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Implementation of the NIAID Peanut Allergy Guidelines Outcomes and experience



The publication of the Learning Early About Peanut Allergy study in 2015 represented a paradigm shift in the field of food allergy with the finding of an 81% reduction in the incidence of peanut allergy when early introduction of peanut was compared with strict avoidance in high-risk infants.¹ In 2017, the National Institute of Allergy and Infectious Disease (NIAID) provided official recommendations for early peanut introduction with the publication of the Addendum Guidelines to the 2010 Guidelines for Diagnosis and Management of Food Allergy in the United States. These guidelines provide risk stratification for at-home introduction, in-office challenge, or strict avoidance for infants at high risk of peanut allergy based on peanut serum immunoglobulin E and peanut skin prick wheal size.² The limitations of widespread implementation of early peanut introduction, including cost, availability of testing, and availability of allergy specialists, have all been topics of expert discussion.^{3–5} However, few reports have examined the practical outcomes of implementing the NIAID guidelines in the clinical setting.

We performed a retrospective chart review and identified infants seen by 1 of our 5 providers in the Vanderbilt Pediatric Allergy clinic between January 2017 and October 2017 who were given recommendations regarding peanut introduction reflective of the NIAID guidelines. Infants met the following inclusion criteria: 12 months of age or younger at the initial allergy clinic visit, a history of severe atopic dermatitis or a history of egg allergy, no prior history of peanut ingestion, and documentation of peanut skin prick test (SPT). All patients identified were referred by a primary care provider or self-referred for the evaluation of atopic dermatitis or suspected food allergy.

Among 26 infants identified, 54% were male, 58% were white, and median age at initial allergy clinic visit was 9 months. Of the 26 infants, 81% had a history of severe atopic dermatitis as defined by either failure of topical steroids or greater than 50% body surface area involvement, and 58% had a history of egg allergy. History of allergy to foods was reported if a clinical history of an index reaction was present and an SPT to the food showed a wheal size 3 mm greater than a negative control. Seventy-three percent of infants had a history of food allergy, with cow's milk the most common allergy after egg at 27% of infants (eTable 1).

Eight of the 26 infants had an initial peanut SPT wheal size of 0 to 2 mm. Five of these 8 infants underwent an oral food challenge (OFC). In all 5 of these cases, the parents elected in-office challenges after the provider presented the options of at-home introduction vs an in-office challenge. All 5 of these patients passed their OFC. The other 3 families elected to introduce peanut at home.

Fourteen of the 26 infants had an initial peanut SPT wheal size of 3 to 7 mm, and all of these children underwent an OFC. Six of these 14 patients failed their challenge, representing a 43% positive challenge rate. The reactions in 4 of these cases were urticarial only and responded to treatment with an age-appropriate dose of oral H1 antihistamines. Two reactions met criteria for

anaphylaxis and required treatment with intramuscular epinephrine. The remaining 8 patients had negative OFCs, and families were educated on how to regularly integrate peanut into the diet.

Finally, 4 of the 26 infants had a peanut SPT wheal of 8 mm or greater, and all were counseled to strictly avoid peanut (Table 1).

This is an observational study, and, based on search methods available, we were unable to determine how many infants did not have a screening skin prick test to peanut placed despite meeting criteria for early peanut introduction. Also, follow-up information on adherence was not available for all patients. However, despite the small cohort size, specific challenges to successful implementation of the NIAID guidelines can be identified.

First, the median age of the patients at their initial allergy clinic visit was 9 months. This highlights the challenge of identifying and referring the appropriate patients to the closest allergist in a timely manner when the goal age of peanut introduction in this group is 4 to 6 months.

Second, the importance of appropriate preparedness for performing oral challenges in this high-risk patient cohort, which has been previously reported,⁶ is further supported by the reaction rate noted during OFCs at our institution. Forty-three percent of our patients with a peanut SPT wheal between 3 and 7 mm developed immunoglobulin E-mediated type reactions, which is consistent with a reported 42% reaction rate among infants in this wheal size range in a recent study of the implementation of these guidelines in a larger cohort of infants.⁷ Of note, the severity of the reactions in our cohort is higher than previously reported, with 2 of 14 (14%) of those in the 3- to 7-mm peanut wheal size group developing anaphylaxis. The first patient that developed anaphylaxis was a 6-month-old with a peanut SPT of 5 mm, severe atopic dermatitis, and no history of food allergy. The patient developed diffuse urticaria, hoarse cry, and cough after the second step of the OFC. The second patient was 13 months old at the time of the OFC, had a peanut SPT of 3 mm, severe atopic dermatitis, and history of cow's milk protein allergic proctocolitis. The patient developed emesis, urticaria and coarse breath sounds also after the second step of the

Table 1
Outcome Based on Skin Prick Test Size (mm Wheal Diameter)

Peanut introduction	0–2	3–7	≥8
Total, n (%)	8 (30.8)	14 (53.8)	4 (15.4)
Recommendations, n (%)			
At-home introduction	3 (37.5)	0	0
In-office challenge	5 (62.5)	14 (100)	0
Strict avoidance	0	0	4 (100)
Reactions, n (%) ^a			
Total	0	6 ^b (42.9)	N/A
Facial hives	0	3 (21.4)	
Generalized hives	0	1 (7.1)	
Anaphylaxis	0	2 (14.3)	

^aPercentage reported according to number of children advised to introduce peanut.

^bTwo of these patients underwent subsequent successful oral challenges to peanut after peanut component testing had been obtained and was reassuring.

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OFC. Both patients responded to 1 dose of intramuscular epinephrine and oral antihistamines, were observed for 4 hours in clinic after the reaction, and did not require treatment in the emergency department (eTable 2).

