systematic review and meta-analysis[4] (based on 65 publications based on 50 primary studies) (Nwaru et al., 2014). In addition, searches of EMBASE and Medline were selectively performed to identify studies and reports in the literature since 2012 (see Appendix B for literature search strategy). Meta-analyses, systematic reviews, and population-based or cohort prevalence studies were included. The summary of the findings of the individual studies and systematic reviews and meta-analysis used are presented in Appendix B.

## DIFFICULTIES IN ASCERTAINING FOOD ALLERGY PREVALENCE

A variety of methodologies have been employed in an attempt to determine the prevalence of food allergy in various populations. Implementing designs and interpreting results from studies on food allergy prevalence have a number of challenges; some are commonly encountered within other research fields and others are unique to the field of food allergy. For example, the type of food allergy being assessed and the methodology used to assess it can have major impacts on the outcome. In this Chapter, prevalence figures will reflect IgE-mediated food allergies (except where otherwise noted), not non-IgE-mediated disorders. Pollen-associated food allergy is considered a form of IgE-mediated food allergy that typically results in oral and pharyngeal pruritus and mild edema. Pollen-associated food allergy occurs in some patients with allergic rhinitis when ingesting certain raw fruits, vegetables, tree nuts or peanuts. Pollen-associated food allergy[5] is the result of sensitization to airborne pollen allergens that cross-react with homologous proteins in plant-derived foods. Ingesting the plant-derived foods elicits symptoms (Kazemi-Shirazi et al., 2000). With 47 to 70 percent of patients with allergic rhinitis reporting such symptoms (Katelaris, 2010), this form of food allergy could account for a food allergy prevalence of 5 to 19 percent in some regions (Sicherer, 2011). Also, the form of a food used in an OFC can affect the prevalence of food allergy (Osborne et al., 2011). Table 3-1 lists the challenges and below is a description of a selected number.

[4] Meta-analysis refers to the use of statistical techniques in a systematic review that are used to integrate the results of included studies.

[5] The homologous food allergens are generally heat-labile and susceptible to gastric digestion, thus limiting symptoms primarily to the oropharynx (Wang, 2013). Examples of allergenic pollens (and cross-reacting foods) that might result in pollen-associated food allergy include birch tree (apple, carrot, hazelnut, etc.), ragweed (melons and bananas), and grass pollens (tomatoes and strawberries).

**TABLE 3-1** Factors Affecting the Accuracy of Prevalence Surveys

| | |
|---|---|
| Methodologies | History only versus history + laboratory data (SPT and/or serum IgE) versus history + laboratory data + physician diagnosis versus history + oral food challenge versus history + double-blind placebo-controlled oral food challenges. |
| Food challenge material | Cooked/baked versus raw food. |
| Selection bias | Selected cohort (e.g., allergy clinic based versus birth cohort) or unselected cohort. |
| Nonparticipation bias | Those affected are more likely to participate. |
| Timing of survey | Children "outgrow" many food allergies; adults may acquire food allergies late; varies with specific food being investigated (e.g., milk versus shrimp). |
| Definition | Pollen-associated food allergy, fairly frequent compared to classic generalized immediate food allergies. |
| Geographical region | Westernized countries tend to have greater prevalence of food allergies than less well developed countries. |
| Statistical analyses | Methods employed to handle missing data and nonparticipation. |

### Selection Bias and Methodologies

Food allergy prevalence studies are conducted either on general populations or on specific cohorts (e.g., hospital cohort of individuals with signs of food allergy). Both approaches have advantages and disadvantages. Earlier prevalence studies often incorporated selected cohorts from hospital-based or allergy practices and extrapolated the results to the general population, which typically led to inflated prevalence figures. Population-based surveys are often employed given the ease of administration and an ability to incorporate large numbers of subjects at relatively low cost. Although tens of thousands of individuals can be included in such surveys, these studies rely on self-reporting of specific food allergies, or "perceived prevalence," which uniformly results in higher prevalence rates than do studies incorporating more rigorous diagnostic methods. For example, the NIAID/NIH-supported Guidelines noted a self-report rate of food allergy in adults of 13 percent compared to a rate of 3 percent when food allergy was confirmed by DBPCOFCs (Boyce et al., 2010). More recent surveys have attempted

to use progressively more extensive questionnaires, inclusion of IgE testing (food-specific SPT and/or serum IgE levels), and rigorous statistical methods in an attempt to derive a more accurate picture of true prevalence.

In this chapter, studies reporting prevalence figures from questionnaires only have generally been excluded unless the investigators appropriately corrected for inherent biases or the study provided insights related to geographic or ethnic variation. Also, only population-based studies have been included as evidence.

### Nonparticipation Bias

Even with increased rigor, such surveys are likely flawed by unintentional selection bias. For example, families and individuals affected by food allergy are more likely than unaffected families to participate in and complete a study involving extensive questionnaires and testing, leading to falsely elevated prevalence rates of food allergy. To minimize such bias, some investigators are now attempting to adjust for "nonresponse" bias. In the Surveying Prevalence of Food Allergy in All Canadian Environments study, Soller et al. telephoned 17,337 households, of which 14,113 were reached (Soller et al., 2015). Of this total, 5,734 households (representing 15,022 individuals) completed the full survey instrument, a 45 percent participation rate, which is a rate similar to that seen in other recent studies. An additional 524 households (4 percent) refused to answer the full questionnaire but agreed to answer an abbreviated form, and 6,504 households (51 percent) answered the phone but refused to provide any information. The self-reported prevalence of food allergy among the full participants was 6.4 percent (95% confidence interval [CI]: 6.0%-6.8%), which was significantly greater than the 2.1 percent (95% CI: 1.4%-2.9%) prevalence reported by those answering the abbreviated questionnaire. This study clearly shows that when assessing the outcome of prevalence surveys, it is essential to determine the percentage of individuals randomly selected who participated in the study, the percentage who dropped out before completion, and whether the rate of food allergy in those dropping out differed from those completing the trial.

### Timing of Survey

It also is essential to note the timing of the evaluation and the type of food involved, as a survey of young children will yield a much higher prevalence of allergy to foods such as cow milk, egg, soy, or wheat than a survey conducted in the same children at age 10 years because the majority of young children will outgrow these food allergies.

## FOOD ALLERGY PREVALENCE IN THE UNITED STATES AND EUROPE

### Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses have become increasingly important for addressing a variety of questions in health care and disease prevalence. International guidelines have evolved over the past decade to improve the quality of systematic reviews, such as the *Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)* (Moher et al., 2009). More recently the *PRISMA-P* (Protocols) contains a checklist of 17 items considered to be essential and lists minimal components of a systematic review or meta-analysis protocol (Shamseer et al., 2015). Relatively few systematic reviews in the literature have incorporated all aspects of the *PRISMA-P* checklist. In this report, systematic reviews have been assessed based on the PRISMA checklist.

Based on a meta-analysis by Rona (Rona et al., 2007) and systematic reviews by the RAND Corporation (Chafen et al., 2010) and Zuidmeer (Zuidmeer et al., 2008), the NIAID/NIH-sponsored Guidelines (Boyce et al., 2010) reported that the prevalence of food allergy in the United States and several European countries was 12 to 13 percent by self-report, but only 3 percent when confirmed by laboratory studies and DBPCOFCs. As depicted in Table 3-2, several foods were analyzed individually, with marked differences dependent upon the stringency of the diagnostic criteria used. In general, the food challenge-proven prevalence of food allergy appears to be about one-quarter to one-third the rate of self-reported food allergy by questionnaire.

In 2012, the European Food Safety Authority published a review of the prevalence data in Europe (EFSA, 2013). In many studies prevalence was self-reported and, when OFC were conducted, protocols varied substantially. This work was not peer-reviewed so its findings are not included in this report. One of the EAACI systematic reviews and meta-analyses reviewed studies published from January 2000 through September 2012 on food allergy prevalence in Europe of eight foods or food groups (cow milk, egg, peanut, tree nuts, wheat, soy, fish, and shellfish) (Nwaru et al., 2014). Their analysis included only systematic reviews, meta-analyses, cohort, case-control, cross-sectional, and routine health care studies. The authors also analyzed the risk of bias in the studies using a modified relevant version of the Critical Appraisal Skills Programme quality assessment tool (http://www.casp-uk.net). Overall, 65 publications were reviewed representing 50 studies of which 27 were cross-sectional studies, 17 cohort studies, 3 systematic reviews, and 3 case-control studies. Only one study had an evidence grading of "strong" and the rest had a "moderate" grading. Although the

**TABLE 3-2** Prevalence (Percent) of Food Allergy to Various Foods Ascertained by Self-Report or Oral Food Challenge

| | Peanut (%) | Milk (%) | Egg (%) | Fish (%) | Crustacean shellfish (%) | Tree nuts (%) | Wheat (%) | Soy (%) |
|---|---|---|---|---|---|---|---|---|
| Diagnostic Criteria | | | | | | | | |
| Self-report | 0.6 | 3 | 1 | 0.6 | 1.2 | 0-4.1 | 0.2-1.3 | 0-0.6 |
| Oral food challenge | Not estimated | 0.9 | 0.3 | 0.3 | Not estimated | 0.1-4.3 | 0-0.5 | 0-0.7 |

SOURCE: Boyce et al., 2010.

**TABLE 3-3** Prevalence (Percent) of Food Allergy to Various Foods Ascertained by Self-Report or Oral Food Challenge (Open Challenge or DBPCOFC)

| | Peanut (%) | Milk (%) | Egg (%) | Fish (%) | Shellfish (%) | Tree nuts (%) | Wheat (%) | Soy (%) |
|---|---|---|---|---|---|---|---|---|
| Diagnostic Criteria | | | | | | | | |
| Self-report | 0.4 | 6 | 2.5 | 2.2 | 1.3 | 1.3 | 3.6 | Not estimated |
| Oral food challenge | 0.2 | 0.6 | 0.2 | 0.1 | 0.1 | 0.5 | 0.1 | 0.3 |

SOURCE: Nwaru et al., 2014.

42 studies included in the meta-analysis showed considerable heterogeneity, the authors ascertained overall lifetime prevalence estimates (see Table 3-3). The perceived prevalence rates of food allergies in the EAACI Guidelines were slightly higher than those noted in the NIAID/NIH-supported Guidelines, but the challenge-proven prevalence rates were generally lower. As noted in the NIAID/NIH-supported Guidelines, the prevalence of allergy to milk and egg were more common in young children, while the prevalence rates to peanut, tree nuts, fish and shellfish tended to be higher in adults. The authors caution about interpreting the results of this report because participation rates varied widely across the studies (17.3 to 99.5 percent) and in several studies no information was provided on participation rates.

More recently, two systematic reviews on the prevalence of specific foods have been published: soy (Katz et al., 2014) and tree nuts (McWilliam et al., 2015). Katz et al. (2014) included 40 studies published between 1909 and 2013 on soy allergy in their systematic review and meta-analysis out of 357 potential studies initially identified. In addition, they judged the quality of the publications using the GRADE scoring system (Atkins et al., 2004). The majority of the studies were cross-sectional or cohort studies with moderate to low quality methodological design and evident bias largely due to insufficient sample size, patients' countries of origin, and the length of time followed in longitudinal studies (follow-up data collection is important because the prevalence of food allergy changes with age). The authors calculated the prevalence of soy allergy in the general population based on self-reporting to be 0.2 percent (95% CI: 0.0%-0.3%). Based on OFC outcomes, the prevalence in the general population was 0.27 percent (95% CI: 0.1%-0.44%) and in patients referred to centers for evaluation of allergy, 1.9 percent (95% CI: 1.1%-2.7%). The prevalence of sensitization based on positive SPT results was 0.1 percent (95% CI: 0%-0.2%) in the general population and 12.7 percent (95% CI: 5.8%-16.7%) in referred patients. In 11 studies where participants had both OFCs and SPTs or sIgE performed, only 11.2 percent of sensitized patients reacted to soy following ingestion. Interestingly, of 1,430 infants younger than age 6 months identified in three studies, only 0.1 percent (2 infants) likely had soy allergy, suggesting that the prevalence of soy allergy is much lower than presently believed. However, it should be noted that 9 out of the 11 studies were conducted in Europe, 1 was conducted in Israel), and none was conducted in the United States, where the prevalence of soy allergy is believed to be higher.

McWilliam et al. performed a systematic review and meta-analysis on the prevalence of tree nut allergy, which was defined as allergy to almond, Brazil nut, cashew, hazelnut, macadamia nut, pecan, pistachio, or walnut (McWilliam et al., 2015). The authors identified 36 studies published between January 1996 and December 2014. The majority of studies were in children (24 of the 36 studies identified) and from European countries (18

from Europe, 8 from the United Kingdom, and 5 from the United States). Studies reporting tree nut allergy based on self-report, allergic sensitization (skin tests and/or serum IgE to individual tree nuts), food challenges (OFC or DBPCOFC) or convincing clinical histories were considered eligible for inclusion. In an attempt to reduce selection bias, only population-based cross-sectional and cohort studies were included. Studies on selected patient groups or those performed in a hospital or allergy clinic settings were excluded. In assessing the quality of the studies included in the analysis, 28 studies were graded as moderate and 8 were graded as poor due to participation rates, objectivity of outcomes, and study design. In seven studies using OFCs or recent convincing history, plus evidence of tree nut–specific IgE to define nut allergy, the overall prevalence of tree nut allergy ranged from 0 to 1.6 percent. In nine studies using less rigorous criteria, namely self-reported allergy with physician diagnosis or evidence of sensitization (positive skin tests or specific IgE to tree nuts), the overall probable prevalence of tree nut allergy was calculated to be 0.05 to 4.9 percent. The majority of studies were based on self-reporting of tree nut allergy and yielded an overall prevalence range of 0.18 to 8.9 percent in adults and 0.0 to 3.8 percent in children. The authors noted regional differences in the prevalence of tree nut allergies, with northern European countries reporting the highest rates, largely due to pollen-associated food allergy. [Pollen-associated food allergy in northern Europe is due primarily to cross-reactivity with a homologous pollen protein (*Bet v 1*) in patients with allergic rhinitis to birch pollen.] The most common tree nut allergy reported in the European studies was hazelnut allergy, accounting for 17 to 100 percent of all tree nut allergies, whereas walnut (20 to 30 percent of all tree nut allergy) and cashew (15 to 30 percent) were the most common tree nut allergies reported in the United States. Brazil nut (24 to 33 percent) was the most common nut allergy reported in the United Kingdom (McWilliam et al., 2015). Limited evidence was available to address the question of whether tree nut allergy has been increasing in prevalence, but as depicted in Figure 3-2, using the same random digit-dial survey, in the United States (an unselected cohort, not a national survey) the prevalence of tree nut allergy in children younger than age 18 years was estimated to have increased significantly from 0.2 percent in 1997 to 1.1 percent in 2008 (Sicherer et al., 2010). In the 1997 survey, 5,300 households (13,534 individuals) participated, of which 188 households (3.6%; 95% CI: 3.1%-4.1%) reported 1 or more individuals with peanut allergy, tree nut allergy, or both. Race/ethnicity was determined only from the responding household member. The authors concluded that heterogeneity in tree nut allergy prevalence in different parts of the world appears to be significant, but that the limited high-quality data make it difficult to ascertain the true prevalence of tree nut allergy, especially to individual tree nuts (McWilliam et al., 2015).

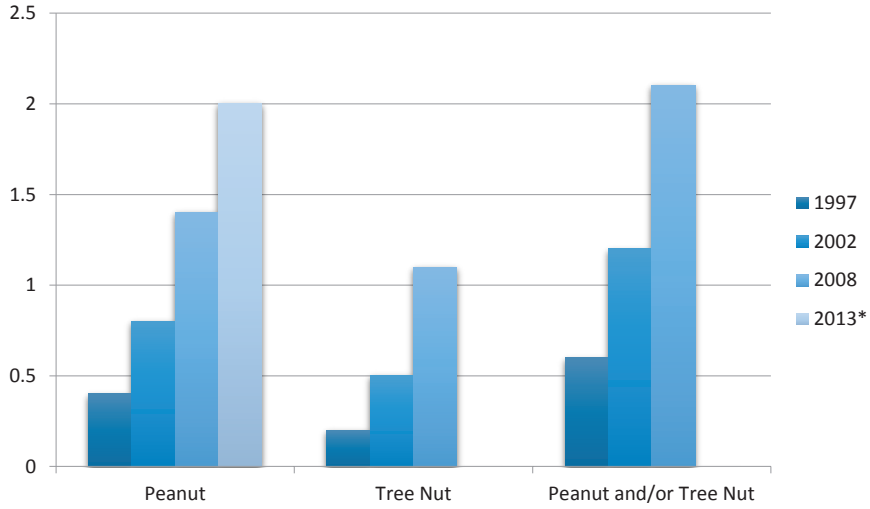


**FIGURE 3-2** Change in the prevalence of peanut and tree nut allergy in children, United States. Data from an unselected cohort, not a national survey.
SOURCES: *Bunyavanich et al., 2014; Sicherer et al., 2010.

Given the known racial disparity in other atopic disorders such as asthma, two recent systematic reviews attempted to address the question of racial disparities of food allergy in the United States. In one report, the authors were able to analyze 20 out of 645 articles initially identified (Greenhawt et al., 2013). The analyzed studies used a variety of criteria to define food allergy, including self-reporting, evidence of IgE sensitization, discharge codes (i.e., ICD-9), chart reviews, and event-reporting databases. Although 12 studies suggested that African American children had significantly increased odds of food sensitization and allergy, major differences in methodology and reporting did not permit calculation of pooled estimates or confirmation of definitive racial or ethnic disparities in food allergy among African American and white children in the United States. In the second study, the authors evaluated 27 different surveys representing more than 450,000 children covering the period from 1988 to 2011 (Keet et al., 2014). As noted in the previous systematic review, no summary estimates of food allergy prevalence in the different racial or ethnic groups could be determined because of the heterogeneity of the surveys.

In summary, both systematic reviews and meta-analyses have examined questions related to the prevalence of food allergy in the United States and in other countries. However, limitations in the quality of the data make it difficult to come to firm conclusions about the prevalence of food allergy.

### Recent Population-Based Studies in the United States

No large population-based or unselected cohort studies that include both laboratory and OFC confirmation of food allergy have been performed in the United States.

A CDC report suggested that 3.9 percent of American children younger than age 18 years had a food allergy (Branum and Lukacs, 2009). The authors' prevalence figure was based on an assessment of cross-sectional survey data from the 1997-2007 National Health Interview Survey, the 2005-2006 National Health and Nutrition Examination Survey (NHANES), 1993-2006 National Hospital Ambulatory Medical Care Survey (NHAMCS) and the 1998-2006 National Hospital Discharge Survey (NHDS). These surveys consisted of reports of food allergy and assessments of serum IgE antibody levels for specific foods, ambulatory care visits, and hospitalizations. A related CDC analysis (Branum and Lukacs, 2008) used NHDS data to show an increase in the rate of hospital discharges related to food allergy (see Figure 3-3).

In 2014, the prevalence of sensitization to food and environmental allergens was published based on the results from NHANES 2005-2006 data and compared to earlier sensitization rates determined in the previous NHANES III survey (Salo et al., 2014). NHANES 2005-2006 included

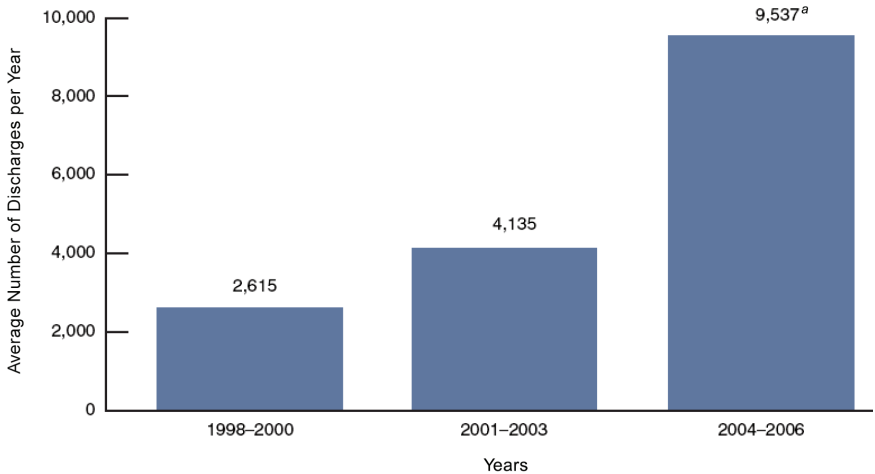


**FIGURE 3-3** Change in the rate of food allergy–related hospital discharges in the United States among children younger than age 18.

[a] Statistically significant trend.

SOURCES: CDC/NCHS (Branum and Lukacs, 2008).

10,348 participants from throughout the United States and, and to ensure adequate samples for subgroup analyses, contained an oversampling of persons of low income, adolescents ages 12 to 19 years, adults ages 60 years and older, African Americans, and Mexican Americans (see http://www.cdc.gov/nchs/nhanes2005-2006/nhanes05_06.htm [accessed August 31, 2016] for a description of survey design and methods). Of the 1,355 children ages 1 to 5 years, 856 (63.2 percent) were determined to have had IgE antibody levels to three food allergens: egg, cow milk, and peanut, and of 8,086 participants, ages 6 years and older, 7,268 (89.9 percent) had IgE determined for egg, cow milk, peanut, and shrimp. Food-specific IgE (sIgE) levels ≥0.35 $kU_A/L$ were considered positive for sensitization. Each group also was tested for IgE antibodies to 6 and 15 inhalant allergens, respectively. Overall, 36.2 percent of children ages 1 to 5 years and 44.6 percent of individuals ages 6 years and older were sensitized to at least one environmental and/or food allergen. Sensitization to milk and egg were significantly greater in the ages 1 to 5 years group (22 percent and 14 percent, respectively), compared to the age 6 years and older group (5 percent and 3.3 percent, respectively), with a marked decline in the prevalence of sensitization occurring over the first decade of life. The prevalence of peanut sensitization was similar in the two groups, about 7 percent and 8 percent, respectively. Among children ages 6 years and older, sensitization to food allergens was most prevalent in the South, and only peanut sensitization showed regional differences. In children ages 1 to 5 years, only sIgE levels to peanut were associated with urbanization. NHANES 2005-2006 data provide a good snapshot of IgE sensitization to the three most common food allergens in the United States—egg, cow milk, and peanut—but as described above, sensitization does not equate with clinical reactivity and so the actual number of Americans at risk of clinical reactions to these foods cannot be determined.

In the past 5 years, a few population-based, cross-sectional surveys have been conducted in an attempt to determine the prevalence and severity of food allergy in the United States. In one study, administered between June 2009 and February 2010, Gupta et al. collected data on 40,104 children from U.S. households (Gupta et al., 2011, 2013b); 6,100 were recruited from a web-enabled panel that was statistically representative of U.S. households with children and an additional 33,900 were obtained from an online sample of U.S. households with children that had access to the Internet. Food allergy was categorized as "convincing" or "confirmed." A convincing history was based on the report of one or more allergic symptoms after ingesting a food and a confirmed food allergy was considered a convincing history plus a physician diagnosis with evidence of IgE antibody testing to the food or a positive OFC. Reportedly, 70.4 percent of children considered with a food allergy in the analysis had a physician's diagnosis

and evidence of sIgE antibodies (47.3 percent were evaluated by SPT and 39.9 percent by serum sIgE levels) or a positive OFC (20.2 percent) (Gupta et al., 2013b). Overall, complete data were available on 38,480 children (96 percent), but due to the method of sampling, a rate of nonparticipation, which could affect selection bias, could not be provided. Based on this study, the overall prevalence of convincing and confirmed food allergy in children in the United States was estimated to be 8 percent (95% CI: 7.7%-8.3%), with more than one food allergy reported in 2.4 percent of all children (95% CI: 2.2%-2.6%), or about one-third of the children with a reported food allergy (Gupta et al., 2011). The prevalences of reported allergy to individual foods in the U.S. pediatric population are depicted in Table 3-4. Severe reactions (defined as reports of anaphylaxis, low blood pressure, trouble breathing or wheezing, or a combination of vomiting, angioedema, and coughing) were reported in 38.7 percent of the children with food allergy, with the odds of severe reactions progressively increasing with age and peaking in adolescent ages 14 to 17 years. The authors noted that the odds of having a food allergy were significantly higher among Asian and African American children compared to Caucasian children, which is in agreement with the NHANES 2005-2006 data described above. Although this study provides some insight into the perceived prevalence of food allergy in children, the survey was not validated and, moreover, results from a self-reporting survey must be interpreted with caution.

In subsequent publications using data from their 2009-2010 survey, Gupta et al. evaluated the geographical variability of food allergy in the United States (Gupta et al., 2012). The odds of having a food allergy was found to be significantly greater in southern and middle latitudes of the United States as compared to northern latitudes, suggesting a north-to-south increase in the prevalence of food allergy. Interestingly, this finding is in contrast to an analysis of food-related admissions to U.S. emergency departments based on the NHAMCS data for emergency department visits to noninstitutional hospitals from 1993 to 2005 (Rudders et al., 2010), which suggested that acute food-allergic reactions are higher in northeastern regions as compared to southern regions. Similarly, a survey of epinephrine auto-injector prescriptions, used as a partial surrogate for food allergy, indicated a strong north-south gradient, with the highest prescription rates found in New England (Camargo et al., 2007). Gupta et al. (2012) also reported that the prevalence of food allergy was higher in urban centers compared to rural areas, 9.8 percent versus 6.2 percent, respectively, with peanut allergy being the most prevalent in urban centers and milk the most prevalent in rural areas (Gupta et al., 2012). There appeared to be a direct correlation between the density of the population in an area and the prevalence of food allergy, but no difference in severe food allergy based on urban versus rural status or latitude.

