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Predicting the Natural Development of Peanut Tolerance using Longitudinal Trajectories of Peanut-specific Serum Immunoglobulin E

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Online Repository Text (Legends):

Figure E1: Predicted probability of passing peanut oral food challenge by annual percent decrease in peanut-specific IgE

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Online Repository Material:

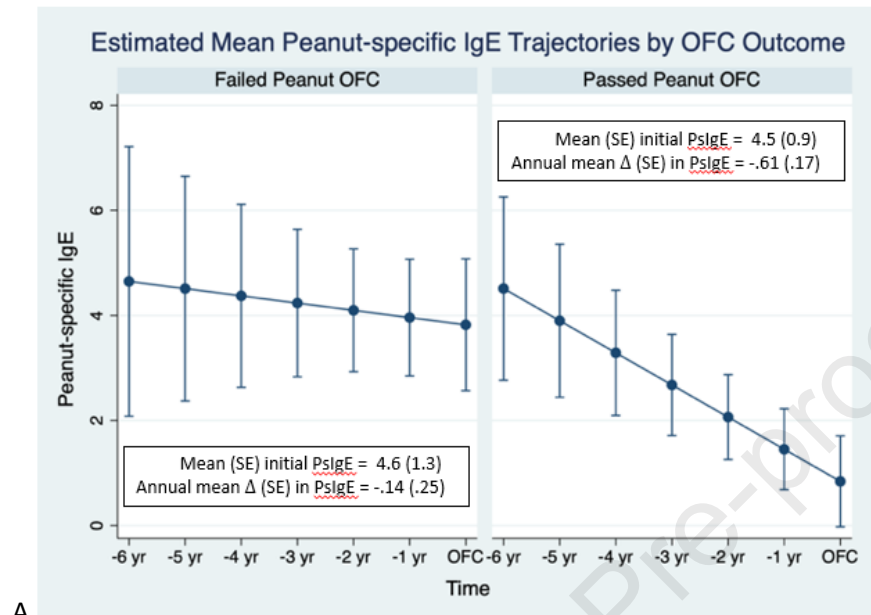
Characteristic	Passed OFC (N=73) N(%) or Mean (SD)	Failed OFC (N=35) N(%) or Mean (SD)	Test statistic; two-sided p value
Male	24 (68.6%)	44 (60.3%)	$\chi^2=0.69$; p=0.40
Age	7.6 (3.9)	8.7 (3.9)	t=1.37; p=0.17
SPT wheal size (mm)	5.8 (4.7)	7.3 (5.1)	t=1.55; p=0.12
Initial IgE upon clinical presentation	2.3 (3.5)	3.7 (4.2)	t=1.79; p=0.08
sIgE at time of OFC	0.9 (1.0)	3.5 (5.8)	t=3.80; p=0.0002
sIgE/total IgE at time of OFC	0.009 (0.010)	0.013 (0.013)	t=1.37; p=0.17
Atopic dermatitis	52 (71.2%)	28 (80.0%)	$\chi^2=0.94$; p=0.33
Other atopic disease (allergic rhinitis , asthma)	42 (57.5%)	28 (80.0%)	$\chi^2=5.24$; p=0.02
Other food allergy	61 (83.6%)	29 (82.9%)	$\chi^2=0.01$; p=0.93
Only cutaneous involvement as initial reaction	35 (48.0%)	17 (48.6%)	$\chi^2=0.004$; p=0.95
Multisystem as initial reaction	4 (5.5%)	3 (8.6%)	$\chi^2=0.37$; p=0.54
Never ingested peanut	32 (43.8%)	10 (28.6%)	$\chi^2=2.31$; p=0.13

Table E1: Characteristics of patients with peanut allergy

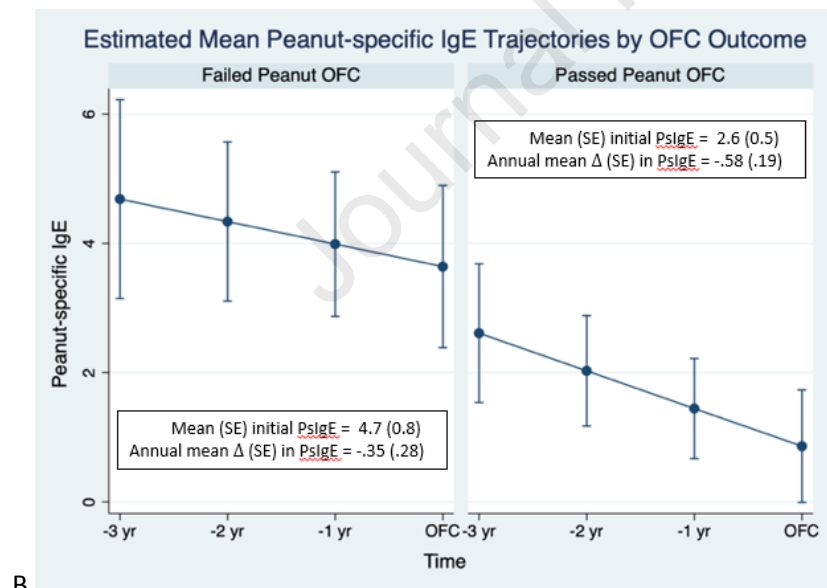
% decrease of pslgE over 12months	Predicted probability* of passing peanut OFC (Last 4 years only)	Predicted probability* of passing peanut OFC (All 7 years)
10	0.68 (.04)	0.68 (.04)
25	0.71 (.04)	0.70 (.05)
50	0.74 (.05)	0.74 (.05)
75	0.78 (.05)	0.77 (.6)
90	0.80 (.06)	0.79 (.06)
99	0.81 (.06)	0.80 (.06)

