapy (EPIT)

EPIT is another alternative therapy where the allergen is delivered via epicutaneous patch. Although very effective in mice, no pilot studies of peanut allergy in humans have been reported.

Monoclonal antibodies

Efforts have also been made to treat food allergy in a more global fashion. A multi-center clinical trial using humanized monoclonal anti-IgE murine IgG1 antibody (TNX-901) in 84 peanut allergic individuals was reported in 2003 (Leung *et al.*, 2003). The individuals were randomized to receive either placebo or TNX-901 at three different doses. Compared to individuals who received placebo, there was a significant increase in the threshold of sensitivity but only in the high dose group. [Omalizumab](#) ([Xolair](#)), an anti-IgE humanized IgG1 antibody that is different from TNX-901, is currently being studied in peanut allergic individuals (<http://clinicaltrials.gov/>). A previous clinical trial investigating the efficacy and safety of [omalizumab](#) was terminated early due to occurrence of two severe allergic reactions during the initial screening peanut challenge (Sampson *et al.*, 2011).

Other therapeutic modalities

Ongoing clinical trials include the use of a rectal suppository containing recombinant Ara h 1, 2, and 3 is currently in clinical trial. This study will evaluate the safety of a rectally administered product, EMP-123, consisting of three recombinant modified peanut protein antigens encapsulated within dead *E. coli*. EMP-123 is designed to act as an allergy vaccine with an eventual goal to induce tolerance to the major peanut proteins responsible for peanut allergy (<http://clinicaltrials.gov/>).

[Peptide immunotherapy](#) with T-cell epitopes where T cells are stimulated to predominantly Th2 responses without cross-linking IgE has been reported (Prickett *et al.*, 2011).

In a phase I clinical trial, the parasitic helminth, *Trichuris suis* ova (TSO), is being investigated as a possible therapy for food allergy. This study is based on preliminary findings that parasitic helminth infections can protect against [allergic airway inflammation](#) and modulate disease in [ulcerative colitis](#), Crohn's disease, and allergic rhinitis (Summers *et al.*, 2005a; 2005b; 2010). It is thought that lack of exposure, particularly during childhood to naturally occurring pathogens, has led to subtle changes in the human immune system resulting in an increased propensity to develop allergic and autoimmune responses. This phase I study will assess whether TSO is safe in adults and children with peanut or tree nut allergy.

Finally, a traditional Chinese herbal medication is being evaluated for its potential therapeutic benefit in peanut allergy. In a murine model, FAHF-1 (Food Allergy Herbal Formula I, a mixture of 11 herbs protected mice with peanut-allergy-induced anaphylaxis (Srivastava *et al.*, 2009). A phase I randomized DBPC study was recently completed and showed that FAHF-1 was safe and well tolerated (Wang *et al.*, 2010). A phase II trial is in progress.

Conclusions

Peanut allergy is an increasingly prevalent problem in westernized countries with potential for severe reactions and fatalities. Our understanding of the risk factors predisposing individuals to peanut allergy is still inadequate, our diagnostic testing is still limited and there are no FDA-approved treatments that can alter the course of this condition. Novel therapeutic approaches are on the horizon, giving hope to finding an effective therapy.

Disclosure

Dr. Dreskin has received research support from NIH NIAID, HAL Allergy, Inc., and the Food Allergy and Anaphylaxis Network (FAAN); is on the Board of Directors of the American Board of Allergy and Immunology and the Aspen Allergy Conference; is a consultant for the Clinical [Immunization](#) and Safety Assessment (CISA) Network, administered by America's Health Insurance Plans (AHIP); is a member of the Medical Expert Panel, Department of Health and Human Services, Division of Vaccine Injury Compensation; and is a consultant for Genentech, Inc., and [Novartis](#), Inc.

Dr. Otsu has no conflicts of interest.

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