**TABLE 3-4** Prevalence of Food Allergy to Various Foods Ascertained by Convincing History Plus a Physician Diagnosis with Evidence of IgE Antibody Testing to the Food or a Positive Oral Food Challenge, Children in the United States

| | Peanut (%) | Milk (%) | Egg (%) | Fish (%) | Shellfish (%) | Tree nuts (%) | Wheat (%) | Soy (%) |
|---|---|---|---|---|---|---|---|---|
| Prevalence | 2 | 1.7 | 0.8 | 0.5 | 1.4 | 1.0 | 0.4 | 0.4 |

SOURCE: Gupta et al., 2011.

In an attempt to ascertain the prevalence of peanut allergy in American children, Bunyavanich et al. used data from the Viva Project's unselected observational birth cohort to determine the frequency of the allergy in children ages 7 to 10 years (Bunyavanich et al., 2014). The study of 2,128 children was designed to examine maternal dietary and other factors that could influence their child's health. Overall, 1,277 children underwent a mid-childhood visit following their baseline visit in early childhood. Of these children, 616 (29 percent of the original cohort) had serum peanut-specific IgE antibody levels measured. Children who returned for the mid-childhood visit tended to be from a higher socioeconomic status than children who failed to follow up, but parental atopy[6] was comparable in both groups. Various criteria for diagnosing peanut allergy to determine prevalence in this cohort were provided: self-reported peanut allergic reactions—4.6 percent; peanut allergy based on serum IgE sensitization (IgE ≥0.35 $kU_A$[7]/L; as used in NHANES 2005-2006)—5.0 percent; peanut-IgE + prescription for epinephrine auto-injector—4.9 percent; peanut-IgE ≥14 $kU_A$/L—2.9 percent; and peanut-IgE ≥14 $kU_A$/L + prescription for epinephrine auto-injector—2.0 percent. Although less than one-third of the children in the original cohort were evaluable and diagnoses were not established by OFC, OCF data suggested a higher prevalence of peanut allergy, i.e., 2.0 percent, than previously reported in the United States. The authors noted that this study was conducted in the northeast, which other studies suggest tends to have higher rates of peanut allergy than other regions in the United States (Salo et al., 2014).

In summary, since the systematic review and meta-analysis published by the RAND Group in 2010 suggesting that food allergy in the United States affects more than 2 percent and less than 10 percent of the population (Chafen et al., 2010), attempts to define the prevalence of food allergy in the U.S. population have been confined to self-reports with variable confirmatory evidence in two large cohort studies and information from the NHANES 2005-2006 survey, but no large prospective studies involving confirmatory food challenges have been conducted. Based on this more recent evidence, it is likely that 3.9 to 8 percent of the U.S. population ages 18 years and younger is affected by food allergy (Branum and Lukacs, 2009; Gupta et al., 2011), but regional and racial differences are likely. Well-designed population-based studies are needed.

[6] The genetic tendency to develop the classic allergic diseases—atopic dermatitis, allergic rhinitis (hay fever), and asthma.

[7] Kilo units of allergen-specific IgE.

### Recent Population-Based Studies in Europe

In 2005, the European Union launched the EuroPrevall Surveys, a series of multinational epidemiological surveys aimed at determining the prevalence of food allergy in children and adults across Europe. These surveys were performed as multicenter, cross-sectional studies in general populations with case-control studies nested within the surveys. Studies were performed in children ages 7 to 10 years and adults between ages 20 to 54 years in the eight centers representing different social and climatic regions in Europe (Kummeling et al., 2009). Participants for these studies were selected in stages. The first stage involved community-based surveys using a short questionnaire to collect basic information on adverse reactions to foods. The sampling for these surveys was not random, but was based on established criteria. Surveys needed to be administered in areas with pre-existing boundaries that had total populations of at least 200,000 people and had current registries that could be used to sample children ages 7 to 10 years and adults ages 20 to 54 years. Each center targeted a population of about 3,000 respondents, and attempts were made to determine and code reasons for nonresponse. In the second stage, all those in the first stage who indicated some type of adverse reaction to priority foods and a random selection of those reporting no reaction completed a detailed questionnaire and provided a blood sample to determine IgE sensitization. In the third stage, all those who indicated a reaction to a food and demonstrated IgE antibodies to the food were invited for a full clinical evaluation, including a standardized DBPCOFC. The study excluded those with a history of anaphylaxis, which could lead to a small error. However, conducting oral challenges in such individuals raises ethical concerns. Aside from this limitation, EuroPrevall and its protocols were well designed. It should be noted, however, that adherence to and completion of the OFC protocols showed considerable variability.

To date, the EuroPrevall group has published self-reporting and IgE sensitization rates on 17,366 adults from the eight centers participating in the study (Burney et al., 2014). Overall, 21 percent of the adults reported reactions to particular foods, ranging from 37 percent in the Alpine area of Europe to less than 2 percent in Northern Europe. Physician-diagnosed food allergy was 4.4 percent overall and ranged from 7.5 percent in Alpine and Mediterranean regions to <1 percent in Northern Europe and the Balkans. The overall prevalence rate of IgE sensitization to all foods was 15.81 percent and ranged from 23.6 percent in the Alpine region to 6.6 percent in the Northern Maritime region. Birch pollen–related foods, i.e., hazelnut, peach, apple, carrot, celery, and peach accounted for highest overall rates of sensitization, from 9.3 percent to 6.3 percent, while egg, milk, and fish accounted for the lowest rates, 0.86 percent to 0.22 percent,

with significant regional variation. The prevalence of true food allergy in European adults remains to be established because DBPCOFCs have not been performed in adults. However, it was noted that in different regions of Europe, the prevalence of sensitization to foods is strongly associated with the prevalence of IgE sensitization to aeroallergens (e.g., birch pollen, mugwort) whereas sensitization to nonpollen-related foods (e.g., egg, milk, and fish) is quite rare.

In an expanded multicenter epidemiologic study involving 12 European centers, the EuroPrevall group identified 731 adults from a cross-sectional survey of 2,273 participants who reported reactions to hazelnut occurring 2 hours or less following ingestion (Datema et al., 2015). Twenty-two individuals had a clear-cut history of anaphylaxis and 124 agreed to undergo a DBPCOFC. In those challenged, 87 (70 percent) were found to be responders. Birch pollen–driven hazelnut sensitization (Cor a 1) dominated in most areas, except in Iceland and the Mediterranean areas. Sensitization to the hazelnut storage proteins Cor a 9 and 14 (i.e., those more often associated with generalized allergic reactions) was significantly more common in children compared to adults, 42.0 percent versus 5.8 percent, respectively, except in the Netherlands where 90 percent of adults were sensitized to Cor a 9 or 14. No potential explanation was given for such high rates.

In parallel with the EuroPrevall study, Dutch investigators sought to determine the difference in reporting and prevalence of food allergy among community participants in the EuroPrevall study and those referred to a tertiary allergy center with suspected food allergy (Le et al., 2015). The investigators confirmed the previously reported discrepancies between self-reported food allergy, food allergy defined by suggestive history plus supporting lab data (sIgE), and food allergy confirmed by DBPCOFC—10.8 percent versus 4.1 percent versus 3.2 percent, respectively. They also found large differences in self-reported food allergies between the community-based EuroPrevall cohort and those referred to allergy centers, but sensitization and DBPCOFC-proven food allergies did not differ significantly between the two groups except for milk and egg allergy. These differences in clinically confirmed food allergy rates in the community versus in the allergy centers reinforce the need to use population-based studies when determining the prevalence of food allergy in the general population and not to extrapolate from referral populations, particularly when using questionnaires.

The EuroPrevall group also enrolled a birth cohort of 12,049 from 9 centers throughout Europe between October 2005 and March 2007 (McBride et al., 2012), and followed up at ages 1 year and 2 years. This is the largest birth cohort reported to date. Overall, 1,928 parents contacted the study centers about possible adverse food reactions in their children

and, based on annual follow-up questionnaires, an additional 684 children were suspected of having potential allergic disease (Schoemaker et al., 2015). Of this group, 358 children met the criteria to undergo a DBPCOFC to milk and 248 (69 percent) agreed to at least one food challenge. Fifty-five children experienced a positive result for an overall incidence of cow milk allergy of 0.54 percent (95% CI: 0.41%-0.70%). The incidence varied by country with the highest incidence of cow milk allergy in the United Kingdom and the Netherlands (1 percent) and the lowest (<0.3 percent) in Germany, Lithuania, and Greece. Nearly 25 percent of the children had non-IgE-mediated cow milk allergy, especially those from the United Kingdom, the Netherlands, and Poland. Of the 32 children with cow milk allergy who were evaluated 1 year later, 22 (69 percent) were tolerant to milk, including all those with non-IgE-mediated cow milk allergy and 57 percent of those with the IgE-mediated form of the allergy. This study reports the lowest incidence of cow milk allergy in recent times, but is subject to a number of limitations. First, about 30 percent of the children did not undergo a DBPCOFC. Second, the numbers of eligible infants in each center who did not participate in the study were not reported so it is not possible to assess the role of selection bias. Finally, only a limited number of children underwent a rechallenge to cow milk at 1 year and so the true proportion of children that became tolerant is less certain.

A similar evaluation of hen egg allergy was conducted in the EuroPrevall birth cohort (Xepapadaki et al., 2016). Overall, 2,612 children were identified by parental report (N=1,928) or during annual follow-up questionnaires (N=684) about possible adverse food reactions in their children to hen egg. Following a standardized evaluation, 298 (27 percent) of the children were invited for a DBPCOFC to egg and 172 (58 percent) agreed to be challenged; 86 (50 percent) experienced a positive challenge to pasteurized egg powder, for an overall raw incidence of 0.84 percent (95% CI: 0.67%-1.03%). After adjusting for eligible children who refused the challenge, the overall incidence of egg allergy in Europe was estimated to be 1.23 percent (95% CI: 0.98%-1.51%), with the United Kingdom reporting the highest prevalence at 2.18 percent (95% CI: 1.27%-3.47%) and Greece reporting the lowest prevalence at 0.07 percent (95% CI: 0.00%-0.37%). This rate of egg allergy was markedly lower than the recently reported 8.9 percent prevalence of egg allergy in a population-based cohort in Australia of infants age 1 (Osborne et al., 2011), discussed below. Overall, one-half of the egg allergic children reportedly became tolerant to egg within 1 year following the initial diagnosis (Xepapadaki et al., 2016). A major limitation of this study was the large numbers of parents who refused to have their children challenged and no indication of the number of eligible children from each site who did not participate, eliminating the possibility of identifying selection bias. Nevertheless, this study represents the largest multi-center birth

cohort evaluated for egg allergy and demonstrated a variable rate of egg allergy across different regions of Europe.

In 2010, a cohort of 2,612 children (ages 11 to 12 years) from three Swedish municipalities (96 percent participation) were evaluated by questionnaire and a random subset was further evaluated by skin testing and DBPCOFC. Overall, 4.8 percent (95% CI: 4%-6%) reported allergy to one or more common foods, i.e., cow milk, egg, fish, and/or wheat (Winberg et al., 2015). About one-fourth of the children who underwent clinical examination (1.4 percent) were diagnosed with a food allergy, and only 0.6 percent were diagnosed after undergoing a DBPCOFC. This study provides some insight on the prevalence of food allergy in Sweden and further evidence that self-reported rates of food allergy consistently overestimate true prevalence of food allergy.

A cross-sectional survey was conducted in 19 children's day care centers from two Portuguese cities selected following randomization and cluster analysis (Gaspar-Marques et al., 2014). Questionnaires derived from the International Study of Asthma and Allergies in Childhood and supplemented with questions on food allergy were distributed to 2,228 parents and returned by 1,225 (55 percent). The median age of the children sampled was 3.5 years; 38.3 percent were ages 0 to 3 years, and 61.7 percent were ages 4 to 6 years. Parents reported that 10.8 percent (95% CI: 9.1%-12.6%) of the children ever had a food allergy and 5.7 percent (95% CI: 4.6%-7.2%) currently had a food allergy. Milk (2.8 percent), strawberry (2.3 percent), chocolate (1.4 percent), egg (1.0 percent) and shellfish (0.7 percent) were the most commonly reported foods. Although no attempt was made to validate food allergy with laboratory studies or OFC, the prevalence of parental-perceived food allergy is considerably lower than that reported for some countries in the EuroPrevall study, such as Germany (30 percent), Iceland, the United Kingdom, and the Netherlands (20 to 22 percent), but similar to those in others, such as Lithuania, Greece, Poland, and Spain (5 to 8 percent) (McBride et al., 2012). Like many epidemiological studies on food allergy, the use of parental reporting by questionnaire may lead to misclassification, which could explain the high perceived prevalence of allergy to strawberry and chocolate, and selection bias due to the high rate of nonresponders.

In summary, a variety of studies have been conducted in European countries to ascertain prevalence of food allergy in various populations and to various food allergens. In the most ambitious study, the EuroPrevall Surveys, 8 European centers enrolled about 3,000 individuals each to conduct questionnaires, IgE sensitization tests, and DBPCOFC. The results from DBPCOFCs in children have been published for milk and eggs; additional prevalence data will be forthcoming. No OFC were performed in adults. Although these studies provide some insights, inconsistencies

in the implementation across countries make it difficult to come to firm generalizations about food allergy prevalence in Europe for children or for adults.

## PREVALENCE OF FOOD ALLERGY IN OTHER PARTS OF THE WORLD

### Australia

One of the most comprehensive population-based studies to date was conducted in Melbourne, Australia, as part of the HealthNuts Study (Osborne et al., 2011). Importantly this study used a formal sampling frame to ensure that the study is truly population-representative (Osborne et al., 2010). Parents of infants between the ages of 11 and 15 months attending one of 120 immunization clinics were enrolled and a short interview was conducted with all nonparticipants to assess potential participation bias. Overall, 3,898 parents were approached and 2,848 (73.1 percent) agreed to participate; 99.1 percent of the nonparticipants completed the nonparticipant interview. Of those infants enrolled, 98.4 percent had SPT to four of five foods (egg, peanut, sesame, shrimp, or cow milk). Any participant with a detectable wheal size (1mm greater than the negative control) was invited for an OFC, which was conducted with research staff blinded to SPT result and history of previous reaction. The challenges were undertaken irrespective of wheal size or history of previous reaction unless the reactions occurred in the previous 1 month and predetermined objective stopping criteria were used (Koplin et al., 2012). At the time of OFC, repeat SPT wheal (i.e., small swelling) diameters 1 mm or greater than the negative control were considered positive, and 21.0 percent (95% CI: 19.5%-22.5%) were positive to one or more foods: raw egg—11.8 percent (95% CI: 10.6%-13.0%); peanut—6.4 percent (95% CI: 5.5%-7.3%); sesame—1.6 percent (95% CI: 1.2%-2.1%); shellfish—0.4 percent (95% CI: 0.2%-0.7%); and milk—5.6 percent (95% CI: 3.2%-8.0%). More than 90 percent of infants with a positive SPT to egg, peanut, and/or sesame underwent a food challenge regardless of skin test size, with an overall prevalence of challenge-confirmed food allergy among participants of 10.4 percent (95% CI: 9.3%-11.5%): raw egg—9.0 percent (95% CI: 7.8%-10.0%); peanut—2.9 percent (95% CI: 2.3%-3.6%); and sesame—0.7 percent (95% CI: 0.4%-1.0%). Of 88 infants reactive to raw egg, 80.3 percent did not react to 1.1 g of egg protein baked in a cake. Oral food challenges to milk were not performed, but IgE-mediated type reactions to milk were reported in 2.7 percent (95% CI: 2.1%-3.4%) of infants. Accounting for differences among participants and nonparticipants only marginally decreased the estimated prevalence of food allergy, e.g., peanut—2.9 percent (95% CI: 2.3%-

3.6%) to 3.0 percent (95% CI: 2.4%-3.8%) (Osborne et al., 2011). One of the greatest strengths of this survey is the diagnosis of food allergy based on challenge-proven outcomes. Despite the use of such rigorous diagnostic criteria, the prevalence of food allergy in this population of children age 1 year is the highest reported to date and may reflect the apparent higher prevalence of allergic disease in Australia or the increasing prevalence of food allergy worldwide. This cohort, which is now being followed and has been re-examined at ages 2, 4, 6, and 10 years (Koplin et al., 2015), will provide interesting insights into the natural history of food allergy.

### Africa

Few epidemiologic studies on the prevalence of food allergy have been performed in other parts of the world. Kung et al. attempted a systematic review of food allergy in Africa and found very limited information from 11 countries (Kung et al., 2014). No population-based surveys and few case-controlled cross-sectional studies have been conducted. Most studies relied on self-reporting and in some cases skin testing in selected populations. Nevertheless, the investigators concluded that while not common, food allergy is an increasing problem in several emerging African countries. A preliminary feasibility study of food sensitization and challenge-proven food allergy was conducted in Cape Town, South Africa (Basera et al., 2015). The authors concluded that future studies in this black African infant cohort will be helpful in determining the prevalence of food sensitization and allergy in an African population.

### Asia

A systematic review of food allergy in Asia yielded 53 original articles from Southeast Asia. Of these, 13 were epidemiologic studies and most had major design limitations resulting in low-grade evidence (Lee et al., 2013). The overall prevalence of self-reported or questionnaire-based food allergy in the pediatric population ranged from 3.4 percent to 11.1 percent. Egg and milk allergy were the most common food allergies in infants and young children, 0.15 percent to 4.4 percent and 0.33 percent to 3.5 percent, respectively. Shellfish (crustaceans and mollusks) allergy was the most common food allergy in older children and adults (reportedly 5.12 percent and 5.23 percent in the Philippines and Singapore, respectively), and it was the leading cause of anaphylaxis in Southeast Asia. Wheat allergy was reportedly the leading cause of anaphylaxis in children in Japan, with a prevalence of 0.37 percent.

A population-based survey of fish allergy in the Philippines, Singapore, and Thailand was conducted in randomly selected secondary schools using

structured written questionnaires followed by an extended questionnaire in those responding positively to the initial survey (Connett et al., 2012). Overall, 19,966 out of 25,842 initial surveys were returned (11,434 [81.1 percent] from the Philippines, 6,498 [67.9 percent] from Singapore and 2,034 [80.2 percent] from Thailand). The prevalence of a convincing history of fish allergy was greatest in the Philippines—2.29 percent (95% CI: 2.02%-2.56%) compared to 0.26 percent (95% CI: 0.14%-0.79%) in Singapore and 0.29 percent (95% CI: 0.06%-0.52%) in Thailand.

Two cross-sectional studies of food allergy prevalence also have been conducted in China showing an increase in food sensitization and allergy prevalence in infants between 1999 and 2009 (Hu et al., 2010). These studies, however, were small and could be subject to selection bias and therefore could report a higher level than the actual prevalence.

A cross-sectional survey of adolescents from 34 state elementary schools in Ankara province in Turkey included an initial survey followed-up by a phone survey with families that reported a food allergy and then a clinical evaluation of children who had a history compatible with food allergy following the phone survey (Kaya et al., 2013). Of 11,233 questionnaires distributed to 6th, 7th, and 8th grade students at the 34 schools, 10,096 (89.9 percent) questionnaires were returned (mean age of students was 12.9 $\pm$ 0.9 years) and 1,139 (11.2 percent) reported a food allergy. The parent-reported lifetime prevalence of food allergy was 11.3 percent (95% CI: 10.7%-11.9%) and the point prevalence[8] was 3.6 percent (95% CI: 3.2%-3.8%). All children's families who reported a food allergy and 200 others who reported no food allergy were contacted by an allergy specialist by phone. After reviewing the case histories, 133 cases were compatible with a food allergy and 107 agreed to participate in a clinical evaluation including SPT, serum IgE levels, open OFC, and in some cases DBPCOFC. Following clinical evaluation, including OFC, the prevalence of IgE-mediated food allergy was found to be 0.15 percent, with allergy to peanut (0.05 percent) and tree nuts (0.05 percent) being the most common. Strengths of this study include its large sample size and progressive diagnostic evaluation, including OFC documentation of food allergy.

In summary, relatively few population-based studies have attempted to determine the prevalence of food allergy in countries outside of Europe and the United States. These data have been limited by a number of shortcomings: small sample size, selection bias related to sampling methodology and low response rates, use of parental reporting of food allergy and/or SPT/serum IgE levels, and when included, variable OFC methodologies. One exception is Australia, which has mounted a robust effort to determine

[8] The proportion of a population that has the condition at a specific point in time.

prevalence. Data emerging from this effort will provide valuable insights into natural history and prevalence.

## PREVALENCE OF FOOD ALLERGY–INDUCED ANAPHYLAXIS

### Systematic Reviews and Meta-Analysis

Umasunthar et al. performed a systematic review and meta-analysis to determine the incidence of food-induced anaphylaxis in individuals with food allergy (Umasunthar et al., 2015). The systematic review identified 34 studies, primarily from North America, Europe, and Australia, out of 2,552 article titles that could be used to contribute data to the meta-analysis. Study results showed marked heterogeneity, most likely due to the variation in study populations, definitions of anaphylaxis used, and data collection methods. In individuals with food allergy, medically coded food anaphylaxis had an incidence rate[9] of 0.14 per 100 person-years (95% CI: 0.05-0.35). At ages 0 to 19 years, the incidence rate for anaphylaxis in those with food allergy was 0.20 (95% CI: 0.09-0.43) and at ages 0 to 4 years, the authors reported an incidence rate of up to 7.00 per 100 person-years. In food-allergic patients, the incidence rate of hospital admission due to food anaphylaxis was 0.09 (95% CI: 0.0-0.67) per 1,000 person-years, with an incidence rate of 0.20 (95% CI: 0.10-0.43) at ages 0 to 19 years based on eight studies and 0.50 (95% CI: 0.26-0.93) at ages 0 to 4 years based on six studies. The authors concluded that "the incidence of medically coded anaphylaxis for a food allergic person is greater than the general population incidence of accidental death, but is likely to be significantly lower than the incidence of Emergency Department attendance due to motor vehicle accidents" (Umasunthar et al., 2015, p. 1624). The highest rates of medically coded food anaphylaxis and hospital admissions for food anaphylaxis were seen in preschool children, in contrast to reports of fatal food anaphylaxis, which are most commonly reported in adolescents and young adults.

Using the *PRISMA* guidelines, Umasunthar et al. also performed a systematic review and meta-analysis to determine the incidence of fatal food anaphylaxis in individuals with food allergy (Umasunthar et al., 2013). Out of 2,552 original titles, 13 studies, conducted in North America, Europe, Australia, Brazil, and Israel, describing a total of 240 fatal food-induced anaphylactic reactions were included in the analysis. Assuming a food allergy prevalence rate of 3 percent (3.9 percent in individuals ages 0 to 19 years and 1 percent in those with peanut allergy), meta-analysis of 10 evaluable studies (which had low-grade evidence and a high level of heterogeneity) estimates the incidence of fatal food anaphylaxis among those

[9] Incidence rate is the number of new cases per population at risk in a given time period.

with a food-allergy as 1.81 (95% CI: 0.94-3.45) per million person-years (equivalent to about 25 deaths per year in the United States, assuming an overall 3 percent prevalence of food allergy), 3.25 (95% CI: 1.73-6.10) per million person-years in children ages 0 to 19 years, and 2.13 (95% CI: 1.09-4.16) per million person-years in peanut-allergic patients. The investigators concluded that in all studies examined and in all subgroups evaluated, "the incidence of fatal food anaphylaxis for a food-allergic person is ≥100 times lower than incidence of death due to any accident in the general population, and at age 0–19, the incidence is ≥10 times lower than the accidental death incidence in the general population" (Umasunthar et al., 2013, p. 1338). In both the systematic review and meta-analysis by Umasunthar et al., the level of evidence in the studies reviewed was low due to variations in case definition of anaphylaxis, methods of data capture, limited information about food allergy prevalence in the populations studied, and likely ascertainment bias across all studies. However, both systematic reviews suggested a number of risk factors for more severe anaphylactic reactions that have been noted in previous studies, including individuals with asthma, previous severe reaction (Bock et al., 2007; Sampson et al., 1992), IgE binding to a diverse range of sequential epitopes (Flinterman et al., 2008; Lewis et al., 2005; Shreffler et al., 2004), and deficient platelet-activating factor acetylhydrolase enzyme activity (Vadas et al., 2008).

A systematic review and meta-analysis of the prevalence of anaphylaxis in Europe was conducted by Panesar et al., who identified 49 articles satisfying their inclusion criteria, but only 3 were suitable for generating a pooled estimate of anaphylaxis (Panesar et al., 2013). Meta-analysis of these studies suggested a pooled European anaphylaxis prevalence of 0.3 percent (95% CI: 0.1%-0.5%), with markedly varying estimates of anaphylaxis due to food allergy based on individual studies ranging from 0.4 percent to 39.9 percent. In children, cow milk, egg, hazelnut, peanut, kiwi, and other tree nuts were the most common triggers, and asthma and reactions in pollen-allergic patients occurring in pollen season were identified as increased risk factors for anaphylaxis.

### Studies in the United States

Virtually no studies have been conducted evaluating the prevalence of food-induced anaphylaxis in the United States. Recently Wood et al. conducted two nationwide, cross-sectional random-digit-dial surveys: a public survey that included unselected adults and a patient survey that collected information from household members who reported a reaction to medications, foods, insect stings, or latex and idiopathic reactions in the previous 10 years (Wood et al., 2014). The public survey included 1,000 adults from which it was estimated that 5.1 percent (95% CI: 3.4%-6.8%) and 1.6

percent (95% CI: 0.8%-2.4%) had probable and very likely anaphylaxis, respectively. In the patient survey 344 of 1,059 respondents reported a history of anaphylaxis; 31 percent of these reactions were to foods, most commonly peanuts, tree nuts, and shellfish. Even though children were included in the patient survey, it had a significant bias toward an older population (median age was age 52 years). This age bias likely misrepresented the relative proportion of anaphylaxis triggers in the overall U.S. population, probably underestimating foods and overestimating medications. As with similar such surveys, both studies were limited by recall bias of interviewees, potential bias caused by using only a landline sample, and high rates of nonparticipation that could potentially result in further selection bias.