Table 1 : Probability of developing tolerance for peanut allergy based on annual decrease of pslgE

*Baseline probability of passing peanut OFC=0.68 (SE=.04));
model adjusts for age, sex, atopic dermatitis and asthma status.



A.

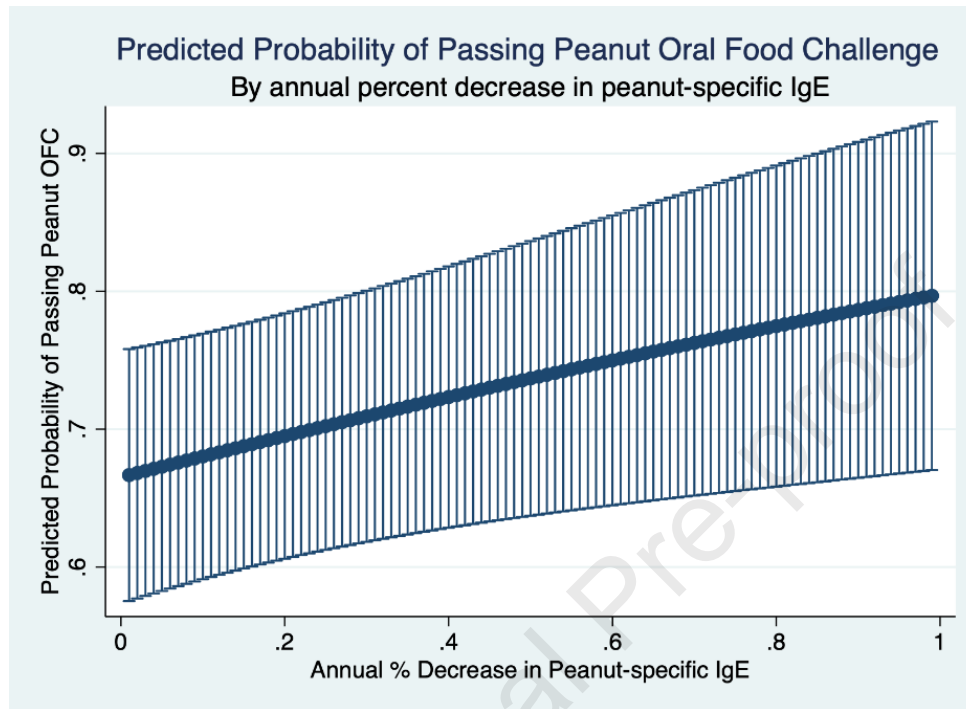


B.

Figure 1: Estimated mean peanut-specific IgE trajectories by OFC outcome modeled over last 7 years (panel A) and last 4 years (panel B)

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Figure E1



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The other authors declare that they have no relevant conflicts of interest.

Clinical Implications:

Annual rates of decrease in peanut specific serum IgE may provide useful parameters to predict peanut allergy tolerance and assist the clinician's decision to offer or withhold an office peanut challenge.

Peanut allergy is one of the most common food-specific allergies and is estimated to affect 2.2% of the US pediatric population (1). Tolerance to peanut can develop in 20-25% of children previously diagnosed with peanut allergy (2, 3). Earlier recognition of children more likely to develop tolerance is useful for counseling on prognosis. Currently, the primary means of diagnosing and trending the natural history of peanut allergy are skin prick tests and peanut specific serum immunoglobulin E (sIgE) levels (4). Ideally, in practice, the goal is to optimally use less invasive testing to identify the likelihood of a favorable outcome prior to performing food challenges. Studies of milk and egg allergy suggest the rate of decline in sIgE is predictive of greater likelihood of developing tolerance (5, 6). In our study, among children diagnosed with a peanut allergy whose peanut sIgE (psIgE) values were assessed at annual clinical allergy visits, we hypothesized a steeper annual rate of decline in psIgE among patients who passed a peanut challenge compared to those who failed.