In conclusion, special consideration should be given to an individual practice's preparedness to manage potentially severe reactions in high-risk infants undergoing evaluation for early introduction of peanut because our data suggest that this is not an infrequent event. Data from various practice settings and populations are needed to provide more stable estimates for the outcomes of early peanut introduction according to the NIAID guideline recommendations so that we may achieve its promising underlying goal: the prevention of peanut allergy.

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Association of estrogen receptor α polymorphism rs1999805 with asthma



Women have higher rates of asthma and allergic disease as well as increased asthma severity compared with men.¹ Premenstrual or perimenstrual worsening of asthma symptoms were reported in 17% of women enrolled in the severe asthma research program, with 52% of these women having severe asthma.^{2,3} Furthermore, use of birth control medications or hormone replacement therapy during perimenopause or postmenopause was also linked to worsening of asthma in some women.^{2,4} Mouse models of asthma found estrogen signaling through estrogen receptor (ER) α and not ER β and increased allergic airway inflammation, mucous production, and/or airway hyperresponsiveness.^{2,4} Collectively, these findings suggest a critical role for ER α signaling in asthma pathogenesis.

In this study, we sought to determine whether single-nucleotide polymorphisms (SNPs) in ER α (*ESR1*) or aromatase (*CYP19A1*), the enzyme that converts testosterone to estrogen, were associated with asthma or allergic disease phenotypes using a phenome-wide association study. A phenome-wide association study is a validated, reverse genetics technique that associates clinical phenotypes with genetic variants. A phenome-wide association study is able to determine whether genetic polymorphisms are associated with clinical phenotypes using deidentified electronic health records (EHRs).⁵ We studied *ESR1* because of the importance of ER α signaling in the pathogenesis of asthma. We also investigated *CYP19A1* because of studies showing an increased risk of breast cancers and other diseases with SNPs in *CYP19A1* (Table 1). Although previous genome-wide association studies (GWASs) have not reported associations between asthma or lung function and

SNPs in *ESR1* or *CYP19A1* in a population of both men and women,^{6,7} the stringent *P* value thresholds for these GWASs likely missed associations. Therefore, we conducted a phenome-wide association study on men and women (≥ 18 years of age) using 14 SNPs in *ESR1* or *CYP19A1* that were previously associated with sex hormone-related diseases in GWASs or identified in the original phenome-wide association study catalog with genotyping information on 13,835 individuals.⁵ In our phenome-wide association study, significant associations ($P < .05$) between the selected SNPs and phecodes, derived from *International Classification of Diseases, Ninth Revision (ICD-9)* codes, for wheezing, asthma, or allergic diseases were determined from Vanderbilt's BioVU databank with deidentified genotyping information on 36,400 individuals linked to the EHR. Genotyping was performed on the Illumina HumanExome BeadChip platform, and a cutoff of 5500 individuals with a respective SNP was needed to sufficiently power the phenome-wide association study analysis.^{5,8}

As indicated in Table 1, significant associations ($P < .05$) were identified for 5 SNPs with ICD-9 codes for wheezing, asthma, or allergic diseases with a female predominance for all 5 SNPs. Table 1 also indicates that 2 SNPs had no significant associations with asthma or allergic diseases and 7 SNPs were found in fewer than 5500 subjects and were not analyzed. *CYP19A1* SNP rs2305707 had an inverse association with allergic rhinitis (odds ratio [OR], 0.90; $P = .01$). *CYP19A1* SNP rs2899472 exhibited an inverse association with anaphylactic shock (OR, 0.59; $P = .006$) and chronic sinusitis (OR, 0.91; $P = .04$) and was associated with asthma exacerbations (OR, 1.28; $P = .008$). *ESR1* SNP rs543650 had an inverse association with wheezing (OR, 0.86; $P = .047$). Furthermore, *ESR1* SNPs rs1999805 and rs2504063 were associated with asthma (OR, 1.07; $P = .04$) and chronic sinusitis (OR, 1.08; $P = .045$), respectively. All the SNPs are located in the intronic region of the respective gene, and the function of these SNPs is currently unknown.

We repeated the phenome-wide association study in an independent cohort of 500,000 individuals in the UK BioBank using

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eTable 1
Demographics and Clinical History

Characteristic	n = 26
Gender, n (%)	
Male	14 (53.8)
Female	12 (46.2)
Median age at initial allergy clinic visit, months	9
Race, n (%)	
White	15 (57.7)
Black/African American	7 (26.9)
Asian	2 (7.7)
Unknown/not reported	2 (7.7)
Ethnicity	
Not Hispanic or Latino	24 (92.3)
Hispanic or Latino	1 (3.8)
Unknown/not reported	1 (3.8)
Atopic dermatitis, n (%)	
Yes	21 (80.7)
No	5 (19.3)
Food allergy, n (%)	
None	7 (26.9)
Egg	15 (57.7)
Cow's milk	7 (26.9)
Tree nut	2 (7.7)
Wheat	1 (3.8)
Other	1 (3.8)

eTable 2
Demographics of Patients That Developed Reactions during Peanut OFCs

Age at OFC (months)	Peanut SPT (mm)	Egg SPT (mm)	Atopic dermatitis (Y/N)	Family history of atopy (Y/N)	Other clinical history	Reaction description
9	3	5	Y	N	Anaphylaxis to cow's milk	Facial urticaria
12	5	5	Y	Y		Diffuse urticaria
6	5	N/A	Y	Y	Cow's milk allergic proctocolitis	Anaphylaxis: urticaria, hoarse cry and cough
15	7	10	Y	N		Facial urticaria
10	4	5	Y	Y		Facial urticaria
13	3	N/A	Y	Y		Anaphylaxis: vomiting, urticaria, coarse breath sounds