Other methods to estimate prevalence have been used, such as the *International Statistical Classification of Diseases and Related Health Problems* (ICD)[10] (Jerschow et al., 2014). However, ICD codes are considered inaccurate for determining the prevalence of food-induced anaphylactic deaths.

In the United States, the National Electronic Injury Surveillance System (NEISS) is an active surveillance system maintained by the Consumer Product Safety Commission (CPSC) designed to identify consumer product-related adverse events at emergency departments. The authors of a 2008 pilot study that analyzed NEISS emergency department data to assess food allergies adverse events concluded that analysis of NEISS data may be a useful tool for assessing the magnitude and severity of food-allergic events (Ross et al., 2008).

### Studies in Europe

Some European countries have developed Web-based surveillance systems to gather food related severe reactions data, such as the French Allergovigilance Network (Moneret-Vautrin et al., 2005) or the European Anaphylaxis Registry. Between July 2007 and March 2015, 1,970 anaphylactic events in children younger than age 18 years were reported to the European Anaphylaxis Registry, which consisted of data retrieved from medical records of referrals to 90 tertiary allergy centers in 10 European countries (Grabenhenrich et al., 2016). Overall, 1,291 out of 1,970 (66 percent) severe allergic events were due to allergic reactions to food. The investigators found that milk (N=120) and egg (N=115) were the most common cause of anaphylaxis in children during the first 2 years of life. Cashew

[10] *The International Statistical Classification of Diseases and Related Health Problems* (or *International Classification of Diseases* [ICD]) is the international standard diagnostic tool for epidemiology, health management, and clinical purposes maintained by the World Health Organization.

(N=87) and hazelnut (N=86) reactions occurred mostly in preschoolers and peanut (N=325) occurred at all ages in European children. Grabenhenrich et al. found that most incidents occurred in private homes (46 percent) and that one-third of the children had experienced a previous reaction (Grabenhenrich et al., 2016). Skin symptoms occurred in 92 percent of children: hives (62 percent), angioedema (53 percent), pruritus (37 percent), and flushing (29 percent). Gastrointestinal symptoms developed in 45 percent of the reactions: vomiting (overall 27 percent) dominating in the preschool children, abdominal pain (16 percent), and nausea (overall 15 percent) dominating in adolescents. Overall, 70 percent of anaphylactic cases due to known factors were due to food allergy, with peanut and milk being the most common elicitors. Overall, 26 children (1.3 percent) experienced severe life-threatening reactions, mostly to foods, and 5 children died. This study represents the largest series of anaphylactic reactions reported in a pediatric population.

In summary, high-quality data on the prevalence of food-induced anaphylaxis in the United States and in other countries are lacking. In addition, it is challenging to make definitive conclusions about prevalence of anaphylaxis due to heterogeneity in populations, definitions of anaphylaxis used, and data collection methods. However, mortality due to food-induced anaphylaxis seems to be low compared to other accidental causes. Still, monitoring anaphylaxis reactions from food allergies is important not only to estimate prevalence but for understanding the causes, identifying interventions, and for bringing the information to patient care and other educational efforts.

## EVIDENCE THAT THE PREVALENCE OF FOOD ALLERGY IS INCREASING

A few studies have employed consistent methodology over time in an attempt to determine whether the prevalence of food allergy has been changing over time. Sicherer et al. performed a random digit-dial telephone survey in the United States using the same methodology at set intervals (1997, 2002, and 2008) to determine the prevalence of peanut and tree nut allergy (Sicherer et al., 2010). In the 2008 study, a total of 5,300 households (13,534 participants) were surveyed (participation rates, 42 percent versus 52 percent in 2002 and 67 percent in 1997). Overall, peanut allergy, tree nut allergy, or both were reported in 1.4 percent of participants (95% CI: 1.2%-1.6%) compared with 1.2 percent in 2002 and 1.4 percent in 1997. The prevalence for adults was 1.3 percent (95% CI: 1.1%-1.6%), which was not significantly different from the earlier surveys, while the prevalence of peanut or tree nut allergy for children younger than 18 years of age was significantly different: 2.1 percent in 2008 (95% CI: 1.6%-2.7%) com-

pared with 1.2 percent in 2002 and 0.6 percent in 1997. The prevalence of peanut allergy in children in 2008 was 1.4 percent (95% CI: 1.0%-1.9%) compared with 0.8 percent in 2002 and 0.4 percent in 1997. Additionally, the prevalence of childhood tree nut allergy increased significantly across the survey waves (1.1 percent in 2008, 0.5 percent in 2002, and 0.2 percent in 1997). However, these studies had a number of limitations, including self-reporting, increasing awareness, and increasing nonparticipation rates, which could have led to increasing selection bias and higher prevalence rates.

As noted above, investigators at the CDC performed a cross-sectional survey of data from several U.S. databases and concluded that the prevalence of food allergy in children younger than age 18 years increased 18 percent from 1997 through 2007 (Branum and Lukacs, 2009). However, it remains unclear whether this represents a true increase in prevalence or a difference in awareness and coding. A recent comparison between the rate of sensitization (sIgE test) to peanut, milk, egg, and shrimp in U.S. children ages 6 to 19 years from 1988-1994 to 2005-2006 was conducted based on NHANES data. The analysis found that sensitization did not increase between 1988 and 1994 (24.3%; 95% CI: 22.1%-26.5%) and 2005-2006 (21.6%; 95% CI: 19.5%-23.7%), except for a trend toward the increased prevalence to the combination of milk, egg, and peanut among non-Hispanic blacks (McGowan et al., 2016). Sensitization, however, is not a good indicator of symptomatic food allergies.

A number of studies from other parts of the world also suggest an increase in the prevalence of sensitization and allergic reactions to foods. Three birth cohorts from the Isle of Wight in the United Kingdom were evaluated for peanut allergy in 1989 (2,181 children age 4), 1996 (1,273 children ages 3 and 4), and 2001-2002 (891 children age 3) (Venter et al., 2010). Peanut sensitization increased significantly, from 1.3 percent in the 1989 cohort to 3.3 percent (P=0.003) in the 1996 cohort before falling back to 2.0 percent in the 2001-2002 cohort (P=0.145). Clinical peanut allergy (based on positive SPT with convincing clinical history or positive OFC in the latter two cohorts) increased significantly from 0.5 percent in the 1989 cohort to 1.4 percent (P=0.023) in 1996 cohort with a subsequent fall to 1.2 percent in the 2001-2002 cohort (P=0.850). However, in this study, the cohorts are not totally comparable because the ages and participation rates varied.

In a cross-sectional survey of grade school children in Montreal, Ben-Shoshan et al. reported a non-significant rise in adjusted peanut allergy prevalence from 1.34 percent (95% CI: 1.08%-1.64%) in a 2000-2002 cohort to 1.62 percent (95% CI: 1.31%-1.98%) in a 2005-2007 cohort (Ben-Shoshan et al., 2009).

In summary, although a general perception that food allergy is increas-

ing exists, especially in westernized countries, very few studies support this likely change.

## OVERALL CONCLUSIONS

An accurate assessment of the true prevalence of food allergy and a determination of whether it is increasing are needed to prioritize food allergy as a public health problem and ensure that adequate resources are directed at the problem. Although a general consensus has emerged and plentiful "soft" data, such as parental reports, surveys of school teachers and nurses, and reports from general practitioners, suggest that the prevalence of food allergy is increasing, few well-designed comprehensive studies exist to support this notion. Because of the low quality of published prevalence data, particularly the use of self-reported data, the true prevalence of food allergy is likely overestimated in most published studies. Even so, it is clear that food allergy has become a major health problem in many countries around the world. The prevalence of atopic dermatitis has increased dramatically over the past two decades (see Figure 3-1), and this may in large part account for the rise in food allergy, as children with eczema are susceptible to sensitization to various allergens, including food, through the defective and inflamed skin barrier. Figure 3-4 depicts the prevalence of food allergy based on convincing histories plus laboratory data or OFCs, primarily in young children, in various countries around the world.

It appears that a few foods, such as milk, egg, peanut and/or tree nuts, and seafood, comprise the vast majority of allergens responsible for allergic reactions around the world, and that the likelihood of severe or fatal reactions due to food allergy in food-allergic individuals is rare, being less likely than the chance of severe injury or death due to accidents in the general public.

Good studies on the prevalence of food allergy are very costly and difficult to perform, often requiring OFCs for accurate diagnosis, which are time-consuming, potentially dangerous and frequently refused by parents, and subject to a variety of biases. In general, prevalence data based on parental surveys or specialty-based practices or hospitals provide the most inflated estimates, followed by population-based surveys, sensitization-based studies, and medical history plus sensitization-based studies. Studies incorporating OFC typically provide the lowest and most accurate assessment of true food allergy prevalence. Population-wide estimates of prevalence of food allergy in both children and adults in Europe are available from the EuroPrevall studies, which encompass questionnaires, testing for IgE antibodies, and more limited testing with DBPCOFC among children. In addition, a comprehensive study of infants has been conducted in Australia in the HealthNuts Study, which is continuing to follow the infants

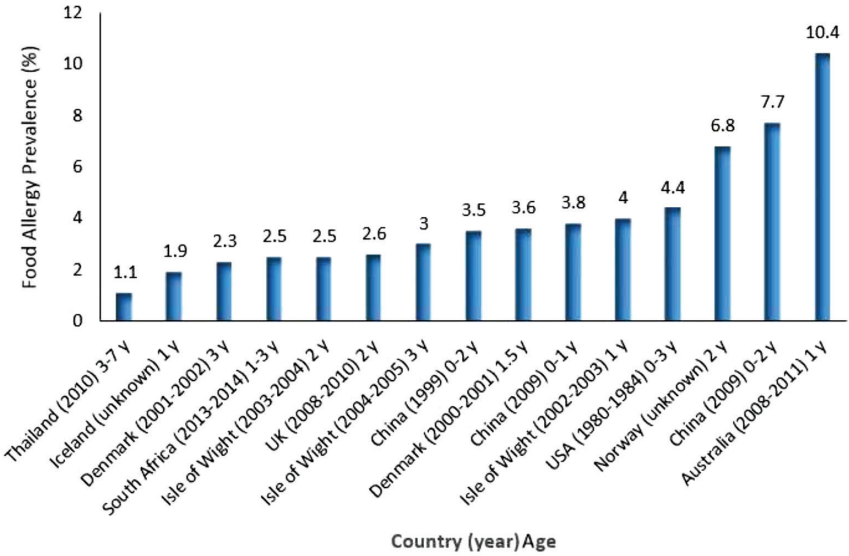


**FIGURE 3-4** Prevalence of IgE-mediated food allergy at different age points younger than the age of 6 in various countries of the world determined by convincing clinical history with evidence of IgE antibodies or by OFC. Countries and median age of population surveyed posted along x-axis, percentage of food-allergic children listed on y-axis.
SOURCES: Courtesy of Michael E. Levine, Cape Town, South Africa. Data from Basera et al., 2015; Bock, 1987; Chen et al., 2011; Eller et al., 2009; Grimshaw et al., 2015; Hu et al., 2010; Kristinsdottir et al., 2011; Kvenshagen et al., 2009; Lao-araya and Trakultivakorn, 2012; Osborne et al., 2011; Osterballe et al., 2005; Venter et al., 2006, 2008.

through childhood. No such population-wide estimates of prevalence exist in the United States.

Given the difficulty of diagnosing food allergy, the committee recommends that estimation of prevalence of food allergies in general and for the specific list of priority allergens in the United States be conducted in a systematic fashion and stratified sampling be used for cost-efficiency, with frequency-weighting used to obtain population-wide estimates. In the United States, while some surveys, such as the National Survey of Children's Health, are limited to questionnaire data, other surveys, possibly including the newly launched Environmental Influences on Child Health Outcomes (ECHO) program, could incorporate more comprehensive assessment of

food allergies, particularly in children. At this time, such information could be incorporated into a population survey sampling already in place, such as NHANES.

## RECOMMENDATIONS

**The committee recommends that the Centers for Disease Control and Prevention obtain prevalence estimates on food allergy in a systematic and statistically sound manner. Prevalence should be assessed in a systematic fashion in a sufficiently large population, with consideration given to using stratified sampling for cost-efficiency, with frequency-weighting used to obtain population-wide estimates. Prevalence estimates should be conducted in both children and adults and in groups defined by race, ethnicity, and socioeconomic status to determine differences in diagnosis and prevalence within these subgroups. To support population risk assessments, the committee also recommends that the dietary intake history of those reporting food allergy be compared to those who do not, particularly for the specific foods of interest.**

Although a new study design (or the use of other data surveillance systems) is possible, the National Health and Nutrition Examination Survey (NHANES) is a feasible option to systematically examine the prevalence of food allergy by collecting data on self-reported food allergies, food-specific immunoglobulin E (sIgE) concentrations, food-specific skin prick test (SPT) results, and oral food challenge (OFC) results.[11]

Specific suggestions for use of NHANES (or other data surveillance systems) include

- Oversample the population of children ages 0 to 6 years, due to the higher prevalence of food allergy in this group and the fact that environmental exposures at this age might affect food allergy development.
- Consistently incorporate questions on food allergy diagnosis as well as intake of common food allergens into questionnaires to capture point prevalence, change in prevalence

[11] The gold standard OFC is an expensive method and must be administered in a clinic and under supervision of a trained physician. The testing sequence, therefore, is meant to lead to a population sample that is enriched with individuals reporting food allergies and that minimizes cost and effort.

of self-reported food allergies over time, and dietary information on intake of common allergens.

- Perform assays of blood specimens for serum food allergen-specific immunoglobulin (IgE), concentrations to obtain population estimates of prevalence of allergen sensitization and assess changes in prevalence over time.
- Invite a stratified sample of participants enriched with individuals reporting food allergies to undergo food-specific SPT during the examination component of the survey.
- Invite a smaller subsample of participants to undergo double blinded placebo-controlled OFCs. This sample should be enriched with individuals reporting food allergies and/or positive SPT or IgE antibody tests.
- Elicit reasons for any nonparticipation in SPT or OFC, particularly whether the individual has had prior testing and a diagnosed food allergy. If possible, obtain medical records containing such test results.
- Obtain population-wide estimates of self-reported food allergies, IgE concentrations, positive SPTs, and positive OFCs through weighted analyses using stratified sampling weights (e.g., as is routinely used in NHANES analyses).
- Establish the sensitivity and specificity of various diagnostics as compared to the OFC.
- Use a diagnostic challenge with progressive series of doses in the subsample undergoing OFCs to establish prevalence of food allergy. Also include testing at a lower dose to validate population thresholds proposed for food labeling purposes.

## RESEARCH NEEDS

In addition to sound information about the true prevalence of food allergy, the committee concluded that better methods to collect information about anaphylaxis reactions are needed. In addition, estimates of the various costs of food allergy are needed. For example, the CDC has developed tools to estimate the costs associated with some chronic diseases, such as arthritis. Medical expenditures for managing food allergy place financial burdens on society, as well as on the individuals affected and their caregivers. Additional costs relate to quality of life, productivity in school or at work, and food recalls. In addition, data from a national survey of caregivers of food-allergic children suggests considerable socioeconomic disparities in the economic impact of childhood food allergy. For instance, children in the lowest income stratum incurred 2.5 times the amount of emergency

department and hospitalization costs related to their food allergies than did higher-income children (Bilaver et al., 2016). Estimates on cost burden are necessary for prioritizing research and resources, and for effectively advocating for implementation of practices and policies that will reduce costs. The accuracy of the estimates will partially depend on collecting better prevalence data, as described in the recommendation above.

The following research needs are warranted to improve data on severe reactions and on cost estimates:

- Evaluate various methods of collecting national data on food allergy severe reactions such as by leveraging the existing surveillance systems (e.g., NHANES or the National Electronic Injury Surveillance System) or by developing a Web-based reporting system for anaphylaxis in the community.
- Collect and analyze data to estimate the economic and social costs of food allergy based on current prevalence of both mild and severe reactions and on objective measures of costs, such as data on medical expenses and time lost from school and work. Collect these data on different ethnicities and socioeconomic strata. The costs to industry due to food recalls and implementation of allergen control strategies also should be estimated.

## REFERENCES

Atkins, D., D. Best, P. A. Briss, M. Eccles, Y. Falck-Ytter, S. Flottorp, G. H. Guyatt, R. T. Harbour, M. C. Haugh, D. Henry, S. Hill, R. Jaeschke, G. Leng, A. Liberati, N. Magrini, J. Mason, P. Middleton, J. Mrukowicz, D. O'Connell, A. D. Oxman, B. Phillips, H. J. Schunemann, T. Edejer, H. Varonen, G. E. Vist, J. W. Williams, Jr., S. Zaza, and G. W. Group. 2004. Grading quality of evidence and strength of recommendations. *BMJ* 328(7454):1490.

Basera, W., M. Botha, C. L. Gray, N. Lunjani, A. S. Watkins, C. Venter, K. J. Allen, C. Hlela, H. J. Zar, and M. E. Levin. 2015. The South African food sensitisation and food allergy population-based study of IgE-mediated food allergy: Validity, safety, and acceptability. *Ann Allergy Asthma Immunol* 115(2):113-119.

Ben-Shoshan, M., R. S. Kagan, R. Alizadehfar, L. Joseph, E. Turnbull, Y. St Pierre, and A. E. Clarke. 2009. Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal. *J Allergy Clin Immunol* 123(4):783-788.

Bilaver, L. A., K. M. Kester, B. M. Smith, and R. S. Gupta. 2016. Socioeconomic disparities in the economic impact of childhood food allergy. *Pediatrics* 137(5)e20153678.

Bock, S. A. 1987. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 79(5):683-688.

Bock, S. A., A. Munoz-Furlong, and H. A. Sampson. 2007. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 119(4):1016-1018.

Boyce, J. A., A. Assa'ad, A. W. Burks, S. M. Jones, H. A. Sampson, R. A. Wood, M. Plaut, S. F. Cooper, M. J. Fenton, S. H. Arshad, S. L. Bahna, L. A. Beck, C. Byrd-Bredbenner, C. A. Camargo, Jr., L. Eichenfield, G. T. Furuta, J. M. Hanifin, C. Jones, M. Kraft, B. D. Levy, P. Lieberman, S. Luccioli, K. M. McCall, L. C. Schneider, R. A. Simon, F. E. Simons, S. J. Teach, B. P. Yawn, and J. M. Schwaninger. 2010. Guidelines for the diagnosis and management of food allergy in the United States: Report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 126(6 Suppl):S1-S58.

Branum, A. M., and S. L. Lukacs. 2008. Food allergy among U.S. children: Trends in prevalence and hospitalizations. *NCHS Data Brief* (10):1-8.

Branum, A. M., and S. L. Lukacs. 2009. Food allergy among children in the United States. *Pediatrics* 124(6):1549-1555.

Bunyavanich, S., S. L. Rifas-Shiman, T. A. Platts-Mills, L. Workman, J. E. Sordillo, M. W. Gillman, D. R. Gold, and A. A. Litonjua. 2014. Peanut allergy prevalence among school-age children in a US cohort not selected for any disease. *J Allergy Clin Immunol* 134(3):753-755.

Burney, P. G., J. Potts, I. Kummeling, E. N. Mills, M. Clausen, R. Dubakiene, L. Barreales, C. Fernandez-Perez, M. Fernandez-Rivas, T. M. Le, A. C. Knulst, M. L. Kowalski, J. Lidholm, B. K. Ballmer-Weber, C. Braun-Fahlander, T. Mustakov, T. Kralimarkova, T. Popov, A. Sakellariou, N. G. Papadopoulos, S. A. Versteeg, L. Zuidmeer, J. H. Akkerdaas, K. Hoffmann-Sommergruber, and R. van Ree. 2014. The prevalence and distribution of food sensitization in European adults. *Allergy* 69(3):365-371.

Camargo, C. A., Jr., S. Clark, M. S. Kaplan, P. Lieberman, and R. A. Wood. 2007. Regional differences in EpiPen prescriptions in the United States: The potential role of vitamin D. *J Allergy Clin Immunol* 120(1):131-136.

Chafen, J. J., S. J. Newberry, M. A. Riedl, D. M. Bravata, M. Maglione, M. J. Suttorp, V. Sundaram, N. M. Paige, A. Towfigh, B. J. Hulley, and P. G. Shekelle. 2010. Diagnosing and managing common food allergies: A systematic review. *JAMA* 303(18):1848-1856.

Chen, J., Y. Hu, K. J. Allen, M. H. Ho, and H. Li. 2011. The prevalence of food allergy in infants in Chongqing, China. *Pediatr Allergy Immunol* 22(4):356-360.

Connett, G. J., I. Gerez, E. A. Cabrera-Morales, A. Yuenyongviwat, J. Ngamphaiboon, P. Chatchatee, P. Sangsupawanich, S. E. Soh, G. C. Yap, L. P. Shek, and B. W. Lee. 2012. A population-based study of fish allergy in the Philippines, Singapore and Thailand. *Int Arch Allergy Immunol* 159(4):384-390.

Datema, M. R., L. Zuidmeer-Jongejan, R. Asero, L. Barreales, S. Belohlavkova, F. de Blay, P. Bures, M. Clausen, R. Dubakiene, D. Gislason, M. Jedrzejczak-Czechowicz, M. L. Kowalski, A. C. Knulst, T. Kralimarkova, T. M. Le, A. Lovegrove, J. Marsh, N. G. Papadopoulos, T. Popov, N. Del Prado, A. Purohit, G. Reese, I. Reig, S. L. Seneviratne, A. Sinaniotis, S. A. Versteeg, S. Vieths, A. H. Zwinderman, C. Mills, J. Lidholm, K. Hoffmann-Sommergruber, M. Fernandez-Rivas, B. Ballmer-Weber, and R. van Ree. 2015. Hazelnut allergy across Europe dissected molecularly: A EuroPrevall outpatient clinic survey. *J Allergy Clin Immunol* 136(2):382-391.

EFSA (European Food Safety Authority). 2013. Literature searches and reviews related to the prevalence of food allergy in Europe. *EFSA Supporting Publications* 10(11):1-343.

Eller, E., H. F. Kjaer, A. Host, K. E. Andersen, and C. Bindslev-Jensen. 2009. Food allergy and food sensitization in early childhood: Results from the DARC cohort. *Allergy* 64(7):1023-1029.

Flinterman, A. E., E. F. Knol, D. A. Lencer, L. Bardina, C. F. den Hartog Jager, J. Lin, S. G. Pasmans, C. A. Bruijnzeel-Koomen, H. A. Sampson, E. van Hoffen, and W. G. Shreffler. 2008. Peanut epitopes for IgE and IgG4 in peanut-sensitized children in relation to severity of peanut allergy. *J Allergy Clin Immunol* 121(3):737-743 e710.

Gaspar-Marques, J., P. Carreiro-Martins, A. L. Papoila, I. Caires, C. Pedro, J. Araujo-Martins, D. Virella, J. Rosado-Pinto, P. Leiria-Pinto, and N. Neuparth. 2014. Food allergy and anaphylaxis in infants and preschool-age children. *Clin Pediatr (Phila)* 53(7):652-657.

Grabenhenrich, L. B., S. Dolle, A. Moneret-Vautrin, A. Kohli, L. Lange, T. Spindler, F. Rueff, K. Nemat, I. Maris, E. Roumpedaki, K. Scherer, H. Ott, T. Reese, T. Mustakov, R. Lang, M. Fernandez-Rivas, M. L. Kowalski, M. B. Bilo, J. O. Hourihane, N. G. Papadopoulos, K. Beyer, A. Muraro, and M. Worm. 2016. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol* 137(4):1128-1137.

Greenhawt, M., C. Weiss, M. L. Conte, M. Doucet, A. Engler, and C. A. Camargo, Jr. 2013. Racial and ethnic disparity in food allergy in the United States: A systematic review. *J Allergy Clin Immunol Pract* 1(4):378-386.

Grimshaw, K. E., T. Bryant, E. M. Oliver, J. Martin, J. Maskell, T. Kemp, E. N. Clare Mills, K. D. Foote, B. M. Margetts, K. Beyer, and G. Roberts. 2015. Incidence and risk factors for food hypersensitivity in UK infants: Results from a birth cohort study. *Clin Transl Allergy* 6:1.

Gupta, R. S., E. E. Springston, M. R. Warrier, B. Smith, R. Kumar, J. Pongracic, and J. L. Holl. 2011. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 128(1):e9-e17.

Gupta, R. S., E. E. Springston, B. Smith, M. R. Warrier, J. Pongracic, and J. L. Holl. 2012. Geographic variability of childhood food allergy in the United States. *Clin Pediatr (Phila)* 51(9):856-861.

Gupta, R., D. Holdford, L. Bilaver, A. Dyer, J. L. Holl, and D. Meltzer. 2013a. The economic impact of childhood food allergy in the United States. *JAMA Pediatr* 167(11):1026-1031.

Gupta, R. S., E. E. Springston, B. Smith, J. Pongracic, J. L. Holl, and M. R. Warrier. 2013b. Parent report of physician diagnosis in pediatric food allergy. *J Allergy Clin Immunol* 131(1):150-156.

Hu, Y., J. Chen, and H. Li. 2010. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. *Pediat Int* 52(5):820-824.