This study was conducted at a private allergy clinic in Chicago, IL. A retrospective chart review of patients with a ICD-9/ICD-10 diagnostic code for peanut allergy or any food allergy (V15.01,995.61,995.89,V15.05,Z91.010,T78.01XA,T78.01XD,T78.1XXA,Z91.018), seen between January 2010 to July 2019, was performed. The resulting 1201 charts were individually reviewed and those patients meeting the following criteria were included in data analysis: physician-confirmed diagnosis of peanut allergy; administration of peanut oral food challenge (OFC) with physician-documented positive or negative outcome; patient aged 0-20 years with two or more psIgE values and at least one value between 0.10-100 kU/L. Peanut sIgE was assessed at the time of diagnosis and repeated annually until the time of OFC. At annual office visits, physician assessment of peanut allergy status was performed prior to psIgE testing. All

oral challenges were open and conducted under allergist supervision in the outpatient clinic. Stata 15 was used to fit multilevel linear growth curve models incorporating random patient-specific coefficients and an interaction term to compare trajectories of pre-challenge annual psIgE levels between patients who passed versus failed peanut OFC. Quadratic models were also evaluated but did not improve fit beyond the linear model (nested likelihood ratio test $p > .05$). This study was approved by the Institutional Review Board of Lurie Children's Hospital in Chicago.

Of the 1201 patients screened based on ICD codes, a total of 108 children underwent a peanut OFC and comprised the present analytic sample. Of these patients, 68% ($n=73$) passed [$\text{Mean}_{\text{psIgE}}=0.9(\text{SD}=1.0)$], while 32% ($n=35$) failed [$\text{Mean}_{\text{psIgE}}=3.5(\text{SD}=5.8)$]. Average model predicted psIgE levels at time of challenge were significantly lower among patients that passed compared to failed peanut OFC. An average of 3.2 years of annual psIgE values were collected. When all years of data were modeled (range 2-7 years), the mean annual rate of change in psIgE for children who passed OFC was -0.61 kU/L ($\text{SE}=0.17$) compared to -0.14 kU/L ($\text{SE}=0.25$) in those who failed ($p_{\text{one-sided}}=0.04$) (Figure 1). The corresponding interaction term for this time (in years) X OFC outcome interaction was -0.47 ($\text{SE}=0.30$). We further developed estimates for the probability of passing a peanut OFC based on the annual percent decrease in sIgE for peanut (Table 1, Figure E1). The probability of a child offered an OFC exhibiting peanut tolerance, when considering the last 7 years of psIgE values prior to challenge, was 0.74 for a decrease of 50% and 0.80 for a decrease of 99%. Modeling only the last 4 years of psIgE prior to challenge yielded similar predicted probabilities. There was no difference in the presence of atopic dermatitis between the groups, although those who failed peanut OFC had more documented

atopic disease than those who passed (Table E1). There were no significant differences between other clinical characteristics in those who passed or failed an OFC.

This study offers a variable for assessing the likelihood of tolerance prior to performing an OFC. We found that a steeper annual decline in psIgE values was associated with a greater probability of passing a peanut OFC among patients offered challenges. Previous studies have defined psIgE levels that predict the likelihood of passing a peanut challenge based on a history of reaction (7). Applying these levels in conjunction with our estimates for tolerance could more accurately predict successful OFC outcomes. Of relevance to the clinician, as an example, if a hypothetical patient had a peanut sIgE of 3kU/L and repeat measurement a year later fell to 1.5kU/L (a decrease of 50%), our model indicates that the patient has approximately a 74% chance of passing a peanut challenge if offered. Alternatively, the clinician may recommend postponing a peanut challenge until a greater annual decline in sIgE is noted, reducing the risks until there is an increased likelihood of passing a peanut challenge.

Study limitations include small sample size and a single center based retrospective chart review. Peanut allergy diagnosis was not confirmed in all patients by peanut oral challenges, and provider-specific decisions were made based on history and absolute psIgE levels that have been previously established and validated (7, 8), and status was assessed annually at visits. This remains a limitation to the study as we examine the time tolerance was confirmed when OFC was performed per physician discretion, but it is probable it developed between the time of OFC and prior assessment. It is also notable that when the analytic sample was restricted to psIgE

values taken within 4 years of OFC, in order to assess robustness of findings since many clinicians lack 7 years of historical lab values, the difference in slopes was not statistically significant. However, the estimated effect retained the same direction. Prospective studies incorporating larger, more diverse samples should be performed to permit more precise estimations of longitudinal trajectories of interest and better establish the generalizability of predictive levels for tolerance. Finally, although there were no diagnostic or double-blinded challenges to determine tolerance acquisition, our analysis mirrors a diagnostic approach commonly used in clinical practice.

We conclude that patients exhibiting steeper annual decreases in psIgE values may have greater probability of passing an offered OFC to peanut. With newer advents in immunotherapy, it may be increasingly helpful for allergists to identify which children with peanut allergy are likely to have persistence of their food allergy. Further studies are needed to better understand the utility of longitudinal sIgE trajectories for predicting tolerance.

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Figure Legends:

Figure 1: Estimated mean peanut-specific IgE trajectories by OFC outcome modeled over last 7 years (panel A) and last 4 years (panel B).

Table 1: Probability of developing tolerance for peanut allergy based on annual decrease of psIgE

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