Jackson, K. D., L. D. Howie, and L. J. Akinbami. 2013. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief* (121):1-8.

Jerschow, E., R. Y. Lin, M. M. Scaperotti, and A. P. McGinn. 2014. Fatal anaphylaxis in the United States, 1999-2010: Temporal patterns and demographic associations. *J Allergy Clin Immunol* 134(6):1318-1328.

Katelaris, C. H. 2010. Food allergy and oral allergy or pollen-food syndrome. *Curr Opin Allergy Clin Immunol* 10(3):246-251.

Katz, Y., P. Gutierrez-Castrellon, M. G. Gonzalez, R. Rivas, B. W. Lee, and P. Alarcon. 2014. A comprehensive review of sensitization and allergy to soy-based products. *Clin Rev Allergy Immunol* 46(3):272-281.

Kaya, A., M. Erkocoglu, E. Civelek, B. Cakir, and C. N. Kocabas. 2013. Prevalence of confirmed IgE-mediated food allergy among adolescents in Turkey. *Pediatr Allergy Immunol* 24(5):456-462.

Kazemi-Shirazi, L., G. Pauli, A. Purohit, S. Spitzauer, R. Froschl, K. Hoffmann-Sommergruber, H. Breiteneder, O. Scheiner, D. Kraft, and R. Valenta. 2000. Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy. *J Allergy Clin Immunol* 105(1 Pt 1):116-125.

Keet, C. A., J. H. Savage, S. Seopaul, R. D. Peng, R. A. Wood, and E. C. Matsui. 2014. Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. *Ann Allergy Asthma Immunol* 112(3):222-229.

Koplin, J. J., M. L. Tang, P. E. Martin, N. J. Osborne, A. J. Lowe, A. L. Ponsonby, M. N. Robinson, D. Tey, L. Thiele, D. J. Hill, L. C. Gurrin, M. Wake, S. C. Dharmage, and K. J. Allen. 2012. Predetermined challenge eligibility and cessation criteria for oral food challenges in the HealthNuts population-based study of infants. *J Allergy Clin Immunol* 129(4):1145-1147.

Koplin, J. J., M. Wake, S. C. Dharmage, M. Matheson, M. L. Tang, L. C. Gurrin, T. Dwyer, R. L. Peters, S. Prescott, A. L. Ponsonby, A. J. Lowe, and K. J. Allen. 2015. Cohort profile: The HealthNuts Study: Population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol* 44(4):1161-1171.

Kristinsdottir, H., M. Clausen, H. S. Ragnarsdottir, I. H. Halldorsdottir, D. McBride, K. Beyer, and S. T. Sigurdardottir. 2011. Prevalence of food allergy in Icelandic infants during first year of life. *Laeknabladid* 97(1):11-18.

Kummeling, I., E. N. Mills, M. Clausen, R. Dubakiene, C. F. Perez, M. Fernandez-Rivas, A. C. Knulst, M. L. Kowalski, J. Lidholm, T. M. Le, C. Metzler, T. Mustakov, T. Popov, J. Potts, R. van Ree, A. Sakellariou, B. Tondury, K. Tzannis, and P. Burney. 2009. The EuroPrevall surveys on the prevalence of food allergies in children and adults: Background and study methodology. *Allergy* 64(10):1493-1497.

Kung, S. J., A. P. Steenhoff, and C. Gray. 2014. Food allergy in Africa: Myth or reality? *Clin Rev Allergy Immunol* 46(3):241-249.

Kvenshagen, B., R. Halvorsen, and M. Jacobsen. 2009. Is there an increased frequency of food allergy in children delivered by caesarean section compared to those delivered vaginally? *Acta Paediatr* 98(2):324-327.

Lao-araya, M., and M. Trakultivakorn. 2012. Prevalence of food allergy among preschool children in northern Thailand. *Pediatr Int* 54(2):238-243.

Le, T. M., E. van Hoffen, I. Kummeling, J. Potts, B. K. Ballmer-Weber, C. A. Bruijnzeel-Koomen, A. F. Lebens, J. Lidholm, T. M. Lindner, A. Mackie, E. C. Mills, R. van Ree, S. Vieths, M. Fernandez-Rivas, P. G. Burney, and A. C. Knulst. 2015. Food allergy in the Netherlands: Differences in clinical severity, causative foods, sensitization and DBPCFC between community and outpatients. *Clin Transl Allergy* 5:8.

Lee, A. J., M. Thalayasingam, and B. W. Lee. 2013. Food allergy in Asia: How does it compare? *Asia Pac Allergy* 3(1):3-14.

Lewis, S. A., K. E. Grimshaw, J. O. Warner, and J. O. Hourihane. 2005. The promiscuity of immunoglobulin E binding to peanut allergens, as determined by Western blotting, correlates with the severity of clinical symptoms. *Clin Exp Allergy* 35(6):767-773.

McBride, D., T. Keil, L. Grabenhenrich, R. Dubakiene, G. Drasutiene, A. Fiocchi, L. Dahdah, A. B. Sprikkelman, A. A. Schoemaker, G. Roberts, K. Grimshaw, M. L. Kowalski, A. Stanczyk-Przyluska, S. Sigurdardottir, M. Clausen, N. G. Papadopoulos, D. Mitsias, L. Rosenfeld, M. Reche, C. Pascual, A. Reich, J. Hourihane, U. Wahn, E. N. Mills, A. Mackie, and K. Beyer. 2012. The EuroPrevall birth cohort study on food allergy: Baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol* 23(3):230-239.

McGowan, E. C., R. D. Peng, P. M. Salo, D. C. Zeldin, and C. A. Keet. 2016. Changes in food-specific IgE over time in the National Health and Nutrition Examination Survey (NHANES). *J Allergy Clin Immunol Pract* 4(4):713-720.

McWilliam, V., J. Koplin, C. Lodge, M. Tang, S. Dharmage, and K. Allen. 2015. The prevalence of tree nut allergy: A systematic review. *Curr Allergy Asthma Rep* 15(9):54.

Moher, D., A. Liberati, J. Tetzlaff, D. G. Altman, and P. Group. 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 151(4):264-269, W264.

Moneret-Vautrin, D., M. Morisset, L. Parisot, G. Kanny. 2005. French Allergovigilance Network report about severe anaphylactic reactions to foods from 2001 to 2004. *J Allergy Clin Immunol* 115(2):S247.

Nwaru, B. I., L. Hickstein, S. S. Panesar, G. Roberts, A. Muraro, and A. Sheikh. 2014. Prevalence of common food allergies in Europe: A systematic review and meta-analysis. *Allergy* 69(8):992-1007.

Osborne, N. J., J. J. Koplin, P. E. Martin, L. C. Gurrin, L. Thiele, M. L. Tang, A. L. Ponsonby, S. C. Dharmage, and K. J. Allen. 2010. The HealthNuts population-based study of paediatric food allergy: Validity, safety and acceptability. *Clin Exper Allergy* 40(10):1516-1522.

Osborne, N. J., J. J. Koplin, P. E. Martin, L. C. Gurrin, A. J. Lowe, M. C. Matheson, A. L. Ponsonby, M. Wake, M. L. Tang, S. C. Dharmage, and K. J. Allen. 2011. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 127(3):668-676.e1-2.

Osterballe, M., T. K. Hansen, C. G. Mortz, A. Host, and C. Bindslev-Jensen. 2005. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 16(7):567-573.

Panesar, S. S., S. Javad, D. de Silva, B. I. Nwaru, L. Hickstein, A. Muraro, G. Roberts, M. Worm, M. B. Bilo, V. Cardona, A. E. Dubois, A. Dunn Galvin, P. Eigenmann, M. Fernandez-Rivas, S. Halken, G. Lack, B. Niggemann, A. F. Santos, B. J. Vlieg-Boerstra, Z. Q. Zolkipli, and A. Sheikh. 2013. The epidemiology of anaphylaxis in Europe: A systematic review. *Allergy* 68(11):1353-1361.

Rona, R. J., T. Keil, C. Summers, D. Gislason, L. Zuidmeer, E. Sodergren, S. T. Sigurdardottir, T. Lindner, K. Goldhahn, J. Dahlstrom, D. McBride, and C. Madsen. 2007. The prevalence of food allergy: A meta-analysis. *J Allergy Clin Immunol* 120(3):638-646.

Ross, M. P., M. Ferguson, D. Street, K. Klontz, T. Schroeder, and S. Luccioli. 2008. Analysis of food-allergic and anaphylactic events in the National Electronic Injury Surveillance System. *J Allergy Clin Immunol* 121(1):166-171.

Rudders, S. A., J. A. Espinola, and C. A. Camargo, Jr. 2010. North-south differences in US emergency department visits for acute allergic reactions. *Ann Allergy Asthma Immunol* 104(5):413-416.

Salo, P. M., S. J. Arbes, Jr., R. Jaramillo, A. Calatroni, C. H. Weir, M. L. Sever, J. A. Hoppin, K. M. Rose, A. H. Liu, P. J. Gergen, H. E. Mitchell, and D. C. Zeldin. 2014. Prevalence of allergic sensitization in the United States: Results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. *J Allergy Clin Immunol* 134(2):350-359.

Sampson, H. A., L. Mendelson, and J. P. Rosen. 1992. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 327(6):380-384.

Schoemaker, A. A., A. B. Sprikkelman, K. E. Grimshaw, G. Roberts, L. Grabenhenrich, L. Rosenfeld, S. Siegert, R. Dubakiene, O. Rudzeviciene, M. Reche, A. Fiandor, N. G. Papadopoulos, A. Malamitsi-Puchner, A. Fiocchi, L. Dahdah, S. T. Sigurdardottir, M. Clausen, A. Stanczyk-Przyluska, K. Zeman, E. N. Mills, D. McBride, T. Keil, and K. Beyer. 2015. Incidence and natural history of challenge-proven cow milk allergy in European children—EuroPrevall birth cohort. *Allergy* 70(8):963-972.

Shamseer, L., D. Moher, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, and L. A. Stewart. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ* 349:g7647.

Shreffler, W. G., K. Beyer, T. H. Chu, A. W. Burks, and H. A. Sampson. 2004. Microarray immunoassay: Association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 113(4):776-782.

Sicherer, S. H. 2011. Epidemiology of food allergy. *J Allergy Clin Immunol* 127(3):594-602.

Sicherer, S. H., A. Munoz-Furlong, J. H. Godbold, and H. A. Sampson. 2010. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 125(6):1322-1326.

Soller, L., M. Ben-Shoshan, D. W. Harrington, M. Knoll, J. Fragapane, L. Joseph, Y. St Pierre, S. La Vieille, K. Wilson, S. J. Elliott, and A. E. Clarke. 2015. Adjusting for nonresponse bias corrects overestimates of food allergy prevalence. *J Allergy Clin Immunol Pract* 3(2):291-293.

Umasunthar, T., J. Leonardi-Bee, M. Hodes, P. J. Turner, C. Gore, P. Habibi, J. O. Warner, and R. J. Boyle. 2013. Incidence of fatal food anaphylaxis in people with food allergy: A systematic review and meta-analysis. *Clin Exp Allergy* 43(12):1333-1341.

Umasunthar, T., J. Leonardi-Bee, P. J. Turner, M. Hodes, C. Gore, J. O. Warner, and R. J. Boyle. 2015. Incidence of food anaphylaxis in people with food allergy: A systematic review and meta-analysis. *Clin Exp Allergy* 45(11):1621-1636.

Vadas, P., M. Gold, B. Perelman, G. M. Liss, G. Lack, T. Blyth, F. E. Simons, K. J. Simons, D. Cass, and J. Yeung. 2008. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 358(1):28-35.

Venter, C., B. Pereira, J. Grundy, C. B. Clayton, G. Roberts, B. Higgins, and T. Dean. 2006. Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. *J Allergy Clin Immunol* 117(5):1118-1124.

Venter, C., B. Pereira, K. Voigt, J. Grundy, C. B. Clayton, B. Higgins, S. H. Arshad, and T. Dean. 2008. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy* 63(3):354-359.

Venter, C., S. Hasan Arshad, J. Grundy, B. Pereira, C. Bernie Clayton, K. Voigt, B. Higgins, and T. Dean. 2010. Time trends in the prevalence of peanut allergy: Three cohorts of children from the same geographical location in the UK. *Allergy* 65(1):103-108.

Wang, J. 2013. Oral allergy syndrome. In *Food Allergy: Adverse Reactions to Foods and Food Additives, 5th* ed., edited by D. Metcalfe, H. A. Sampson, R. A. Simon and G. Lack. Chichester, UK: John Wiley & Sons, Ltd.

Winberg, A., C. E. West, A. Strinnholm, L. Nordstrom, L. Hedman, and E. Ronmark. 2015. Assessment of allergy to milk, egg, cod, and wheat in Swedish schoolchildren: A population based cohort study. *PLoS One* 10(7):e0131804.

Wood, R. A., C. A. Camargo, Jr., P. Lieberman, H. A. Sampson, L. B. Schwartz, M. Zitt, C. Collins, M. Tringale, M. Wilkinson, J. Boyle, and F. E. Simons. 2014. Anaphylaxis in America: The prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol* 133(2):461-467.

Xepapadaki, P., A. Fiocchi, L. Grabenhenrich, G. Roberts, K. E. Grimshaw, A. Fiandor, J. I. Larco, S. Sigurdardottir, M. Clausen, N. G. Papadopoulos, L. Dahdah, A. Mackie, A. B. Sprikkelman, A. A. Schoemaker, R. Dubakiene, I. Butiene, M. L. Kowalski, K. Zeman, S. Gavrili, T. Keil, and K. Beyer. 2016. Incidence and natural history of hen's egg allergy in the first 2 years of life—The EuroPrevall birth cohort study. *Allergy* 71(3):350-357.

Zuidmeer, L., K. Goldhahn, R. J. Rona, D. Gislason, C. Madsen, C. Summers, E. Sodergren, J. Dahlstrom, T. Lindner, S. T. Sigurdardottir, D. McBride, and T. Keil. 2008. The prevalence of plant food allergies: A systematic review. *J Allergy Clin Immunol* 121(5):1210-1218 e1214.

# 4

# Assessments, Diagnostic Testing, Disease Monitoring, and Prognosis

## OVERVIEW

A diagnosis of food allergy carries numerous health, emotional, social, and nutritional consequences. Therefore, a proper diagnosis is imperative. Unfortunately, studies suggest that many individuals needlessly avoid foods on the presumption of a food allergy without seeking medical confirmation, a practice that can lead to unnecessary risk and burden (Boyce et al., 2010; Fleischer et al., 2011; Rona et al., 2007). For example, in one meta-analysis, the rate of self-reported food allergy was 12 percent and 13 percent for children and adults compared to 3 percent when confirmation with testing was applied (Boyce et al., 2010; Rona et al., 2007). One of the major issues in food allergy is the common misconception that having a "positive test," by a blood test or allergy skin prick test (SPT, otherwise known as sensitization, or a condition in which an individual produces detectable food-specific immunoglobulin E [IgE] antibody), is equivalent to having a clinical food allergy. For example, Fleischer et al. performed 111 supervised feeding tests with 44 children avoiding foods because of positive skin or serum allergy tests and, overall, 93 percent of the children were tolerant of the avoided food (Fleischer et al., 2011). Although this was a subpopulation of children with high rate of atopic dermatitis, on a population level, many more persons are also sensitized to foods than are clinically reactive upon ingestion. For example, 2005-2006 National Health and Nutrition Examination Survey (NHANES) data showed a 7.6 percent rate of positive serum IgE tests to peanut (10.7 percent in children ages 6 to 19 years), clearly higher than the prevalence of clinical peanut allergy (Liu et al., 2010). Compounding

the problem, many physicians lack an understanding of how to apply common diagnostic tests and interpret the results. In a survey of 407 primary care physicians, less than 30 percent of the participants reported that they were comfortable interpreting laboratory tests to diagnose food allergy, and 38 percent indicated incorrectly that skin or blood tests were sufficient for a diagnosis (Gupta et al., 2010). Clearly, the lack of understanding among physicians is compounded among the lay public.

Although overdiagnosis is a concern, conversely, assuming that an allergen has been identified as a trigger of a serious allergic response, a lack of confirmation could lead to re-exposure to the true culprit, with serious consequences. It is therefore imperative that individuals with suspected food allergy seek a medical diagnosis to identify whether the cause of symptoms is a food allergy and to identify culprit foods.

Considering the various symptoms (e.g., rashes, respiratory symptoms, gastrointestinal [GI] symptoms) and medical illnesses (e.g., atopic dermatitis, anaphylaxis) attributable to food allergy, many of which have alternate diagnoses (i.e., intolerance, pharmacologic reactions), or nonfood triggers (i.e., pollen allergy, irritants), food allergy diagnosis is complicated. Additionally, no simple tests exist that, in isolation, diagnose a specific food allergy (Boyce et al., 2010; Sampson et al., 2014). The primary tools currently available for diagnosis include the medical history, elimination diets, SPT, food-specific IgE (sIgE) (serum tests for food-specific IgE against specific proteins in foods), component resolved diagnostics (CRD), and medically supervised oral food challenges (OFCs).

This chapter includes relevant aspects of mechanisms of food allergy in relation to the current accepted methods for diagnostic testing and prognosis, including misconceptions about the methods, limitations, and factors that might affect diagnosis. The chapter also describes some promising methods that need further research, validation, or standardization before being used routinely, and methods that are not recommended for use routinely. The chapter ends with overall conclusions, recommendations, and research needs.

## APPROACH TO LITERATURE REVIEW

In preparing this chapter, new individual systematic reviews or meta-analyses were not conducted. The primary resources for discussion, findings, conclusions, and recommendations were derived from the National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH)–supported Guidelines (Boyce et al., 2010), the European Academy of Allergy & Clinical Immunology (EAACI) Guidelines (Muraro et al., 2014), and associated systematic reviews (Soares-Weiser et al., 2014) as well as the American Academy of Allergy, Asthma & Immunology

(AAAAI) Guidelines (Sampson et al., 2014; see Chapter 1, Table 1-1). Additional PubMed searches were selectively performed to identify studies and reports in the literature, especially focusing on papers published after the aforementioned reports. Meta-analyses, systematic reviews, expert reports, and practice guidelines were selected when available and supplemented with more recent publications.

## REASONS TO INITIATE ASSESSMENTS FOR FOOD ALLERGY

The NIAID/NIH-supported Guidelines (Boyce et al., 2010) suggest that food allergy should be considered in a number of specific circumstances. Having allergic symptoms within minutes to hours after ingestion, especially from a specific food on more than one occasion, is suggestive of a food allergy and warrants investigation. Symptoms can include skin symptoms of itchy rashes, hives, or swelling; eye symptoms of itching, tearing, redness, or swelling; oral symptoms of itching or swelling of the lips, tongue, or palate; upper airway symptoms of congestion, itching, sneezing, nasal discharge, or hoarseness; lower airway symptoms of cough, chest tightness, wheezing, or trouble breathing; gastrointestinal symptoms of nausea, pain, vomiting, or diarrhea; cardiovascular symptoms of fast or slow heart rate, dizziness, low blood pressure, confusion, loss of consciousness; uterine contractions; and a sense of "impending doom."

Food allergy diagnostic testing also may be warranted for infants, young children, and selected older individuals with moderate to severe atopic dermatitis because a higher rate of food allergy occurs in these populations, whether or not the food allergy may be contributing to the rash (Boyce et al., 2010; Sidbury et al., 2014). Disorders with subacute or chronic symptoms that indicate food-related disorders, such as food protein–induced enterocolitis (FPIES), enteropathy, and allergic colitis, also warrant investigation for food-allergic triggers. Food allergy also should be considered in children and adults with eosinophilic esophagitis (Boyce et al., 2010; Liacouras et al., 2011; Markowitz et al., 2003). Importantly, food allergy is not a typical trigger of chronic asthma or chronic rhinitis in childhood (Boyce et al., 2010; Sampson et al., 2014), although it can cause occupational asthma in certain groups, such as bakers or shellfish handlers.

The initiation of food allergy diagnostic testing also has some areas of uncertainty. For example, one expert panel (Boyce et al., 2010) concluded that there was insufficient evidence to recommend routine food allergy testing before introducing highly allergenic foods to children at high risk of food allergy, such as those with pre-existing severe allergic disease or family history of food allergy. However, they indicated value in such evaluations for selected patients, such as those having a peanut allergy or evidence of

another underlying food allergy. For example, testing for tree nut allergy in a child with peanut allergy who has not yet been exposed to tree nuts would be appropriate. Similarly, consensus recommendations regarding introduction of peanut to high-risk infants with early-onset atopic disease, such as severe eczema or egg allergy, have suggested that infants might benefit from evaluation to diagnose any food allergy and to evaluate an infant for introduction of peanut (Fleischer et al., 2015).

A common misconception or concern among caregivers is that if one sibling develops a food allergy, other siblings also will become allergic. However, a recent study of a large cohort of families with food allergies found that only a small proportion of siblings are both sensitized (based on SPT and IgE) and clinically reactive to a food (based on history of typical symptoms of an allergic reaction to a food) (Gupta el al., 2016). In support of NIAID/NIH-supported Guidelines (Boyce et al., 2010), the authors concluded that testing for food allergy in siblings without a history of clinical reactivity appears to be unjustified and that screening may lead to negative consequences related to potential misdiagnosis and unnecessary avoidance of a food.

## MECHANISMS OF FOOD ALLERGY IN RELATIONSHIP TO DIAGNOSTIC TESTING

Chapter 2 described specific food allergic disorders and pathophysiology. With regard to diagnostic testing, the pathophysiology of the disorder is relevant. For example, tests for food-specific IgE antibodies (i.e., SPT, sIgE, and CRD) are relevant for IgE-mediated disorders. These tests may sometimes be performed in disorders that are non-IgE-mediated to identify a potential for acute allergic reactions if the previously consumed food has been removed from the diet after having been a part of the diet (Liacouras et al., 2011), or to determine whether there has been a change in pathophysiology to an IgE-mediated disorder, as can occur with FPIES (Caubet et al., 2014). In contrast, the medical history, elimination diets, and physician-supervised OFCs are useful in all food allergic disorder evaluations.

## CURRENTLY AVAILABLE MODALITIES ROUTINELY USED TO DIAGNOSE FOOD ALLERGY

A number of modalities have been recommended for diagnosing food allergy (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). These are reviewed briefly in the following section with an emphasis on utility and limitations. The diagnostic tests discussed below are generally not used in isolation (see "General Diagnostic Algorithms").

### Medical History and Physical Examination

A thorough medical history and physical examination are imperative in the diagnosis of food allergy (Boyce et al., 2010; Muraro et al., 2014). They can help to identify the likelihood of the diagnosis, and suggest whether the pathophysiology is IgE or non-IgE, which is important for test selection. The history and physical examination also identify potential triggers, which help to hone specific test selection. Importantly, details of the history may disclose alternative reasons for symptoms, other than a food allergy. For example, an acute allergic reaction attributed to a food may actually be triggered by other allergens, such as medications or insect stings. Numerous triggers, such as environmental irritants, change in temperature, and infections, can initiate atopic dermatitis flares. Chronic GI symptoms can be attributed to food but may actually be caused by medical conditions such as reflux or inflammatory bowel disease. In fact, a broad differential diagnosis exists to distinguish food allergy from other allergic disorders or from disorders that are not immunologically mediated and associated with food. Food poisoning or pharmacologic effects from food components may be masqueraders of a food allergy. Many patients confuse food allergy and food intolerance (Sicherer et al., 2012). Food intolerance is not mediated by the immune system, and is characterized by symptoms such as gas, bloating, and diarrhea in the case of lactose intolerance.

No evidence-based, standard series of questions has been developed for use in taking a medical history to evaluate a possible food allergy, although creating this type of question set is under study (Skypala et al., 2015). The clinical history should include possible eliciting allergens, the timing and chronicity of the ingestion and symptoms, symptom severity, reproducibility, risk factors, identification of foods that are tolerated, and coexisting medical and allergic problems. The use of structured questionnaires on symptoms, foods, and other background information may be beneficial. However, based on limited data, the predictive value of the clinical history for immediate symptoms, either alone or in combination with SPT or sIgE, ranges from 50 percent to 100 percent (Muraro et al., 2014). Nonetheless, the clinical history is central to provide reasoning (prior probability) applicable to additional test selection and interpretation on a patient-specific basis, as will be reviewed further below.

### Elimination Diets

Elimination diets, with removal of one or a few specific foods, is considered useful in diagnosing food allergy, especially for disorders with chronic symptoms, such as eosinophilic esophagitis (EoE), atopic dermatitis, and allergic proctocolitis (Boyce et al., 2010; Muraro et al., 2014). A

diagnostic elimination diet is different from a treatment elimination diet, where an identified food allergen is removed from the diet as a form of therapy. When a properly performed diagnostic elimination diet does not ameliorate the symptoms, food allergy to the eliminated food(s) is unlikely. If elimination does result in amelioration of symptoms, re-administration of the food, for example during an OFC, may be needed to prove a cause-and-effect relationship. However, experts have recognized that for some disorders, such as FPIES, a successful elimination diet in combination with a convincing history may be sufficient for diagnosis (Boyce et al., 2010; Sampson et al., 2014). The rationale for this decision is based on the concern that the OFC may provoke significant morbidity and may be better reserved for evaluating later resolution of the disorder.

Determining which foods should be eliminated is based on medical history, allergy testing, and/or the epidemiology of the illness considering common triggers. The results of the elimination diet are monitored and evaluated over a pre-specified period, such as 2 to 4 weeks. There are many caveats regarding the interpretation of a diagnostic elimination diet because chronic symptoms may vary for reasons other than ones related to foods (e.g., eczema flaring due to infection). Studies evaluating their diagnostic value are lacking, and malnutrition resulting from prolonged elimination diets that exclude multiple foods is a concern (Boyce et al., 2010).

### Skin Prick Tests

Guidelines recommend using SPTs for assistance in diagnosing IgE-mediated food allergies, but the test results alone are not considered sufficient for diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). The test can be done in any age group, although reactivity may be lower in infants and the elderly. The test involves puncturing the surface of the skin to introduce an allergen and evaluating the area for a wheal (small swelling) and flare (redness) response that can be measured. The test is applied to the forearm or back and the results of the allergen tests are compared with a negative saline and a positive histamine control test. The choice of tests is guided by the clinical history. Results are read at 15 or 20 minutes. A positive test correlates with the presence of specific IgE antibodies bound to the surface of cutaneous mast cells. The test is considered safe, because systemic allergic reactions are rare. In contrast, intradermal testing[1] with food is not recommended because it is overly sensitive and could induce systemic reactions (Boyce et al., 2010; Sampson et al., 2014).

[1] Intradermal test consist of delivering the food into the dermis, the skin layer underneath the epidermis (which is the upper skin layer where an SPT is performed). The dermis is, on most places of the human body, only a few mm thick.

Various caveats have been identified regarding SPTs. Trained health care personnel are needed because of a risk of serious allergic reactions. Variables that can affect outcomes include the device used to introduce the allergen (a number of devices are on the market), operator error, the extract (not standardized), the manner of recording and reporting test results, and the timing of day, age, and sex of the patient, the patient's use of any antihistamines, and anatomical site of testing (forearm versus back). Extracts may lack relevant allergens and testing using fresh extracts of food has been suggested for some circumstances, such as testing fruits and vegetables for pollen-food allergy syndrome. False negative tests (i.e., a skin test that is negative despite the fact that the patient experiences a reaction from ingesting the tested food) are possible, requiring caution if suspicion of allergy is high. The SPT reagents and methods have not been standardized. A systematic review and meta-analysis identified varying sensitivity and specificity according to the food evaluated, at a cut-off value of 3 mm wheal diameter in studies using OFCs as the diagnostic standard (Soares-Weiser et al., 2014) (see Table 4-1). Sensitivity is generally high, whereas specificity is lower.

These tests have a low positive predictive value for making a diagnosis of food allergy but high negative predictive value. Although a positive test is generally considered a wheal diameter equal to or greater than 3 mm, studies suggest that larger mean wheal diameters correlate with a higher likelihood of clinical reactivity (Pucar et al., 2001; Saarinen et al., 2001; Sporik et al., 2000; Verstege et al., 2005). A systematic review (Peters et al., 2012) evaluated studies reporting SPT wheal sizes that correspond to high predictive values for allergy (i.e., skin tests sizes above which allergy is almost certain). However, this review (Peters et al., 2012) noted that predictive values vary between studies, likely for numerous reasons including patient selection, food challenge protocols, reagents used for testing, and manner of reporting.

### Food-Specific Serum IgE

Guidelines recommend using sIgE tests to identify foods that may provoke IgE-mediated reactions, but the test result alone is not considered sufficient for diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). The choice of tests is guided by the clinical history. Modern tests use fluorescence enzyme-labeled assays and have replaced radioallergosorbent tests (RAST). The term "RAST" is therefore antiquated. In the United States, the Food and Drug Administration (FDA) has approved three automated systems to measure sIgE. Each system has slightly different methods for test development, and results from one system are not directly comparable to others (Hamilton and Williams, 2010; Hamilton et

**TABLE 4-1** Sensitivity and Specificity of SPT for Selected Foods

| | Sensitivity | Specificity |
|---|---|---|
| Cow milk | 88% (95% CI: 76%-94%) | 68% (95% CI: 56%-77%) |
| Egg | 92% (95% CI: 80%-97%) | 58% (95% CI: 49%-67%) |
| Wheat | 73% (95% CI: 56%-85%) | 73% (95% CI: 48%-89%) |
| Soy | 55% (95% CI: 33%-75%) | 68% (95% CI: 52%-80%) |
| Peanut | 95% (95% CI: 88%-98%) | 61% (95% CI: 47%-74%) |

NOTE: CI = confidence interval; SPT = skin prick test.
SOURCE: Soares-Weiser et al., 2014.

al., 2011; Wang et al., 2008). sIgE is not affected by antihistamine use, as SPTs are.

The sensitivity and specificity of SPT and sIgE were evaluated in a 2010 meta-analysis with a conclusion that neither test was statistically superior (Chafen et al., 2010). However, SPTs and sIgE tests do not always correlate, and so doing both tests can be advantageous, as can doing one followed by the other, if clinically warranted. A 2014 systematic review and meta-analysis (Soares-Weiser et al., 2014) considered mixed cut-off levels for sIgE but chose a >0.35 $kU_A/L$[2] value when possible. The sensitivities and specificities for various allergenic food are in Table 4-2.

Laboratory reports of undetectable sIgE concentrations occasionally occur in patients who go on to react to the food tested probably for reasons similar to the ones described above for SPT, so caution and additional evaluation is necessary in this circumstance if a history is highly suggestive of food allergy. In addition, different laboratories or test systems may report test results at different detection limits, for example <0.10 or <0.35 $kU_A/L$.

Studies have correlated increasing sIgE levels with increasing risk of clinical allergy. Some studies have calculated cut-off levels suggesting 95 percent predictive values for clinical reactivity (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Although 95 percent predictive cutoff values have been calculated in specific studies, these values vary between studies, likely due to differences in patient selection, age, clinical disorders evaluated, and many other factors. The predictive values of certain cut-offs are dependent on the frequency of the food allergy and may therefore differ widely in different populations.

[2] Kilounit allergen per liter.

**TABLE 4-2** Sensitivity and Specificity of Food-Specific Serum IgE (sIgE) Test for Selected Foods

| | Sensitivity | Specificity |
|---|---|---|
| Cow milk | 87% (95% CI: 75%-94%) | 48% (95% CI: 36%-59%) |
| Egg | 93% (95% CI: 82%-98%) | 49% (95% CI: 40%-58%) |
| Wheat | 83% (95% CI: 69%-92%) | 43% (95% CI: 20%-69%) |
| Soy | 83% (95% CI: 64%-93%) | 38% (95% CI: 24%-54%) |
| Peanut | 96% (95% CI: 92%-98%) | 59% (95% CI: 45%-72%) |

NOTE: CI = confidence interval.
SOURCE: Soares-Weiser et al., 2014.

### Component Resolved Diagnostics

CRD, sometimes referred to as molecular testing, involves measuring sIgE against individual allergenic food proteins. This testing is available in single allergen formats and microarray. The comparative utility of the two approaches has not been extensively studied. Commercially available microarray provides semi-quantitative results that correlate with single allergen formats and may be more susceptible to antibody competition due to lack of allergen excess (Canonica et al., 2013). The aim of the test is to increase specificity, based on the understanding that some food proteins may be more potent for causing symptoms than others within the same food. For example, relevant proteins may resist digestion, and IgE immune responses against such proteins may have a greater diagnostic value for systemic allergy than immune responses against more labile proteins that degrade easily and are not systemically absorbed. The AAAAI Guidelines indicate that CRD can be considered for diagnosis, but is not routinely recommended because clinical utility is not fully elucidated (Sampson et al., 2014). Nonetheless, its utility in certain clinical scenarios is recognized. The EAACI Guidelines (Muraro et al., 2014) indicate that the test is promising and broadly studied, but that evidence from additional well-designed randomized controlled trials on the diagnostic test accuracy are required to assess its diagnostic value. A World Allergy Organization expert panel report suggests these tests as a third line approach following clinical history and extract-based testing, but that they may be included in second line testing for experienced users (Canonica et al., 2013). When SPT and sIgE are inconclusive, the EAACI Guidelines (Muraro et al., 2014) suggest that CRD, if available, provides additional information. The *Japanese Guideline for Food Allergy* (Urisu et al., 2014) describes advantages of using CRD for peanut, soy, and wheat allergies.

An accumulating number of studies have evaluated CRD for a variety

of foods; the best studied is CRD for peanut allergy. A systematic review (Klemans et al., 2015) found that sIgE testing to Ara h 2 had diagnostic superiority to other peanut protein components and to SPT and peanut-specific IgE using whole peanut extracts. The studies were primarily pediatric cohorts (21 of 22), and authors concluded that Ara h 2 testing should replace the other tests in clinical practice, especially in children. Although some disagreement may exist, various studies have determined that increasing levels of IgE against Ara h 2 correlates with risk of clinical reactivity (undetectable Ara h 2 does not exclude peanut allergy). Sensitivity and specificity of the test varies among studies, similar to the limitations described for sIgE and SPT, and some studies suggest geographic differences in correlation to clinical reactivity to different proteins (Agabriel et al., 2014; Ballmer-Weber et al., 2015; Beyer et al., 2015; Ebisawa et al., 2012; Eller and Bindslev-Jensen, 2013; Keet et al., 2013; Klemans et al., 2015; Kukkonen et al., 2015; Lieberman et al., 2013; Lopes de Oliveira et al., 2013). If sensitization to peanut is solely caused by Ara h 8 (the birch pollen–related protein in peanut) in regions with birch pollen exposure, systemic clinical allergy is unlikely (Asarnoj et al., 2012).

Numerous other foods have been less comprehensively evaluated by CRD. Sensitization to the hazelnut proteins Cor a 9 and Cor a 14 are associated with higher risk of food allergy to hazelnut and provide better diagnostic utility than the extract tests or other protein components (Beyer et al., 2015; Faber et al., 2014; Kattan et al., 2014; Masthoff et al., 2013). The soy proteins Gly m 4 and Gly m 5 (Berneder et al., 2013; Kattan and Sampson, 2015) appear relevant in soy allergy diagnostics. Literature on the utility of CRD testing on a number of foods is growing, including wheat, cashew, milk, egg, shrimp, carrot, and celery (Muraro et al., 2014; Savvatianos et al., 2015; Soares-Weiser et al., 2014). Sensitization to the cashew nut (Ana o 3, a protein belonging to the 2S albumin family of proteins) is highly predictive of cashew and pistachio allergy in Greek children (Savvatianos et al., 2015). Fruits typically induce mild oral allergic symptoms related to oral allergy syndrome induced by labile pollen-homologous fruit proteins. If IgE binds to stable fruit proteins, such as lipid transfer proteins, it may be associated with more severe reactions, but literature to characterize the role of component allergen testing in fruit and vegetable allergy is limited, and current studies show variable results (Lopez-Matas et al., 2015; Novembre et al., 2012; Tolkki et al., 2013; van Winkle and Chang, 2014; Vieira et al., 2014).

In summary, CRD is an emerging testing methodology in widespread use for select foods. They provide additional insights on diagnosis in specific circumstances. More studies are needed, however, to draw specific conclusions about their diagnostic utility. Component testing for peanut should be used when indicated (Dang et al., 2012; Klemans et al., 2015).

Like judicious use of the medical history, SPT and sIgE, CRD testing provides clinically useful results and can reduce the need for OFCs.

### Oral Food Challenges

The OFC is a feeding test that typically involves a gradual, medically-supervised ingestion of increasingly larger doses of the food being tested as a possible food allergen. Guidelines recommend using OFCs to diagnose food allergy (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Most OFCs are conducted with the food in its natural form; this is called an open OFC. Oral food challenges also can be performed in a single-blind protocol with the food masked from the patient's perspective so less patient bias occurs because of anxiety. Bias is a concern with OFC because anticipation of a reaction can result in subjective symptoms (e.g., abdominal pain, nausea, or eczema flare) and possibly objective ones (e.g. hives). To address this concern a double-blind, placebo-controlled oral food challenge (DBPCOFC) can be conducted. This challenge, which is considered the "gold standard" for diagnosis of food allergy, involves masking the tested allergen and feeding it or indistinguishable placebo randomly without the patient or observer knowing if the allergen or placebo is being tested. However, the double-blind challenge is time-consuming and expensive, and is used more often for research, whereas open food challenges are routinely used in clinical settings. An open or single-blind OFC is considered reliable if no symptoms occur. An open feeding of a meal-sized portion of the food prepared in a usual fashion (e.g., scrambled egg, cooked fish) is also typically performed to confirm tolerance following a negative DBPCOFC with a smaller portion. If only subjective symptoms occur during a food challenge, a false impression of allergy is possible. If objective symptoms occur (e.g., urticaria, angioedema, or anaphylaxis) and the result correlates with medical history and laboratory tests, then the diagnosis is supported. Ambiguous results from an open or single-blind OFC can be evaluated by a DBPCOFC. This challenge also may be considered when patients have primary symptoms of chronic eczema or suspected anxiety.

The OFC is generally indicated to demonstrate allergy or tolerance when the medical history and supporting tests are not sufficient to make a conclusion. This may include circumstances such as a suspected allergy with ambiguous test results, or with the expectation that a food allergy has resolved. The OFC also may be used for individuals with ongoing allergy to evaluate thresholds or response to therapy. As the generally accepted gold standard, the test is highly specific. However, patients uncommonly experience reactions on subsequent ingestion despite tolerance during the test; the rate of this occurrence may vary by dosing regimen (Caffarelli and Petroccione, 2001; Miceli Sopo et al., 2016; Niggemann et al., 2012).

The OFC is useful for evaluating food allergy whatever the underlying pathophysiology or time course of symptoms, and can be used for all age groups. The test carries a risk of allergic reactions and anaphylaxis, and so caution, content monitoring, experienced personnel and equipment, and medications for managing reactions are required. Feeding a small amount of the suspected allergen and gradually increasing the amount mitigates some risk. The test is stopped at the judgment of the supervising health professional due to the onset of symptoms or at the request of the patient. Immediate symptoms typically occur within 2 hours after ingestion, but increases in atopic dermatitis symptoms may occur over hours or days. Rigorous objective criteria for determining tolerance or reactivity, consistent application of procedures, and good record keeping and documentation are paramount. No universally accepted manner of dosing, scoring, and monitoring the OFC procedure has been established, and potential dosing regimens have not been compared prospectively. Various approaches have been suggested, and issues such as indications and contraindications have been summarized (Sampson et al., 2012, 2014). Standardized dosing protocols have been published but not validated (Muraro et al., 2014; Sampson et al., 2012, 2014). For infants, open OFCs with objective scoring criteria are generally sufficient to make or refute a diagnosis of food allergy. Application of the OFC to infants, and additional limitations of the test are additionally reviewed in Chapter 5, Methodological Limitations.

The OFC is usually undertaken with the goal of the patient ingesting an age-appropriate, meal-size portion of the food prepared in a manner that will be ingested in the future. Processing and cooking methods can alter its allergenic properties. For example baked egg or milk products are less allergenic than raw forms. The matrix in which the tested allergen is mixed also can affect outcomes, as absorption rates may vary. For example, fatty foods are absorbed more slowly than other foods (Grimshaw et al., 2003). Although foods could be freeze-dried and placed into opaque capsules to mask the taste as well as early signs of reaction involving the oral mucosa, this approach is not in favor due to alteration of proteins and lack of control of release of the food from the capsules. The initial dose is generally selected to be less than a likely threshold for a reaction, or significant reaction (e.g., less than 3 mg) if the patient is suspected of being highly sensitive (Rolinck-Werninghaus et al., 2012). If a threshold-determining OFC is being undertaken, a lower starting dose may be used. Doses are given at 15- to 30-minute intervals although adjustments can be made. If symptoms occur after several doses, it cannot be concluded that the "last dose" independently triggered a reaction, as symptoms could be caused by prior doses or a cumulative effect (Blumchen et al., 2014). Also, escalating dose OFCs are similar to certain immunotherapy protocols and may therefore result in a reaction at a higher dose than would be the case if this were

the first and only dose. The time of testing can vary but is typically 3 to 8 hours depending on the doses, symptoms, and challenge format. The test may be formatted differently for non-IgE-mediated food allergies, such as FPIES, where the feeding may be dosed more rapidly and the expectation of reaction is delayed, occurring approximately 2 hours later. The test is generally undertaken when the food has been excluded from the diet. In the case of suspected chronic symptoms, the time of exclusion is typically 2 to 8 weeks to obtain a baseline.

The risk of OFC tests includes an anaphylactic reaction. On the other hand, the test might have nutritional (when the food can be added back to the diet) social, emotional, and educational (learning which trigger foods must be avoided, providing safety, and learning about reaction characteristics, treatment, and threshold) benefits. Some evidence suggests that the OFC procedure does not increase long-term post-study anxiety and can improve quality of life whether the food is tolerated or not (Franxman et al., 2015; Knibb et al., 2012). Guidelines promoting the OFC as a recommended procedure use terminology of "positive" challenge test outcome to denote that the test elicited symptoms and a "negative" test outcome to indicate the food was tolerated. (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). This use of terms is deliberate to avoid terms such as "passed" and "failed" as outcomes, which carry negative implications of the patient having "failed" in some manner.

Patients may avoid having the procedure due to fear, disinterest in the food offered, or misunderstanding about risks or odds of tolerating the food. They might ingest the food on their own, against medical advice to undergo the procedure before reintroducing the food into the diet plan (Davis et al., 2015). Physicians may not offer the procedure due to patient safety risk, time constraints, lack of trained personnel, and poor reimbursement (Pongracic et al., 2012). Failure to reintroduce the food into the routine diet after tolerating the OFC has been noted, but the reasons not fully explored (Miceli Sopo et al., 2016; van Erp et al., 2014). Considering that OFC is often required to determine a definitive diagnosis of food allergy, it is clearly underused.

## MODALITIES NOT RECOMMENDED FOR ROUTINE USE

### Atopy Patch Test

The atopy patch test (APT) is performed in a manner similar to patch testing that is routinely used to evaluate allergic contact dermatitis, except that foods are used. The food, presented as a fresh extract or powder, is generally placed under an aluminum disc on the skin for 48 hours then removed and with the final test result determined at 72 hours after applica-

tion. Current guidelines do not recommend the APT for the routine diagnosis of food allergies (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014), based partly on a lack of standardized reagents, methods, and interpretation of results. The APT may have utility in evaluating non-IgE-mediated allergy in the context of atopic dermatitis and EoE. Its utility in the diagnosis of FPIES has not been substantiated (Jarvinen et al., 2012; Ruffner et al., 2013).

In a systematic review and meta-analysis, three studies were identified that evaluated the diagnostic utility of the milk APT. Sensitivity was 53 percent (95% CI: 33%-72%) and specificity 88 percent (95% CI: 76%-95%) (Soares-Weiser et al., 2014). It is notable that despite a rather large number of studies, few meet criteria for meta-analysis (Isolauri and Turjanmaa, 1996; Keskin et al., 2005; Roehr et al., 2001). Several studies suggest poor utility of the APT (Alves et al., 2015; Caglayan Sozmen et al., 2015; Celakovska et al., 2010; Mehl et al., 2006). Other studies suggest some utility of APT for milk, especially for gastrointestinal symptoms or dermatitis (Boonyaviwat et al., 2015; Chung et al., 2010; Levy et al., 2012; Mowszet et al., 2014; Nocerino et al., 2013; Yang et al., 2014). The relevance of APT for EoE remains uncertain, but some studies suggest utility (Chadha et al., 2014; Rodriguez-Sanchez et al., 2014; Spergel et al., 2012). An updated expert panel report on EoE (Liacouras et al., 2011) summarized the results from seven studies, with negative predictive values of more than 90 percent and only 50 percent for milk, and variable positive predictive values. They suggested the APT (along with SPT and sIgE) can be used to identify foods associated with EoE, but alone the test is not sufficient to make a diagnosis of food-driven disease.

### Total IgE

Guidelines recommend against the routine measurement of total IgE to diagnose food allergy (Boyce et al., 2010; Sampson et al., 2014). It is recognized that atopic persons may have elevated serum total IgE, but this does not provide guidance regarding the risk of specific food allergies. However, there is a notion that total IgE concentration may relate to sIgE (Federly et al., 2013) and that very high concentration of total IgE may influence the clinical relevance of sIgE for diagnostic purposes (Muraro et al., 2014).

Theoretically, the influence of total IgE on the clinical relevance of sIgE includes assay and in vivo effects due to competition for binding to allergen and effector cells (Hamilton and Williams, 2010). The FDA recommends that very low concentrations of sIgE antibodies should be evaluated with caution when total IgE values are above 1,000 kU/L (Merkel et al., 2015) (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm109367.htm [accessed August 30, 2016]). One

of the few clinical studies (Mehl et al., 2005) evaluated 992 controlled OFCs performed in 501 children, looking at the utility of sIgE:total IgE ratio and found a correlation with challenge outcomes for milk, egg, and wheat, but not for soy. The diagnostic value of the ratio was not better than for sIgE alone. In contrast, another study looking at the ratio evaluated 195 OFCs among 161 children, and found that the ratio was more informative than sIgE alone for peanut, tree nuts, seeds, and shellfish but not milk, egg, wheat, or soy (Gupta et al., 2014). In contrast, the component specific to total IgE ratio did not improve peanut or hazelnut diagnosis (Grabenhenrich et al., 2016).

Although the NIAID/NIH-supported Guidelines and AAAAI Guidelines concluded that total IgE is not recommended for routine use in diagnosis (Boyce et al., 2010; Sampson et al., 2014), the EAACI Guidelines based on low-level evidence and expert opinion suggested that total IGE concentration may be useful in patients with severe eczema because a very high total IgE suggests that positive sIgE should be interpreted with care, as possibly representing asymptomatic sensitization (Muraro et al., 2014).

### Basophil Activation Test

Basophils are allergy effector cells found in whole blood. Basophils degranulate upon cross-linking of sIgE, which is bound to the high affinity IgE cell surface receptors, and release mediators such as histamine. The granule marker, CD63, or CD203c, an activation marker, can be measured by flow cytometry and provide a measure of basophil activation. The basophil activation test (BAT) is conducted by exposing the basophil cells to various concentrations of the allergen to be tested, either an extract or individual component proteins in the test tube. The readout is the number of cells responding, or the concentration of allergen at which 50 percent of the cells respond. About 10 percent of people are BAT nonresponders, even though they are allergic and have positive skin tests. The test is a functional assay akin to a provocation test, such as a SPT.

Guidelines suggest not using the BAT clinically on the grounds that it is nonstandardized, but recognize its use as a research tool (Boyce et al., 2010). A position paper from a task force of the EAACI reviewed the BAT and made a number of recommendations in favor of using the test for diagnosis and monitoring of food allergy, and a recommendation to pursue standardization to make it available in diagnostic laboratories (Hoffmann et al., 2015). The EAACI task force evaluated diagnostic studies on peanut (N=4), hazelnut (N=2), peach (N=3), wheat (N=4), milk (N=2), egg (N=2), shellfish (N=1), and pollen-associated food allergy syndrome (PFAS) (N=5). The reported sensitivity ranged from 77 to 98 percent and specificity from 75 to 100 percent. In some studies BAT was more accurate than SPT or

sIgE. In a series of peanut allergy studies from one research group, which included a validation substudy, the BAT significantly improved diagnosis over SPT and sIgE, reducing the number of OFCs required for diagnosis (Santos et al., 2014) and provided predictive value for severity and threshold of reactivity (Santos et al., 2015). The position paper also reviewed the use of BAT to predict development of tolerance in food allergic children (N=4 studies), and to monitor responses to immunomodulatory therapy (N=11 studies). Overall, while the test is not available for widespread use, the potential utility is recognized and will require additional validation and standardization.

## NONSTANDARDIZED AND UNPROVEN PROCEDURES

A number of tests have been referred to as "unproven," "unconventional," or "nonstandardized and unproven" by guidelines and are not recommended for food allergy diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). These tests or procedures include: allergen-specific IgA, IgG or $IgG_4$, provocation neutralization, immune complexes, HLA screening, lymphocyte stimulation, facial thermography, gastric juice analysis, endoscopic allergen provocation, hair analysis, applied kinesiology, cytotoxic assays, electrodermal testing, mediator release assays, bioresonance, and iridology. The rationale for not recommending these tests or procedures is the lack of evidence demonstrating the value of each method in diagnosis of food allergy. There is a concern that use of these methods may result in false positive or false negative diagnoses that may lead to unnecessary dietary restriction or may delay appropriate diagnostic evaluations.

For example, $IgG_4$ testing against foods as a diagnostic modality was reviewed in the 2008 EAACI Task Force report (Stapel et al., 2008). Many serum samples have positive $IgG_4$ results without corresponding clinical symptoms. The report noted a lack of convincing evidence for histamine-releasing properties of $IgG_4$, and a lack of controlled studies to determine diagnostic value. Conversely, evidence suggests that food-specific $IgG_4$ reflects exposure, and may indicate a state of immunological tolerance. The task force concluded that testing of $IgG_4$ to foods is irrelevant to the laboratory work-up for diagnosis of food allergy. It should be noted, however, that food-specific IgG and $IgG_4$ responses, when monitored during immune therapy with allergen exposure, is associated with clinical improvement in threshold. Thus, IgG and $IgG_4$ may be markers or mechanisms of desensitization and may have some role in diagnosis, especially during treatments, when considered along with other measurements, such as sIgE. Studies have begun to evaluate the diagnostic or prognostic potential of the IgE/IgG ratio or antibody classes. More studies are needed to validate these approaches,

as currently available data are conflicting (Ahrens et al., 2010; Caubet et al., 2012; Dannaeus and Inganas, 1981; Okamoto et al., 2012; Savilahti et al., 2012, 2014; Sverremark-Ekström et al., 2012; Tomicic et al., 2009).

## PREDICTION OF SEVERITY OR THRESHOLD OF REACTIONS

Severity of an allergy is typically defined by symptoms triggered during an allergic reaction, and threshold of exposure for a reaction refers to the dose of allergen that triggers symptoms. There is strong interest in, and need for, a test for severity or threshold. Dosing during OFC is generally stopped before severe symptoms, limiting the ability of this study design to predict severe reactions (Wainstein et al., 2010). No comprehensive reviews have been published on the prediction of severity or on simple tests to diagnose the severity of a reaction. One might surmise that increasing sIgE concentrations correlate with severity because they correlate with risk of clinical reactivity. Although a number of studies suggest this correlation, it has not been universally substantiated (Benhamou et al., 2008; Blumchen et al., 2014; Clark and Ewan, 2003; Neuman-Sunshine et al., 2012; Rolinck-Werninghaus et al., 2012; Summers et al., 2008; Ta et al., 2011; van der Zee et al., 2011; Wainstein et al., 2010). In addition, CRD could be considered a means to possibly diagnose severity of a reaction because, for example, isolated binding to Ara h 8 is associated with no or mild allergy (oral-pharyngeal symptoms, related to PFAS) while binding to Ara h 2 is associated with systemic peanut allergy. However, on an individual patient or research study participant basis, degree of binding to Ara h 2 does not appear to accurately predict severity (Astier et al., 2006; Klemans et al., 2013a,b; Leo et al., 2015; Peeters et al., 2007). Studies have suggested that modalities such as BAT (Homsak et al., 2013; Santos et al., 2015; Song et al., 2015) or analysis of epitope[3] binding patterns (Flinterman et al., 2008; Shreffler et al., 2004) may hold promise for determining severity. Disparities in prediction of severity based on testing may have many methodological reasons, but on an individual basis, outside of studies that control for such variables, the tests may not or do not currently consider specific patient-circumstance variables, such as whether the individual with food allergy has asthma, is currently ill, exercising, or experiencing other factors that may cause increased sensitivity (i.e., eliciting factors, other factors regarding physiologic responses) (Summers et al., 2008; Vadas et al., 2008). A recent paper describes the lack of predictability, perceptions about severity, and the types of factors that may affect the severity of a reaction, including those related to a person's behaviors (e.g., exercise) and other factors (e.g., infections) (Turner et al., 2016).

[3] Epitopes are segments of a protein that are recognized by antibodies.

## PROGNOSIS AND DISEASE MONITORING

The rate of allergy resolution varies based on the food, patient's age, pathophysiology of the allergy, and other factors (Boyce et al., 2010; Sampson et al., 2014). Table 4-3 summarizes resolution rates of common food allergies (Savage et al., 2016). Most children with allergies to cow milk, egg, soy, and wheat will develop tolerance by adulthood, whereas resolution of peanut, tree nut, and seafood allergies is less likely (less than or equal to 20 percent) (Boyce et al., 2010; Sampson et al., 2014). Adults with food allergies may have experienced persistence from childhood or may have a new onset in adulthood, and these allergies tend to persist. The natural course of food allergy is not known for most foods. Periodic re-evaluation with testing is recommended and can be individualized based on patient characteristics, the food, and underlying food allergic disorder (Boyce et al., 2010; Sampson et al., 2014). In general, periodic re-evaluation is undertaken with history, SPT, sIgE, and OFC depending on the specific results of each test and history. This testing might be performed more frequently (e.g., yearly) for a young child with food allergies, and less frequently (e.g., every few years) for an adult with allergies to foods such as peanut, tree nuts, and seafood.

Unfortunately, no simple accurate prognostic tests exist. Having tests that could be performed early in life that reflect prognosis would be helpful in selecting the best periodicity of retesting, providing anticipatory guidance, and identifying which patients might benefit from interventional treatments (as these become available). Studies have suggested that higher compared to lower concentrations of sIgE or skin test size are a poor prognostic marker (Ho et al., 2008; Keet et al., 2009; Peters et al., 2013, 2015; Savage et al., 2007, 2010; Sicherer et al., 2014; Skripak et al., 2007; Wood et al., 2013). However, additional clinical factors are associated with prognosis, including severity of symptoms, threshold dose, family history, change in sIgE over time, ability to tolerate milk or egg in baked goods (for cow milk and egg allergy), comorbid asthma, and comorbid atopic dermatitis (including severity), and other factors (Cantani and Micera, 2004; Elizur et al., 2012; Ho et al., 2008; Peters et al., 2013, 2014, 2015; Savage et al., 2007; Shek et al., 2004; Sicherer et al., 2014; Skripak et al., 2007; Wood et al., 2013). Studies have used multivariate analysis to create predictive models using the variables with the greatest impact (especially sIgE levels), but validation is needed (Sicherer et al., 2014; Wood et al., 2013). Studies using newer in vitro tests, such as CRD and BAT, have not been extensively applied to develop prognostic algorithms. A 2013 systematic search and review on this topic identified 26 articles, noting heterogeneity and biases in the studies, and concluded that population-based, prospective studies are needed that use OFC—without bias of test results—to diagnose food allergy

**TABLE 4-3** Natural Course of Food Allergy

| Food | Resolution Likely |
|---|---|
| Milk, egg, wheat, soy | Early-late childhood (~>70-80%) |
| Peanut | Childhood (~20%) |
| Tree nut | Childhood (~10%) |
| Fish, shellfish, seeds | Less certain but likely similar to tree nuts |

SOURCE: Savage et al., 2016.

at baseline and then to follow up to develop thresholds for SPT and sIgE that predict the course of food allergy (Peters et al., 2013). Little is known about food allergy prognosis after diagnosis in adulthood.

Many of the modalities discussed here also have been evaluated during treatment studies, to identify markers that may indicate desensitization or tolerance of food(s) to which individuals are initially allergic, including sIgE, SPT, CRD, BAT, sIgE/total IgE ratio, $sIgG_4$, and ratio of sIgE to $sIgG_4$ (Nozawa et al., 2014; Savilahti et al., 2014; Thyagarajan et al., 2012; Vickery et al., 2013, 2014). Additional markers have been followed, including cytokines, regulatory T cells, T cell number and function, and B cell activity (Bedoret et al., 2012; Hoh et al., 2016; Syed et al., 2014; Varshney et al., 2011). However, biomarkers to confirm desensitization and tolerance without OFC remain to be found.

## GENERAL DIAGNOSTIC ALGORITHMS

Guidelines and reviews have suggested general algorithms (i.e., panels) for diagnostic approaches (Greenhawt et al., 2013; Muraro et al., 2014; Sicherer, 2002; Urisu et al., 2014; Venter et al., 2013). Approaches typically begin with a medical history to identify the nature of the symptoms (whether likely reflecting food allergy or another disorder), the pathophysiology (IgE mediated or not), and the potential food triggers. Testing based on the initial impressions is conducted and interpreted based on the results of the history and suspected foods and related pathophysiology. This may include tests for IgE, elimination diets and/or OFCs, depending on the circumstances.

Different algorithms may fit specific disorders. For example, evaluation of food allergy in acute anaphylaxis, where symptoms come on quickly and are associated with sIgE antibodies, differs from evaluation of the role of food allergy in atopic dermatitis or EoE (Greenhawt et al., 2013; Sicherer,

2002; Urisu et al., 2014; Venter et al., 2013). No overarching approach has been universally accepted. However, because the sensitivity and specificity of individual tests are generally not 100 percent, using pretest probability obtained from one test (e.g., the medical history) is recognized as beneficial for interpreting the post-test probability of allergy following a second test (Muraro et al., 2014). Indiscriminately performing multiple tests is not recommended (Boyce et al., 2010), but a case can be made for using more than one test when additional diagnostic value may be obtained. Specific algorithms may, for example, consider diagnostic values of several tests performed in series to improve accuracy (Ben-Shoshan et al., 2010; Dang et al., 2012). Additionally, it may be possible to isolate a number of factors from the medical history and simple diagnostic tests to estimate the risk of an allergy, using a standardized approach, but this also needs validation (DunnGalvin et al., 2011). In summary, although no evidence-based, universally accepted overarching diagnostic algorithm exists, guidelines promote step-wise evaluations rather than solely depending upon single tests to conclude a diagnosis of food allergy in children (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Information on adults is limited.

## TESTING FOR SPECIFIC DISEASE STATES OTHER THAN ANAPHYLAXIS AND ATOPIC DERMATITIS

As indicated above, diagnostic approaches may vary depending upon the pathophysiology, epidemiology, and clinical characteristics of particular food-allergic disorders (Greenhawt et al., 2013; Muraro et al., 2014; Sicherer, 2002; Urisu et al., 2014; Venter et al., 2013).

### Food Protein–Induced Enterocolitis Syndrome

FPIES and food protein-induced allergic proctocolitis are non-IgE-mediated disorders that lack current means of simple laboratory testing to identify causal foods or to confirm the diagnosis. Guidelines suggest using the medical history, resolution of symptoms during dietary elimination, and recurrence of symptoms upon exposure; for example, during a food challenge (although not typically necessary for proctocolitis), as a means of diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). For FPIES, guidelines indicate that factors in the history may be so suggestive of the diagnosis that an OFC is not needed. For example, a patient may have experienced repeated reactions with typical symptoms or severe symptoms (Boyce et al., 2010; Sampson et al., 2014). It also is recognized that a subset of children may develop IgE antibodies (especially for cow milk) signifying prolonged course and possibly anaphylactic symptoms that can warrant periodic testing before using an OFC to evaluate for resolution

(Caubet et al., 2014; Sampson et al., 2014). The APT does not appear to be useful for diagnosing FPIES (Jarvinen et al., 2012; Ruffner et al., 2013). Endoscopy and biopsies are not typically needed for diagnosis (Boyce et al., 2010; Muraro et al., 2014). The OFC for evaluation of FPIES could induce severe symptoms (e.g., hypotension, methemoglobinemia [unexpected], acidemia) and requires caution.

### Eosinophilic Gastrointestinal Diseases

Eosinophilic gastrointestinal diseases may have both a cellular and IgE antibody component. No specific diagnostic strategies other than elimination and OFC have been proposed for identifying the food-specific triggers in eosinophilic gastroenteritis, and no biomarkers to identify responses are currently available, making repeated endoscopy/biopsy necessary to identify responses to treatment. Guidelines suggest considering tests for food-specific IgE and APT to help identify causal foods, specifically for evaluating EoE (Boyce et al., 2010; Sampson et al., 2014). Testing for food-specific sIgE also derives from the observation that 15 to 43 percent of patients are diagnosed with typical IgE-mediated food allergies and up to 80 percent are sensitized to aeroallergens (Muraro et al., 2014). However, these tests are not to be depended on to identify causal foods, and the diagnosis of EoE also requires a trial of proton pump inhibitors, and evaluations to identify characteristic biopsy results for diagnosis (and to exclude other diagnoses) (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Ultimately, trial elimination diets are needed, with follow-up biopsy to assess resolution of inflammation.

### Pollen-Associated Food Allergy Syndrome

The best approaches for diagnostic testing for PFAS have not been systematically evaluated. A number of recommendations have been published (Sampson et al., 2014). The detailed medical history is important because the diagnosis should be considered in patients experiencing limited oropharyngeal symptoms when eating foods (raw) that have cross-reacting proteins with pollens; it may be noted that symptoms are increased during and just following the pollen season. Testing for sIgE to pollens is suggested, and performing SPT with fresh food (sometimes termed "prick-prick" testing which may be performed by pricking the raw fruit or some of its extracted juice with the skin test device and then pricking the skin) can also be used to aid diagnosis (Begin et al., 2011; Vlieg-Boerstra et al., 2013). Such testing is not standardized. The use of commercial extracts may be less useful because the responsible proteins are labile and may not be present. It is not understood why only some persons with pollen aller-

gies experience reactions, or why people with similar pollen allergies may have different patterns of reactions to different fruits and vegetables. Simple diagnostic tests lack the ability to differentiate or predict these variations (Crespo et al., 2002; Pastorello et al., 1994; Rodriguez et al., 2000; Ta et al., 2015). Variations in reactivity are noted even among cultivars of the same fruit, or with ripening or storage (Carnes et al., 2006; Sancho et al., 2006). Systemic reactions to the same foods that trigger PFAS can occur. The reason for systemic reactions could be explained by having reactivity to a higher dose of the labile allergen, a greater sensitivity to that allergen (possibly varying with cofactors such as exercise or illness), or having an immune response to proteins that are not labile (e.g., lipid transfer proteins) (Cudowska et al., 2008; Gomez et al., 2014; Pascal et al., 2012; Zuidmeer and van Ree, 2007). It is possible that CRD or BAT represent a means to evaluate this difference in risk, but studies have had mixed results (Asero, 2014; Ebo et al., 2010; Erdmann et al., 2005; Gamboa et al., 2009; Guhsl et al., 2015; Hofmann et al., 2013; Tolkki et al., 2013).

## COMMON PITFALLS AND MISCONCEPTIONS IN DIAGNOSTICS

As indicated previously, diagnostic and monitoring tests have a variety of limitations that, if not appreciated, can result in over- or underdiagnosing food allergy in patients. Table 4-4 summarizes common misconceptions.

### Sensitization Is Not Diagnostic of Clinical Allergy

Key among potential pitfalls is the fact that sensitization (demonstrated by a positive test) is not a sole indication for a diagnosis. Testing with panels (i.e., preselected lists) of foods without a consideration of the medical history can result in unnecessary concerns and is not recommended (Bernstein et al., 2008; Cox et al., 2008; Sampson et al., 2014; Sicherer and Wood, 2012). Physicians may not appreciate this test limitation (Gupta et al., 2010) and, as reviewed above, patients and clinicians may misinterpret test results with low values versus higher values as reflecting severity of the allergy.

### Clinically Relevant and Nonrelevant Cross Reactivity

Another potential pitfall is recognizing the difference between cross reactivity identified on testing (sIgE or SPT) that may or may not be clinically relevant (Sampson et al., 2014; Sicherer, 2001). When food allergens share sufficient homology, antibodies may be detected to multiple allergen proteins, but the clinical relevance of the test finding can vary. For example, a large proportion of individuals with peanut allergy will test positive to

**TABLE 4-4** Common Misconceptions About Food Allergy and Testing

| Misconception | Reality |
|---|---|
| It is possible to do a comprehensive test that finds which foods should be avoided to stop the symptoms. | No comprehensive test exists to identify all food allergies. Diagnosis requires a careful medical history and thoughtful selection of tests. Doing evaluative "panels" of preselected tests/foods can be misleading. |
| A positive skin or blood test identifies an allergy. | Many people "test positive" to foods that they can eat without any symptoms. For example, about 8 percent of people test positive to peanut, but can eat it without symptoms. |
| A negative allergy test means that a food is safe to eat. | Although this is often true, with some types of food allergies, or circumstances, the test can be negative despite a true allergy. |
| The level on a blood test or the size of a skin test indicates the severity of a reaction. | The severity of a reaction is not well reflected by the tests, because underlying asthma, individual sensitivity, and other factors, such as how much of the allergen is eaten, may influence severity. However, the stronger a positive test, the more likely a true allergy exists. |
| Allergy to one type of food means the person will have allergy to related foods. | This is not a general rule. For example, allergy to peanut, a bean, does not necessarily mean the person will have allergy to other beans. |
| Food allergy and food intolerance are the same. | A food can make a person ill in many ways. Allergic reactions involve the immune system and can be severe or fatal. Intolerance, such as lactose intolerance, does not involve the immune system and is not life-threatening. |

other legumes, such as soy (up to 79 percent), but only a small proportion of patients (up to 5 percent) will experience allergic reactions to them. Although the test rate of cross reactivity is higher than the observed rate of clinical cross reactivity, studies on this topic are limited and likely reflect results that vary depending upon methodology, patient selection, and geographic influences, including pollen sensitization. Estimated rates of clinical cross reactivity among crustacean shellfish is 38 percent, among fish 30 to 75 percent, among tree nuts 12 to 37 percent (varies depending on the nuts; for example, walnut and pecan are more similar, cashew and pistachio are more similar), and between wheat and other grains 21 percent. An OFC is often needed to confirm tolerance if a potentially cross reactive food has not

already been tolerated in the diet. A serious pitfall can occur if a food tests positive in panels (and the patient removes it from the diet) when tolerance has already been proven by inclusion of the food in the diet.

### Delayed Anaphylaxis Associated with Mammalian Meats

Although most pitfalls in food allergy diagnosis may occur from overdiagnosis related to misunderstanding of pathophysiology and test utility, a special case of under- or misdiagnosis involves mammalian meat allergy (beef, pork, lamb) attributed to sIgE antibodies against a sugar moiety, galactose-alpha-1,3-galactose (alpha-gal) (Commins et al., 2011, 2014; Hamsten et al., 2013; Kennedy et al., 2013). The syndrome is likely associated with initial sensitization to allergen in tick bites. In contrast to typical food anaphylaxis that occurs within minutes to 2 hours following ingestion of the trigger food, alpha-gal-related reactions to mammalian meat, with the same allergic symptoms, occur 3 to 6 hours after ingestion. Skin testing to the trigger foods may not be strongly positive but in vitro sIgE testing to alpha-gal is commercially available and can be used to confirm the diagnosis. The reason for the delay in onset of anaphylactic symptoms is not known with certainty.

## ROLE OF ELICITING FACTORS

Eliciting factors, also referred to as cofactors and augmentation factors, are circumstances or ingestants that can alter threshold or severity of an allergy, resulting in more serious reactions or allowing clinical expression of a food allergic response to an otherwise tolerated food (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). These factors can include exercise, nonsteroidal anti-inflammatory drug (NSAID) agents, alcohol, body temperature, menstruation, infections, stress, and antacid medications (Niggemann and Beyer, 2014). These factors may influence absorption or immune responses. The best described entity is food-associated (dependent), exercise-induced anaphylaxis, where the food is tolerated when exercise does not occur, but reactions may occur when the food is ingested before exercise. Common food allergenic foods that trigger a reaction with exercise are wheat, shrimp, and celery, but numerous triggers have been reported (Romano et al., 2001).

The possibility that a cofactor is responsible for the expression of a food allergy is assessed by history, and assessment may include evaluation by SPT or sIgE of foods ingested before exercise or concomitant ingestion of alcohol or NSAIDs. A case can be made for evaluating specific allergens associated with these syndromes, such as gliadin and lipid transfer proteins in some settings, but the diagnostic utility is not fully understood (Muraro

et al., 2014; Romano et al., 2012; Urisu et al., 2014). The history and supporting test evidence may warrant the diagnosis, but OFC with exposure to the eliciting factor may be needed. The reliability of such testing is variable, and the symptoms can recur despite an OFC not triggering reactions. Many factors may confuse the diagnostic approach, such as the need for multiple different or a combination of augmenting factors to result in a reaction, various degrees of the factor (amount of food, exercise, alcohol), and testing methodology (Asaumi et al., 2016; Brockow et al., 2015; Jo et al., 2012; Medrala et al., 2014; Niggemann and Beyer, 2014).

## FUTURE DIAGNOSTIC MODALITIES

Food allergy guidelines have recognized a large number of approaches under investigation to improve diagnosis and provide insights on prognosis and severity (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Many of these approaches have been reviewed above (CRD, BAT, and others). The diagnostic value of determining the pattern of IgE binding to synthetic sequential epitopes (binding segments) of allergens has been evaluated, with results suggesting that this testing can provide information on phenotype (i.e., ability to tolerate extensively heated milk in those with cow milk allergy), prognosis, and severity (e.g., diversity of binding associated with severity of reactions) (Cerecedo et al., 2008; Flinterman et al., 2008; Jarvinen et al, 2001, 2002; Lin et al., 2012; Shreffler et al., 2004; Wang et al., 2010).

As reviewed above, a number of cellular markers are being evaluated to improve diagnosis and prognosis, including cytokines, regulatory T cells, T cell number and function, B cell activity, and epitope binding (Bedoret et al., 2012; Hoh et al., 2016; Syed et al., 2014; Varshney et al., 2011). One study suggests value in determining deoxyribonucleic acid (DNA) methylation signatures (Martino et al., 2015). Martino et al. performed genome-wide DNA methylation profiling on subjects who had undergone OFC, concurrent SPTs, and specific IgE tests (Martino et al., 2015). Fifty-eight were food-sensitized patients (ages 11 to 15 months), half of whom were clinically reactive, and 13 were nonallergic control subjects. Reproducibility was assessed in another 48 samples from an independent population of patients with food allergy. This study revealed a methylation signature consisting of 96 CpG sites that predict clinical outcomes. This methylation signature was superior to allergen-specific IgE and SPTs for predicting OFC outcomes. Therefore, in addition to elucidating mechanisms involved in the epigenetic regulation of food allergies and the interplay between genetic and environment, this evidence can be used to develop novel, practical, and improved diagnostic assays. Bioinformatics approaches that take into consideration multiple variables should support improved diagnostics (Lin

et al., 2012). These approaches, which could include data from numerous biologic markers such as genomic, transcriptomic, proteomic, metabolomics, microbiome, and various laboratory tests, will allow for assessment of billions of variables (Chen et al., 2012).

## OVERALL CONCLUSIONS

Currently, no simple diagnostic tests exist for food allergy. Selection and interpretation of tests depend on the disorder being considered (epidemiology, pathophysiology) and the individual medical history. A common pitfall in diagnosis results from performing tests for sIgE without considering the medical history, resulting in unnecessary avoidance or removal of tolerated foods from the diet (a positive test alone may not indicate a clinical allergy). The gold standard test, the OFC, carries risk and expense, and is underused. The history and available test results can often suggest a likelihood of a food allergy, presenting a reasonable pretest probability for deciding upon the need for an OFC. Understanding how the size of skin tests, concentration of sIgE, and the clinical history can provide pretest probability estimations for providing a diagnosis at this point or proceeding to other tests, including the OFC is key. CRD is currently providing improved diagnosis in some circumstances. Developing "calculators" that evaluate these currently available parameters is promising. The BAT shows promising preliminary data, but validation and commercialization are needed. Sorely missing are simple tests that would indicate, for an individual with current possible allergy symptoms, degree of severity or threshold or both, as well as prognosis.

As reviewed in the discussion above, food allergy testing strategies (history, diagnostic elimination diet, OFC, SPT, sIgE, CRD, APT) are generally not well standardized, including the various factors involved with the history, elimination diets, and food challenge. Many methodologic issues are involved in evaluating test utility, and comparisons of diagnostic utility of specific tests among different populations often show some level of disparity. Regarding SPTs, extracts are not uniformly standardized and the individual allergenic protein content may vary (Hefle et al., 1995). The FDA has approved three automated systems to determine sIgE. Each system uses slightly different methods and results from one system are not directly comparable to others (Hamilton and Williams, 2010; Hamilton et al., 2011; Wang et al., 2008). The manner of reporting SPT skin test sizes varies (e.g., reporting greatest wheal diameter, mean wheal diameter, size in relation to controls), as does the representation of sIgE levels from serum tests (e.g., classes versus concentration, $kU_A/L$). Different OFC regimens have been proposed in the literature as well as different means to report

results. Attention to these issues affects research approaches as well as clinical care. Studies are under way to improve standardization.

Additional standardization and validation would require extensive study in different patient populations (e.g., ages, illnesses, geographic regions) and consideration of the role of eliciting factors, and circumstances where interventions are being applied to the patient (immunotherapeutic strategies as they become available). This is similarly the case for emerging diagnostics, such as epitope analysis.

Education is needed for patients and physicians to understand the meaning and limitations of commonly used food allergy test results, to know about unconventional and unproven tests, and to understand how to effectively use existing tests (or when to refer from primary care to specialist care). No comprehensive studies on the cost effectiveness of testing and misdiagnosis have been conducted. Studies on diagnostics have been primarily focused on children, and more studies of adults or comparison of adults and children are needed. Numerous potential diagnostic tests are in development. At this point, they are labor-intensive or expensive, but they may identify novel factors of use in the future.

## RECOMMENDATIONS

**The committee recommends that physicians use evidence-based, standardized procedures as the basis for food allergy diagnosis and avoid nonstandardized and unproven procedures (e.g., applied kinesiology, immunoglobulin G panels, electrodermal testing). When food allergy is suspected, a patient should be evaluated by a physician who has the training and experience to select and interpret appropriate diagnostic tests.**

Although this process often may include an initial evaluation by a primary physician, it is important that those with suspected food allergy be diagnosed appropriately, which is likely to involve referral to or consultation with a physician specialist who can diagnose, comprehensively evaluate, and manage the food allergy.

Food allergy evaluation procedures include a medical history and physical examination, and also may include food-specific skin prick test, food-specific serum immunoglobulin E test, diagnostic food elimination diet, and oral food challenge (OFC). Selection of the specific tests needs to be individualized based on the medical history of each patient. Health care providers trained in food allergy, leaders of health care facilities, and health care payor groups can facilitate the appropriate use of OFCs, including personnel, facilities, and safety guards, so that physicians are not

deterred from performing the types of diagnostic testing that are appropriate for the patient's diagnosis and care.

## RESEARCH NEEDS

Diagnosis of food allergy is complex, currently requiring expertise in assessing the medical history, understanding allergen cross-reactivity, understanding eliciting factors that may alter reactivity, selecting and interpreting imperfect tests, and possibly conducting a medically supervised OFC test. The OFC is currently the best diagnostic test to confirm an allergy, but it is time consuming, expensive, carries risks (e.g., the risk of triggering an allergic reaction), and is often deferred due to patient and physician concerns. Therefore, the OFC is underused. In addition, commonly available simple allergy tests (sIgE antibody tests or SPT) have limitations that can result in misdiagnosis, primarily overdiagnosis, requiring procedures such as OFCs to confirm a proper diagnosis. For example, currently available, simple diagnostic tests that are often used to diagnose IgE-mediated food allergies, the sIgE test and SPT, actually diagnose sensitization, not food allergy. A variety of diagnostic tests, such as CRD, the basophil activation test, and many others, are emerging or under study and may better inform diagnosis, prognosis, severity, and threshold.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Optimize the currently available diagnostic tests and validate methods, such as OFC (including in special contexts, such as OFC in infants and young children), as well as pursue additional novel tests to improve diagnosis, prognosis, determination of severity of disease, and assessment of antigen thresholds, and to monitor host responses. These tests will be valuable in assessing the effectiveness and durability of interventions, such as immunotherapy. These studies should include all affected patient populations (ages, sexes, ethnicities, co-morbidities, socioeconomic strata, should consider the role of eliciting factors (such as exercise and infections), and also should be assessed in those circumstances where interventions are being applied to the patient (immunotherapeutic strategies as they become available).
- Comprehensively examine the utility, cost-effectiveness of, and barriers to testing, especially regarding the OFC, with a goal of maximizing the use of appropriate tests.
- Examine and assess educational approaches and tools to improve physician and health care provider education about both the natu-

ral history of food allergies and the appropriate approaches to use to diagnose food allergies.

- Study the utility of emerging technologies in the area of "omics" methodologies (e.g., genomics, epigenomics, metabolomics). In particular, identify reliable and clinically useful biomarkers for the following important goals:
  - Assessing the severity of a food allergy (e.g., to identify those at high risk for anaphylaxis),
  - Evaluating and monitoring responses to therapy (e.g., immunotherapy),
  - Predicting prognosis (e.g., predicting severity),
  - Identifying populations at risk of developing a food allergy so that they can be included when conducting research on prevention and management strategies and on public health guidelines, and
  - Diagnosing food allergy in individuals and populations (e.g., for collecting data on prevalence).

## REFERENCES

Agabriel, C., O. Ghazouani, J. Birnbaum, V. Liabeuf, F. Porri, M. Gouitaa, I. Cleach, J. J. Grob, P. Bongrand, J. Sarles, and J. Vitte. 2014. Ara h 2 and Ara h 6 sensitization predicts peanut allergy in Mediterranean pediatric patients. *Pediatr Allergy Immunol* 25(7):662-667.

Ahrens, B., L. C. Lopes de Oliveira, G. Schulz, M. P. Borres, B. Niggemann, U. Wahn, and K. Beyer. 2010. The role of hen's egg-specific IgE, IgG and IgG4 in the diagnostic procedure of hen's egg allergy. *Allergy* 65(12):1554-1557.

Alves, F. A., M. F. Cheik, A. C. de Napolis, E. R. Rezende, C. P. Barros, and G. R. Segundo. 2015. Poor utility of the atopy patch test in infants with fresh rectal bleeding. *Ann Allergy Asthma Immunol* 115(2):161-162.

Asarnoj, A., C. Nilsson, J. Lidholm, S. Glaumann, E. Ostblom, G. Hedlin, M. van Hage, G. Lilja, and M. Wickman. 2012. Peanut component Ara h 8 sensitization and tolerance to peanut. *J Allergy Clin Immunol* 130(2):468-472.

Asaumi, T., N. Yanagida, S. Sato, A. Shukuya, M. Nishino, and M. Ebisawa. 2016. Provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis. *Pediatr Allergy Immunol* 27(1):44-49.

Asero, R. 2014. In patients with LTP syndrome food-specific IgE show a predictable hierarchical order. *Eur Ann Allergy Clin Immunol* 46(4):142-146.

Astier, C., M. Morisset, O. Roitel, F. Codreanu, S. Jacquenet, P. Franck, V. Ogier, N. Petit, B. Proust, D. A. Moneret-Vautrin, A. W. Burks, B. Bihain, H. A. Sampson, and G. Kanny. 2006. Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol* 118(1):250-256.

Ballmer-Weber, B. K., J. Lidholm, M. Fernandez-Rivas, S. Seneviratne, K. M. Hanschmann, L. Vogel, P. Bures, P. Fritsche, C. Summers, A. C. Knulst, T. M. Le, I. Reig, N. G. Papadopoulos, A. Sinaniotis, S. Belohlavkova, T. Popov, T. Kralimarkova, F. de Blay, A. Purohit, M. Clausen, M. Jedrzejczak-Czechowcz, M. L. Kowalski, R. Asero, R. Dubakiene, L. Barreales, E. N. Clare Mills, R. van Ree, and S. Vieths. 2015. IgE recognition patterns in peanut allergy are age dependent: Perspectives of the EuroPrevall study. *Allergy* 70(4):391-407.

Bedoret, D., A. K. Singh, V. Shaw, E. G. Hoyte, R. Hamilton, R. H. DeKruyff, L. C. Schneider, K. C. Nadeau, and D. T. Umetsu. 2012. Changes in antigen-specific T-cell number and function during oral desensitization in cow's milk allergy enabled with omalizumab. *Mucosal Immunol* 5(3):267-276.

Begin, P., A. Des Roches, M. Nguyen, M. S. Masse, J. Paradis, and L. Paradis. 2011. Freezing does not alter antigenic properties of fresh fruits for skin testing in patients with birch tree pollen-induced oral allergy syndrome. *J Allergy Clin Immunol* 127(6):1624-1626.

Benhamou, A. H., S. A. Zamora, and P. A. Eigenmann. 2008. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Pediatr Allergy Immunol* 19(2):173-179.

Ben-Shoshan, M., R. Kagan, M. N. Primeau, R. Alizadehfar, E. Turnbull, L. Harada, C. Dufresne, M. Allen, L. Joseph, Y. St Pierre, and A. Clarke. 2010. Establishing the diagnosis of peanut allergy in children never exposed to peanut or with an uncertain history: A cross-Canada study. *Pediatr Allergy Immunol* 21(6):920-926.

Berneder, M., M. Bublin, K. Hoffmann-Sommergruber, T. Hawranek, and R. Lang. 2013. Allergen chip diagnosis for soy-allergic patients: Gly m 4 as a marker for severe food-allergic reactions to soy. *Int Arch Allergy Immunol* 161(3):229-233.

Bernstein, I. L., J. T. Li, D. I. Bernstein, R. Hamilton, S. L. Spector, R. Tan, S. Sicherer, D. B. Golden, D. A. Khan, R. A. Nicklas, J. M. Portnoy, J. Blessing-Moore, L. Cox, D. M. Lang, J. Oppenheimer, C. C. Randolph, D. E. Schuller, S. A. Tilles, D. V. Wallace, E. Levetin, and R. Weber. 2008. Allergy diagnostic testing: An updated practice parameter. *Ann Allergy Asthma Immunol* 100(3 Suppl 3):S1-S148.

Beyer, K., L. Grabenhenrich, M. Hartl, A. Beder, B. Kalb, M. Ziegert, A. Finger, N. Harandi, R. Schlags, M. Gappa, L. Puzzo, H. Roblitz, M. Millner-Uhlemann, S. Busing, H. Ott, L. Lange, and B. Niggemann. 2015. Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. *Allergy* 70(1):90-98.

Blumchen, K., A. Beder, J. Beschorner, F. Ahrens, A. Gruebl, E. Hamelmann, G. Hansen, A. Heinzmann, K. Nemat, B. Niggemann, U. Wahn, and K. Beyer. 2014. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. *J Allergy Clin Immunol* 134(2):390-398.

Boonyaviwat, O., P. Pacharn, O. Jirapongsananuruk, P. Vichyanond, and N. Visitsunthorn. 2015. Role of atopy patch test for diagnosis of food allergy-related gastrointestinal symptoms in children. *Pediatr Allergy Immunol* 26(8):737-741.

Boyce, J. A., A. Assa'ad, A. W. Burks, S. M. Jones, H. A. Sampson, R. A. Wood, M. Plaut, S. F. Cooper, M. J. Fenton, S. H. Arshad, S. L. Bahna, L. A. Beck, C. Byrd-Bredbenner, C. A. Camargo, Jr., L. Eichenfield, G. T. Furuta, J. M. Hanifin, C. Jones, M. Kraft, B. D. Levy, P. Lieberman, S. Luccioli, K. M. McCall, L. C. Schneider, R. A. Simon, F. E. Simons, S. J. Teach, B. P. Yawn, and J. M. Schwaninger. 2010. Guidelines for the diagnosis and management of food allergy in the United States: Report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 126(6 Suppl):S1-S58.

Brockow, K., D. Kneissl, L. Valentini, O. Zelger, M. Grosber, C. Kugler, M. Werich, U. Darsow, H. Matsuo, E. Morita, and J. Ring. 2015. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 135(4):977-984.

Caffarelli, C., and T. Petroccione. 2001. False-negative food challenges in children with suspected food allergy. *Lancet* 358(9296):1871-1872.

Caglayan Sozmen, S., C. Povesi Dascola, E. Gioia, C. Mastrorilli, L. Rizzuti, and C. Caffarelli. 2015. Diagnostic accuracy of patch test in children with food allergy. *Pediatr Allergy Immunol* 26(5):416-422.

Canonica, G. W., I. J. Ansotegui, R. Pawankar, P. Schmid-Grendelmeier, M. van Hage, C. E. Baena-Cagnani, G. Melioli, C. Nunes, G. Passalacqua, L. Rosenwasser, H. Sampson, J. Sastre, J. Bousquet, and T. Zuberbier. 2013. A WAO - ARIA - GA$^2$LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 6(1):17.

Cantani, A., and M. Micera. 2004. Natural history of cow's milk allergy. An eight-year follow-up study in 115 atopic children. *Eur Rev Med Pharmacol Sci* 8(4):153-164.

Carnes, J., A. Ferrer, and E. Fernandez-Caldas. 2006. Allergenicity of 10 different apple varieties. *Ann Allergy Asthma Immunol* 96(4):564-570.

Caubet, J. C., R. Bencharitiwong, E. Moshier, J. H. Godbold, H. A. Sampson, and A. Nowak-Wegrzyn. 2012. Significance of ovomucoid- and ovalbumin-specific IgE/IgG(4) ratios in egg allergy. *J Allergy Clin Immunol* 129(3):739-747.

Caubet, J. C., L. S. Ford, L. Sickles, K. M. Jarvinen, S. H. Sicherer, H. A. Sampson, and A. Nowak-Wegrzyn. 2014. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol* 134(2):382-389.

Celakovska, J., J. Vaneckova, K. Ettlerova, K. Ettler, and J. Bukac. 2010. The role of atopy patch test in diagnosis of food allergy in atopic eczema/dermatitis syndrom in patients over 14 years of age. *Acta Medica (Hradec Kralove)* 53(2):101-108.

Cerecedo, I., J. Zamora, W. G. Shreffler, J. Lin, L. Bardina, M. C. Dieguez, J. Wang, A. Muriel, B. de la Hoz, and H. A. Sampson. 2008. Mapping of the IgE and IgG4 sequential epitopes of milk allergens with a peptide microarray-based immunoassay. *J Allergy Clin Immunol* 122(3):589-594.

Chadha, S. N., L. Wang, H. Correa, D. Moulton, and D. S. Hummell. 2014. Pediatric eosinophilic esophagitis: The Vanderbilt experience. *Ann Allergy Asthma Immunol* 113(4): 445-451.

Chafen, J. J., S. J. Newberry, M. A. Riedl, D. M. Bravata, M. Maglione, M. J. Suttorp, V. Sundaram, N. M. Paige, A. Towfigh, B. J. Hulley, and P. G. Shekelle. 2010. Diagnosing and managing common food allergies: A systematic review. *JAMA* 303(18):1848-1856.

Chen, R., G. I. Mias, J. Li-Pook-Than, L. Jiang, H. Y. Lam, R. Chen, E. Miriami, K. J. Karczewski, M. Hariharan, F. E. Dewey, Y. Cheng, M. J. Clark, H. Im, L. Habegger, S. Balasubramanian, M. O'Huallachain, J. T. Dudley, S. Hillenmeyer, R. Haraksingh, D. Sharon, G. Euskirchen, P. Lacroute, K. Bettinger, A. P. Boyle, M. Kasowski, F. Grubert, S. Seki, M. Garcia, M. Whirl-Carrillo, M. Gallardo, M. A. Blasco, P. L. Greenberg, P. Snyder, T. E. Klein, R. B. Altman, A. J. Butte, E. A. Ashley, M. Gerstein, K. C. Nadeau, H. Tang, and M. Snyder. 2012. Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell* 148(6):1293-1307.

Chung, B. Y., H. O. Kim, C. W. Park, and C. H. Lee. 2010. Diagnostic usefulness of the serum-specific IgE, the skin prick test and the atopy patch test compared with that of the oral food challenge test. *Ann Dermatol* 22(4):404-411.

Clark, A. T., and P. W. Ewan. 2003. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy* 33(8):1041-1045.

Commins, S. P., H. R. James, L. A. Kelly, S. L. Pochan, L. J. Workman, M. S. Perzanowski, K. M. Kocan, J. V. Fahy, L. W. Nganga, E. Ronmark, P. J. Cooper, and T. A. Platts-Mills. 2011. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 127(5):1286-1293.

Commins, S. P., H. R. James, W. Stevens, S. L. Pochan, M. H. Land, C. King, S. Mozzicato, and T. A. Platts-Mills. 2014. Delayed clinical and ex vivo response to mammalian meat in patients with IgE to galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 134(1):108-115.

Cox, L., B. Williams, S. Sicherer, J. Oppenheimer, L. Sher, R. Hamilton, and D. Golden. 2008. Pearls and pitfalls of allergy diagnostic testing: Report from the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology Specific IgE Test Task Force. *Ann Allergy Asthma Immunol* 101(6):580-592.

Crespo, J. F., J. Rodriguez, J. M. James, P. Daroca, M. Reano, and R. Vives. 2002. Reactivity to potential cross-reactive foods in fruit-allergic patients: Implications for prescribing food avoidance. *Allergy* 57(10):946-949.

Cudowska, B., M. Kaczmarski, and P. Restani. 2008. Lipid transfer protein in diagnosis of birch-apple syndrome in children. *Immunobiology* 213(2):89-96.

Dang, T. D., M. Tang, S. Choo, P. V. Licciardi, J. J. Koplin, P. E. Martin, T. Tan, L. C. Gurrin, A. L. Ponsonby, D. Tey, M. Robinson, S. C. Dharmage, and K. J. Allen. 2012. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol* 129(4):1056-1063.

Dannaeus, A., and M. Inganas. 1981. A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish. *Clin Allergy* 11(6):533-539.

Davis, N., M. Egan, and S. H. Sicherer. 2015. Factors resulting in deferral of diagnostic oral food challenges. *J Allergy Clin Immunol Pract* 3(5):811-812.

DunnGalvin, A., D. Daly, C. Cullinane, E. Stenke, D. Keeton, M. Erlewyn-Lajeunesse, G. C. Roberts, J. Lucas, and J. O. Hourihane. 2011. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol* 127(3):633-639.

Ebisawa, M., R. Moverare, S. Sato, N. Maruyama, M. P. Borres, and T. Komata. 2012. Measurement of Ara h 1-, 2-, and 3-specific IgE antibodies is useful in diagnosis of peanut allergy in Japanese children. *Pediatr Allergy Immunol* 23(6):573-581.

Ebo, D. G., C. H. Bridts, M. M. Verweij, K. J. De Knop, M. M. Hagendorens, L. S. De Clerck, and W. J. Stevens. 2010. Sensitization profiles in birch pollen-allergic patients with and without oral allergy syndrome to apple: Lessons from multiplexed component-resolved allergy diagnosis. *Clin Exp Allergy* 40(2):339-347.

Elizur, A., N. Rajuan, M. R. Goldberg, M. Leshno, A. Cohen, and Y. Katz. 2012. Natural course and risk factors for persistence of IgE-mediated cow's milk allergy. *J Pediatr* 161(3):482-487.

Eller, E., and C. Bindslev-Jensen. 2013. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy* 68(2):190-194.

Erdmann, S. M., B. Sachs, A. Schmidt, H. F. Merk, O. Scheiner, S. Moll-Slodowy, I. Sauer, R. Kwiecien, B. Maderegger, and K. Hoffmann-Sommergruber. 2005. In vitro analysis of birch-pollen-associated food allergy by use of recombinant allergens in the basophil activation test. *Int Arch Allergy Immunol* 136(3):230-238.

Faber, M. A., M. De Graag, C. Van Der Heijden, V. Sabato, M. M. Hagendorens, C. H. Bridts, L. S. De Clerck, and D. G. Ebo. 2014. Cor a 14: Missing link in the molecular diagnosis of hazelnut allergy? *Int Arch Allergy Immunol* 164(3):200-206.

Federly, T. J., B. L. Jones, H. Dai, and C. Dinakar. 2013. Interpretation of food specific immunoglobulin E levels in the context of total IgE. *Ann Allergy Asthma Immunol* 111(1):20-24.

Fleischer, D. M., S. A. Bock, G. C. Spears, C. G. Wilson, N. K. Miyazawa, M. C. Gleason, E. A. Gyorkos, J. R. Murphy, D. Atkins, and D. Y. Leung. 2011. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr* 158(4):578-583.

Fleischer, D. M., S. Sicherer, M. Greenhawt, D. Campbell, E. Chan, A. Muraro, S. Halken, Y. Katz, M. Ebisawa, L. Eichenfield, H. Sampson, G. Lack, G. Du Toit, G. Roberts, H. Bahnson, M. Feeney, J. Hourihane, J. Spergel, M. Young, A. As'aad, K. Allen, S. Prescott, S. Kapur, H. Saito, I. Agache, C. A. Akdis, H. Arshad, K. Beyer, A. Dubois, P. Eigenmann, M. Fernandez-Rivas, K. Grimshaw, K. Hoffman-Sommergruber, A. Host, S. Lau, L. O'Mahony, C. Mills, N. Papadopoulos, C. Venter, N. Agmon-Levin, A. Kessel, R. Antaya, B. Drolet, and L. Rosenwasser. 2015. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol* 136(2):258-261.

Flinterman, A. E., E. F. Knol, D. A. Lencer, L. Bardina, C. F. den Hartog Jager, J. Lin, S. G. Pasmans, C. A. Bruijnzeel-Koomen, H. A. Sampson, E. van Hoffen, and W. G. Shreffler. 2008. Peanut epitopes for IgE and IgG4 in peanut-sensitized children in relation to severity of peanut allergy. *J Allergy Clin Immunol* 121(3):737-743.e710.

Franxman, T. J., L. Howe, E. Teich, and M. J. Greenhawt. 2015. Oral food challenge and food allergy quality of life in caregivers of children with food allergy. *J Allergy Clin Immunol Pract* 3(1):50-56.

Gamboa, P. M., M. L. Sanz, M. Lombardero, D. Barber, R. Sanchez-Monje, M. J. Goikoetxea, I. Antepara, M. Ferrer, and G. Salcedo. 2009. Component-resolved in vitro diagnosis in peach-allergic patients. *J Investig Allergol Clin Immunol* 19(1):13-20.

Gomez, F., A. Aranda, P. Campo, A. Diaz-Perales, N. Blanca-Lopez, J. Perkins, M. Garrido, M. Blanca, C. Mayorga, and M. J. Torres. 2014. High prevalence of lipid transfer protein sensitization in apple allergic patients with systemic symptoms. *PLoS One* 9(9):e107304.

Grabenhenrich, L. B., S. Dolle, A. Moneret-Vautrin, A. Kohli, L. Lange, T. Spindler, F. Rueff, K. Nemat, I. Maris, E. Roumpedaki, K. Scherer, H. Ott, T. Reese, T. Mustakov, R. Lang, M. Fernandez-Rivas, M. L. Kowalski, M. B. Bilo, J. O. Hourihane, N. G. Papadopoulos, K. Beyer, A. Muraro, and M. Worm. 2016. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol* 137(4):1128-1137.

Greenhawt, M., S. S. Aceves, J. M. Spergel, and M. E. Rothenberg. 2013. The management of eosinophilic esophagitis. *J Allergy Clin Immunol Pract* 1(4):332-340; quiz 341-332.

Grimshaw, K. E., R. M. King, J. A. Nordlee, S. L. Hefle, J. O. Warner, and J. O. Hourihane. 2003. Presentation of allergen in different food preparations affects the nature of the allergic reaction—A case series. *Clin Exp Allergy* 33(11):1581-1585.

Guhsl, E. E., G. Hofstetter, N. Lengger, W. Hemmer, C. Ebner, R. Froschl, M. Bublin, C. Lupinek, H. Breiteneder, and C. Radauer. 2015. IgE, IgG4 and IgA specific to Bet v 1-related food allergens do not predict oral allergy syndrome. *Allergy* 70(1):59-66.

Gupta, R. S., E. E. Springston, J. S. Kim, B. Smith, J. A. Pongracic, X. Wang, and J. Holl. 2010. Food allergy knowledge, attitudes, and beliefs of primary care physicians. *Pediatrics* 125(1):126-132.

Gupta, R. S., C. H. Lau, R. G. Hamilton, A. Donnell, and K. K. Newhall. 2014. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. *J Allergy Clin Immunol Pract* 2(3):300-305.

Gupta, R. S., M. M. Walkner, M. Greenhawt, C. H. Lau, D. Caruso, X. Wang, J. A. Pongracic, and B. Smith. 2016. Food allergy sensitization and presentation in siblings of food allergic children. *J Allergy Clin Immunol Pract*. 4(5):956-962.

Hamilton, R. G., and P. B. Williams. 2010. Human IgE antibody serology: A primer for the practicing North American allergist/immunologist. *J Allergy Clin Immunol* 126(1):33-38.

Hamilton, R. G., K. Mudd, M. A. White, and R. A. Wood. 2011. Extension of food allergen specific IgE ranges from the ImmunoCAP to the IMMULITE systems. *Ann Allergy Asthma Immunol* 107(2):139-144.

Hamsten, C., M. Starkhammar, T. A. Tran, M. Johansson, U. Bengtsson, G. Ahlen, M. Sallberg, H. Gronlund, and M. van Hage. 2013. Identification of galactose-alpha-1,3-galactose in the gastrointestinal tract of the tick *Ixodes ricinus*; Possible relationship with red meat allergy. *Allergy* 68(4):549-552.

Hefle, S. L., R. M. Helm, A. W. Burks, and R. K. Bush. 1995. Comparison of commercial peanut skin test extracts. *J Allergy Clin Immunol* 95(4):837-842.

Ho, M. H., W. H. Wong, R. G. Heine, C. S. Hosking, D. J. Hill, and K. J. Allen. 2008. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 121(3):731-736.

Hoffmann, H. J., A. F. Santos, C. Mayorga, A. Nopp, B. Eberlein, M. Ferrer, P. Rouzaire, D. G. Ebo, V. Sabato, M. L. Sanz, T. Pecaric-Petkovic, S. U. Patil, O. V. Hausmann, W. G. Shreffler, P. Korosec, and E. F. Knol. 2015. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 70(11):1393-1405.

Hofmann, C., S. Scheurer, K. Rost, E. Graulich, A. Jamin, K. Foetisch, J. Saloga, S. Vieths, K. Steinbrink, and H. S. Adler. 2013. Cor a 1-reactive T cells and IgE are predominantly cross-reactive to Bet v 1 in patients with birch pollen-associated food allergy to hazelnut. *J Allergy Clin Immunol* 131(5):1384-1392.

Hoh, R. A., S. A. Joshi, Y. Liu, C. Wang, K. M. Roskin, J. Y. Lee, T. Pham, T. J. Looney, K. J. Jackson, V. P. Dixit, J. King, S. C. Lyu, J. Jenks, R. G. Hamilton, K. C. Nadeau, and S. D. Boyd. 2016. Single B-cell deconvolution of peanut-specific antibody responses in allergic patients. *J Allergy Clin Immunol* 137(1):157-167.

Homsak, M., M. Silar, V. Berce, M. Tomazin, M. Skerbinjek-Kavalar, N. Celesnik, M. Kosnik, and P. Korosec. 2013. The relevance of basophil allergen sensitivity testing to distinguish between severe and mild peanut-allergic children. *Int Arch Allergy Immunol* 162(4):310-317.

Isolauri, E., and K. Turjanmaa. 1996. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 97(1 Pt 1):9-15.

Jarvinen, K. M., P. Chatchatee, L. Bardina, K. Beyer, and H. A. Sampson. 2001. IgE and IgG binding epitopes on alpha-lactalbumin and beta-lactoglobulin in cow's milk allergy. *Int Arch Allergy Immunol* 126(2):111-118.

Jarvinen, K. M., K. Beyer, L. Vila, P. Chatchatee, P. J. Busse, and H. A. Sampson. 2002. B-cell epitopes as a screening instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 110(2):293-297.

Jarvinen, K. M., J. C. Caubet, L. Sickles, L. S. Ford, H. A. Sampson, and A. Nowak-Wegrzyn. 2012. Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome. *Ann Allergy Asthma Immunol* 109(3):221-222.

Jo, E. J., M. S. Yang, Y. J. Kim, H. S. Kim, M. Y. Kim, S. H. Kim, S. H. Cho, K. U. Min, and Y. S. Chang. 2012. Food-dependent exercise-induced anaphylaxis occurred only in a warm but not in a cold environment. *Asia Pac Allergy* 2(2):161-164.

Kattan, J. D., and H. A. Sampson. 2015. Clinical reactivity to soy is best identified by component testing to Gly m 8. *J Allergy Clin Immunol Pract* 3(6):970-972.

Kattan, J. D., S. H. Sicherer, and H. A. Sampson. 2014. Clinical reactivity to hazelnut may be better identified by component testing than traditional testing methods. *J Allergy Clin Immunol Pract* 2(5):633-634.

Keet, C. A., E. C. Matsui, G. Dhillon, P. Lenehan, M. Paterakis, and R. A. Wood. 2009. The natural history of wheat allergy. *Ann Allergy Asthma Immunol* 102(5):410-415.

Keet, C. A., K. Johnson, J. H. Savage, R. G. Hamilton, and R. A. Wood. 2013. Evaluation of Ara h2 IgE thresholds in the diagnosis of peanut allergy in a clinical population. *J Allergy Clin Immunol Pract* 1(1):101-103.

Kennedy, J. L., A. P. Stallings, T. A. Platts-Mills, W. M. Oliveira, L. Workman, H. R. James, A. Tripathi, C. J. Lane, L. Matos, P. W. Heymann, and S. P. Commins. 2013. Galactose-alpha-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. *Pediatrics* 131(5):e1545-1552.

Keskin, O., A. Tuncer, G. Adalioglu, B. E. Sekerel, C. Sackesen, and O. Kalayci. 2005. Evaluation of the utility of atopy patch testing, skin prick testing, and total and specific IgE assays in the diagnosis of cow's milk allergy. *Ann Allergy Asthma Immunol* 94(5):553-560.

Klemans, R. J., H. C. Broekman, E. F. Knol, C. A. Bruijnzeel-Koomen, H. G. Otten, S. G. Pasmans, and A. C. Knulst. 2013a. Ara h 2 is the best predictor for peanut allergy in adults. *J Allergy Clin Immunol Pract* 1(6):632-638.

Klemans, R. J., X. Liu, A. C. Knulst, M. J. Knol, F. Gmelig-Meyling, E. Borst, S. G. Pasmans, and E. F. Knol. 2013b. IgE binding to peanut components by four different techniques: Ara h 2 is the most relevant in peanut allergic children and adults. *Clin Exp Allergy* 43(8):967-974.

Klemans, R. J., H. van Os-Medendorp, M. Blankestijn, C. A. Bruijnzeel-Koomen, E. F. Knol, and A. C. Knulst. 2015. Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: A systematic review. *Clin Exp Allergy* 45(4):720-730.

Knibb, R. C., N. F. Ibrahim, G. Stiefel, R. Petley, A. J. Cummings, R. M. King, D. Keeton, L. Brown, M. Erlewyn-Lajeunesse, G. Roberts, and J. S. Lucas. 2012. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. *Clin Exp Allergy* 42(3):451-459.

Kukkonen, A. K., A. S. Pelkonen, S. Makinen-Kiljunen, H. Voutilainen, and M. J. Makela. 2015. Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: A double-blind placebo-controlled study. *Allergy* 70(10):1239-1245.

Leo, S. H., J. M. Dean, B. Jung, B. Kuzeljevic, and E. S. Chan. 2015. Utility of Ara h 2 sIgE levels to predict peanut allergy in Canadian children. *J Allergy Clin Immunol Pract* 3(6):968-969.

Levy, S. A., S. D. Dortas Junior, A. H. Pires, A. T. Abe, S. O. Valle, V. P. Coelho, L. R. Hahnstadt, and A. T. Franca. 2012. Atopy patch test (APT) in the diagnosis of food allergy in children with atopic dermatitis. *An Bras Dermatol* 87(5):724-728.

Liacouras, C. A., G. T. Furuta, I. Hirano, D. Atkins, S. E. Attwood, P. A. Bonis, A. W. Burks, M. Chehade, M. H. Collins, E. S. Dellon, R. Dohil, G. W. Falk, N. Gonsalves, S. K. Gupta, D. A. Katzka, A. J. Lucendo, J. E. Markowitz, R. J. Noel, R. D. Odze, P. E. Putnam, J. E. Richter, Y. Romero, E. Ruchelli, H. A. Sampson, A. Schoepfer, N. J. Shaheen, S. H. Sicherer, S. Spechler, J. M. Spergel, A. Straumann, B. K. Wershil, M. E. Rothenberg, and S. S. Aceves. 2011. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 128(1):3-20; quiz 21-22.

Lieberman, J. A., S. Glaumann, S. Batelson, M. P. Borres, H. A. Sampson, and C. Nilsson. 2013. The utility of peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations.*J Allergy Clin Immunol Pract* 1(1):75-82.

Lin, J., F. M. Bruni, Z. Fu, J. Maloney, L. Bardina, A. L. Boner, G. Gimenez, and H. A. Sampson. 2012. A bioinformatics approach to identify patients with symptomatic peanut allergy using peptide microarray immunoassay. *J Allergy Clin Immunol* 129(5):1321-1328.

Liu, A. H., R. Jaramillo, S. H. Sicherer, R. A. Wood, S. A. Bock, A. W. Burks, M. Massing, R. D. Cohn, and D. C. Zeldin. 2010. National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 126(4):798-806.

Lopes de Oliveira, L. C., M. Aderhold, M. Brill, G. Schulz, C. Rolinck-Werninghaus, E. N. Clare Mills, B. Niggemann, C. K. Naspitz, U. Wahn, and K. Beyer. 2013. The value of specific IgE to peanut and its component Ara h 2 in the diagnosis of peanut allergy. *J Allergy Clin Immunol Pract* 1(4):394-398.

Lopez-Matas, M. A., C. H. Larramendi, A. J. Huertas, A. Ferrer, R. Moya, J. A. Pagan, L. A. Navarro, J. L. Garcia-Abujeta, and J. Carnes. 2015. Tomato nsLTP as an "in vivo" diagnostic tool: Sensitization in a Mediterranean population. *J Allergy Clin Immunol* 25(3):196-204.

Markowitz, J. E., J. M. Spergel, E. Ruchelli, and C. A. Liacouras. 2003. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol* 98(4):777-782.

Martino, D., T. Dang, A. Sexton-Oates, S. Prescott, M. L. Tang, S. Dharmage, L. Gurrin, J. Koplin, A. L. Ponsonby, K. J. Allen, and R. Saffery. 2015. Blood DNA methylation biomarkers predict clinical reactivity in food-sensitized infants. *J Allergy Clin Immunol* 135(5):1319-1328.

Masthoff, L. J., L. Mattsson, L. Zuidmeer-Jongejan, J. Lidholm, K. Andersson, J. H. Akkerdaas, S. A. Versteeg, C. Garino, Y. Meijer, P. Kentie, A. Versluis, C. F. den Hartog Jager, C. A. Bruijnzeel-Koomen, A. C. Knulst, R. van Ree, E. van Hoffen, and S. G. Pasmans. 2013. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. *J Allergy Clin Immunol* 132(2):393-399.

Medrala, W., K. Cieslik, W. Barg, A. Skotny, E. Siwak, and A. Wolanczyk-Medrala. 2014. Naproxen increases the severity of food-dependent exercise-induced anaphylaxis: A case report. *J Investig Allergol Clin Immunol* 24(6):461-462.

Mehl, A., A. Verstege, U. Staden, M. Kulig, M. Nocon, K. Beyer, and B. Niggemann. 2005. Utility of the ratio of food-specific IgE/total IgE in predicting symptomatic food allergy in children. *Allergy* 60(8):1034-1039.

Mehl, A., C. Rolinck-Werninghaus, U. Staden, A. Verstege, U. Wahn, K. Beyer, and B. Niggemann. 2006. The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J Allergy Clin Immunol* 118(4):923-929.

Merkel, P. A., M. D. O'Sullivan, C. Ridge, and V. Knight. 2015. Critique on the quantitative nature of IgE antibody measurements. *J Allergy Clin Immunol Pract* 3(6):973-975.

Miceli Sopo, S., S. Monaco, M. Greco, and R. Onesimo. 2016. Prevalence of adverse reactions following a passed oral food challenge and factors affecting successful re-introduction of foods. A retrospective study of a cohort of 199 children. *Allergol Immunopathol (Madr)* 44(1):54-58.

Mowszet, K., K. Matusiewicz, and B. Iwanczak. 2014. Value of the atopy patch test in the diagnosis of food allergy in children with gastrointestinal symptoms. *Adv Clin Exp Med* 23(3):403-409.

Muraro, A., T. Werfel, K. Hoffmann-Sommergruber, G. Roberts, K. Beyer, C. Bindslev-Jensen, V. Cardona, A. Dubois, G. duToit, P. Eigenmann, M. Fernandez Rivas, S. Halken, L. Hickstein, A. Host, E. Knol, G. Lack, M. J. Marchisotto, B. Niggemann, B. I. Nwaru, N. G. Papadopoulos, L. K. Poulsen, A. F. Santos, I. Skypala, A. Schoepfer, R. Van Ree, C. Venter, M. Worm, B. Vlieg-Boerstra, S. Panesar, D. de Silva, K. Soares-Weiser, A. Sheikh, B. K. Ballmer-Weber, C. Nilsson, N. W. de Jong, and C. A. Akdis. 2014. EAACI food allergy and anaphylaxis guidelines: Diagnosis and management of food allergy. *Allergy* 69(8):1008-1025.

Neuman-Sunshine, D. L., J. A. Eckman, C. A. Keet, E. C. Matsui, R. D. Peng, P. J. Lenehan, and R. A. Wood. 2012. The natural history of persistent peanut allergy. *Ann Allergy Asthma Immunol* 108(5):326-331.

Niggemann, B., and K. Beyer. 2014. Factors augmenting allergic reactions. *Allergy* 69(12): 1582-1587.

Niggemann, B., L. Lange, A. Finger, M. Ziegert, V. Muller, and K. Beyer. 2012. Accurate oral food challenge requires a cumulative dose on a subsequent day. *J Allergy Clin Immunol* 130(1):261-263.

Nocerino, R., V. Granata, M. Di Costanzo, V. Pezzella, L. Leone, A. Passariello, G. Terrin, R. Troncone, and R. Berni Canani. 2013. Atopy patch tests are useful to predict oral tolerance in children with gastrointestinal symptoms related to non-IgE-mediated cow's milk allergy. *Allergy* 68(2):246-248.

Novembre, E., F. Mori, S. Contestabile, M. E. Rossi, and N. Pucci. 2012. Correlation of anti-Pru p 3 IgE levels with severity of peach allergy reactions in children. *Ann Allergy Asthma Immunol* 108(4):271-274.

Nozawa, A., Y. Okamoto, R. Moverare, M. P. Borres, and K. Kurihara. 2014. Monitoring Ara h 1, 2 and 3-sIgE and sIgG4 antibodies in peanut allergic children receiving oral rush immunotherapy. *Pediatr Allergy Immunol* 25(4):323-328.

Okamoto, S., S. Taniuchi, K. Sudo, Y. Hatano, K. Nakano, T. Shimo, and K. Kaneko. 2012. Predictive value of IgE/IgG4 antibody ratio in children with egg allergy. *Allergy Asthma Clin Immunol* 8(1):9.

Pascal, M., R. Munoz-Cano, Z. Reina, A. Palacin, R. Vilella, C. Picado, M. Juan, J. Sanchez-Lopez, M. Rueda, G. Salcedo, A. Valero, J. Yague, and J. Bartra. 2012. Lipid transfer protein syndrome: Clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. *Clin Exp Allergy* 42(10):1529-1539.

Pastorello, E. A., C. Ortolani, L. Farioli, V. Pravettoni, M. Ispano, A. Borga, A. Bengtsson, C. Incorvaia, C. Berti, and C. Zanussi. 1994. Allergenic cross-reactivity among peach, apricot, plum, and cherry in patients with oral allergy syndrome: An in vivo and in vitro study. *J Allergy Clin Immunol* 94(4):699-707.

Peeters, K. A., S. J. Koppelman, E. van Hoffen, C. W. van der Tas, C. F. den Hartog Jager, A. H. Penninks, S. L. Hefle, C. A. Bruijnzeel-Koomen, E. F. Knol, and A. C. Knulst. 2007. Does skin prick test reactivity to purified allergens correlate with clinical severity of peanut allergy? *Clin Exp Allergy* 37(1):108-115.

Peters, R. L., L. C. Gurrin, and K. J. Allen. 2012. The predictive value of skin prick testing for challenge-proven food allergy: A systematic review. *Pediatr Allergy Immunol* 23(4):347-352.

Peters, R. L., L. C. Gurrin, S. C. Dharmage, J. J. Koplin, and K. J. Allen. 2013. The natural history of IgE-mediated food allergy: Can skin prick tests and serum-specific IgE predict the resolution of food allergy? *Int J Environ Res Public Health* 10(10):5039-5061.

Peters, R. L., S. C. Dharmage, L. C. Gurrin, J. J. Koplin, A. L. Ponsonby, A. J. Lowe, M. L. Tang, D. Tey, M. Robinson, D. Hill, H. Czech, L. Thiele, N. J. Osborne, and K. J. Allen. 2014. The natural history and clinical predictors of egg allergy in the first 2 years of life: A prospective, population-based cohort study. *J Allergy Clin Immunol* 133(2):485-491.

Peters, R. L., K. J. Allen, S. C. Dharmage, J. J. Koplin, T. Dang, K. P. Tilbrook, A. Lowe, M. L. Tang, L., C. Gurrin, and HealthNuts Study. 2015. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. *J Allergy Clin Immunol* 135(5):1257-1266.

Pongracic, J. A., S. A. Bock, and S. H. Sicherer. 2012. Oral food challenge practices among allergists in the United States. *Journal of Allergy and Clinical Immunology* 129(2):564-566.

Pucar, F., R. Kagan, H. Lim, and A. E. Clarke. 2001. Peanut challenge: A retrospective study of 140 patients. *Clin Exp Allergy* 31(1):40-46.

Rodriguez, J., J. F. Crespo, W. Burks, C. Rivas-Plata, S. Fernandez-Anaya, R. Vives, and P. Daroca. 2000. Randomized, double-blind, crossover challenge study in 53 subjects reporting adverse reactions to melon (*Cucumis melo*). *J Allergy Clin Immunol* 106(5):968-972.

Rodriguez-Sanchez, J., E. Gomez Torrijos, B. Lopez Viedma, E. de la Santa Belda, F. Martin Davila, C. Garcia Rodriguez, F. Feo Brito, J. Olmedo Camacho, P. Reales Figueroa, and J. Molina-Infante. 2014. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. *Allergy* 69(7):936-942.

Roehr, C. C., S. Reibel, M. Ziegert, C. Sommerfeld, U. Wahn, and B. Niggemann. 2001. 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(3):548-553.

Rolinck-Werninghaus, C., B. Niggemann, L. Grabenhenrich, U. Wahn, and K. Beyer. 2012. Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE. *Allergy* 67(7):951-957.

Romano, A., M. Di Fonso, F. Giuffreda, G. Papa, M. C. Artesani, M. Viola, A. Venuti, V. Palmieri, and P. Zeppilli. 2001. Food dependent exercise-induced anaphylaxis: Clinical and laboratory findings in 54 subjects. *Int Arch Allergy Immunol* 125(3):264-272.

Romano, A., E. Scala, G. Rumi, F. Gaeta, C. Caruso, C. Alonzi, M. Maggioletti, R. Ferrara, P. Palazzo, V. Palmieri, P. Zeppilli, and A. Mari. 2012. Lipid transfer proteins: The most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 42(11):1643-1653.

Rona, R. J., T. Keil, C. Summers, D. Gislason, L. Zuidmeer, E. Sodergren, S. T. Sigurdardottir, T. Lindner, K. Goldhahn, J. Dahlstrom, D. McBride, and C. Madsen. 2007. The prevalence of food allergy: A meta-analysis. *J Allergy Clin Immunol* 120(3):638-646.

Ruffner, M. A., K. Ruymann, S. Barni, A. Cianferoni, T. Brown-Whitehorn, and J. M. Spergel. 2013. Food protein-induced enterocolitis syndrome: Insights from review of a large referral population. *J Allergy Clin Immunol Pract* 1(4):343-349.

Saarinen, K. M., H. Suomalainen, and E. Savilahti. 2001. 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(3):423-429.

Sampson, H. A., R. Gerth van Wijk, C. Bindslev-Jensen, S. Sicherer, S. S. Teuber, A. W. Burks, A. E. Dubois, K. Beyer, P. A. Eigenmann, J. M. Spergel, T. Werfel, and V. M. Chinchilli. 2012. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 130(6):1260-1274.

Sampson, H. A., S. Aceves, S. A. Bock, J. James, S. Jones, D. Lang, K. Nadeau, A. Nowak-Wegrzyn, J. Oppenheimer, T. T. Perry, C. Randolph, S. H. Sicherer, R. A. Simon, B. P. Vickery, and R. Wood. 2014. Food allergy: A practice parameter update—2014. *J Allergy Clin Immunol* 134(5):1016-1025.

Sancho, A. I., R. Foxall, T. Browne, R. Dey, L. Zuidmeer, G. Marzban, K. W. Waldron, R. van Ree, K. Hoffmann-Sommergruber, M. Laimer, and E. N. Mills. 2006. Effect of postharvest storage on the expression of the apple allergen Mal d 1. *J Agric Food Chem* 54(16):5917-5923.

Santos, A. F., A. Douiri, N. Becares, S. Y. Wu, A. Stephens, S. Radulovic, S. M. Chan, A. T. Fox, G. Du Toit, V. Turcanu, and G. Lack. 2014. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. *J Allergy Clin Immunol* 134(3):645-652.

Santos, A. F., G. Du Toit, A. Douiri, S. Radulovic, A. Stephens, V. Turcanu, and G. Lack. 2015. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. *J Allergy Clin Immunol* 135(1):179-186.

Savage, J. H., E. C. Matsui, J. M. Skripak, and R. A. Wood. 2007. The natural history of egg allergy. *J Allergy Clin Immunol* 120(6):1413-1417.

Savage, J. H., A. J. Kaeding, E. C. Matsui, and R. A. Wood. 2010. The natural history of soy allergy. *J Allergy Clin Immunol* 125(3):683-686.

Savage, J., S. Sicherer, and R. Wood. 2016. The natural history of food allergy. *J Allergy Clin Immunol Pract* 4(2):196-203.

Savilahti, E. M., M. Viljanen, M. Kuitunen, and E. Savilahti. 2012. Cow's milk and ovalbumin-specific IgG and IgA in children with eczema: Low beta-lactoglobulin-specific IgG4 levels are associated with cow's milk allergy. *Pediatr Allergy Immunol* 23(6):590-596.

Savilahti, E. M., M. Kuitunen, E. Savilahti, and M. J. Makela. 2014. Specific antibodies in oral immunotherapy for cow's milk allergy: Kinetics and prediction of clinical outcome. *Int Arch Allergy Immunol* 164(1):32-39.

Savvatianos, S., A. P. Konstantinopoulos, A. Borga, G. Stavroulakis, J. Lidholm, M. P. Borres, E. Manousakis, and N. G. Papadopoulos. 2015. Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children. *J Allergy Clin Immunol* 136(1):192-194.

Shek, L. P., L. Soderstrom, S. Ahlstedt, K. Beyer, and H. A. Sampson. 2004. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol* 114(2):387-391.

Shreffler, W. G., K. Beyer, T. H. Chu, A. W. Burks, and H. A. Sampson. 2004. Microarray immunoassay: Association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 113(4):776-782.

Sicherer, S. H. 2001. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 108(6):881-890.

Sicherer, S. H. 2002. Food allergy. *Lancet* 360(9334):701-710.

Sicherer, S. H., and R. A. Wood. 2012. Allergy testing in childhood: Using allergen-specific IgE tests. *Pediatrics* 129(1):193-197.

Sicherer, S. H., P. A. Vargas, M. E. Groetch, L. Christie, S. K. Carlisle, S. Noone, and S. M. Jones. 2012. Development and validation of educational materials for food allergy. *J Pediatr* 160(4):651-656.

Sicherer, S. H., R. A. Wood, B. P. Vickery, S. M. Jones, A. H. Liu, D. M. Fleischer, P. Dawson, L. Mayer, A. W. Burks, A. Grishin, D. Stablein, and H. A. Sampson. 2014. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol* 133(2):492-499.

Sidbury, R., W. L. Tom, J. N. Bergman, K. D. Cooper, R. A. Silverman, T. G. Berger, S. L. Chamlin, D. E. Cohen, K. M. Cordoro, D. M. Davis, S. R. Feldman, J. M. Hanifin, A. Krol, D. J. Margolis, A. S. Paller, K. Schwarzenberger, E. L. Simpson, H. C. Williams, C. A. Elmets, J. Block, C. G. Harrod, W. Smith Begolka, and L. F. Eichenfield. 2014. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol* 71(6):1218-1233.

Skripak, J. M., E. C. Matsui, K. Mudd, and R. A. Wood. 2007. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 120(5): 1172-1177.

Skypala, I. J., C. Venter, R. Meyer, N. W. deJong, A. T. Fox, M. Groetch, J. N. Oude Elberink, A. Sprikkelman, L. Diamandi, and B. J. Vlieg-Boerstra. 2015. The development of a standardised diet history tool to support the diagnosis of food allergy. *Clin Transl Allergy* 5:7.

Soares-Weiser, K., Y. Takwoingi, S. S. Panesar, A. Muraro, T. Werfel, K. Hoffmann-Sommergruber, G. Roberts, S. Halken, L. Poulsen, R. van Ree, B. J. Vlieg-Boerstra, and A. Sheikh. 2014. The diagnosis of food allergy: A systematic review and meta-analysis. *Allergy* 69(1):76-86.

Song, Y., J. Wang, N. Leung, L. X. Wang, L. Lisann, S. H. Sicherer, A. M. Scurlock, R. Pesek, T. T. Perry, S. M. Jones, and X. M. Li. 2015. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. *Ann Allergy Asthma Immunol* 114(4):319-326.

Spergel, J. M., T. F. Brown-Whitehorn, A. Cianferoni, M. Shuker, M. L. Wang, R. Verma, and C. A. Liacouras. 2012. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 130(2):461-467.

Sporik, R., D. J. Hill, and C. S. Hosking. 2000. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 30(11):1540-1546.

Stapel, S. O., R. Asero, B. K. Ballmer-Weber, E. F. Knol, S. Strobel, S. Vieths, and J. Kleine-Tebbe. 2008. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI task force report. *Allergy* 63(7):793-796.

Summers, C. W., R. S. Pumphrey, C. N. Woods, G. McDowell, P. W. Pemberton, and P. D. Arkwright. 2008. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol* 121(3):632-638.

Sverremark-Ekström, E., E. H. Hultgren, M. P. Borres, and C. Nilsson. 2012. Peanut sensitization during the first 5 yr of life is associated with elevated levels of peanut-specific IgG. *Pediatr Allergy Immunol* 23(3):224-229.

Syed, A., M. A. Garcia, S. C. Lyu, R. Bucayu, A. Kohli, S. Ishida, J. P. Berglund, M. Tsai, H. Maecker, G. O'Riordan, S. J. Galli, and K. C. Nadeau. 2014. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol* 133(2):500-510.

Ta, V., B. Weldon, G. Yu, O. Humblet, S. Neale-May, and K. Nadeau. 2011. Use of specific IgE and skin prick test to determine clinical reaction severity. *Br J Med Med Res* 1(4):410-429.

Ta, V., D. R. Scott, W. K. Chin, N. E. Wineinger, J. M. Kelso, and A. A. White. 2015. Differential skin test reactivity to pollens in pollen food allergy syndrome versus allergic rhinitis. *Allergy Asthma Proc* 36(5):379-385.

Thyagarajan, A., S. M. Jones, A. Calatroni, L. Pons, M. Kulis, C. S. Woo, M. Kamalakannan, B. P. Vickery, A. M. Scurlock, A. Wesley Burks, and W. G. Shreffler. 2012. Evidence of pathway-specific basophil anergy induced by peanut oral immunotherapy in peanut-allergic children. *Clin Exp Allergy* 42(8):1197-1205.

Tolkki, L., K. Alanko, L. Petman, M. B. Skydtsgaard, P. G. Milvang, U. Seppala, and A. Ranki. 2013. Clinical characterization and IgE profiling of birch (*Betula verrucosa*)—allergic individuals suffering from allergic reactions to raw fruits and vegetables. *J Allergy Clin Immunol Pract* 1(6):623-631.

Tomicic, S., G. Norrman, K. Falth-Magnusson, M. C. Jenmalm, I. Devenney, and M. F. Bottcher. 2009. High levels of IgG4 antibodies to foods during infancy are associated with tolerance to corresponding foods later in life. *Pediatr Allergy Immunol* 20(1):35-41.

Turner, P. J., J. L. Baumert, K. Beyer, R. J. Boyle, C. H. Chan, A. T. Clark, R. W. Crevel, A. DunnGalvin, M. Fernandez-Rivas, M. H. Gowland, L. Grabenhenrich, S. Hardy, G. F. Houben, J. O'B Hourihane, A. Muraro, L. K. Poulsen, K. Pyrz, B. C. Remington, S. Schnadt, R. van Ree, C. Venter, M. Worm, E. N. Mills, G. Roberts, and B. K. Ballmer-Weber. 2016. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy* 71(9):1241-1255.

Urisu, A., M. Ebisawa, K. Ito, Y. Aihara, S. Ito, M. Mayumi, Y. Kohno, and N. Kondo. 2014. Japanese Guideline for Food Allergy 2014. *Allergol Int* 63(3):399-419.

Vadas, P., M. Gold, B. Perelman, G. M. Liss, G. Lack, T. Blyth, F. E. Simons, K. J. Simons, D. Cass, and J. Yeung. 2008. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 358(1):28-35.

van der Zee, T., A. Dubois, M. Kerkhof, S. van der Heide, and B. Vlieg-Boerstra. 2011. The eliciting dose of peanut in double-blind, placebo-controlled food challenges decreases with increasing age and specific IgE level in children and young adults. *J Allergy Clin Immunol* 128(5):1031-1036.

van Erp, F. C., J. Boot, A. C. Knulst, S. G. Pasmans, C. K. van der Ent, and Y. Meijer. 2014. Reintroduction failure after negative peanut challenges in children. *Pediatr Allergy Immunol* 25(6):580-585.