

# Epitope-specific IgE profiles are predictive of desensitization and remission in the IMPACT trial



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**Background:** Results from the IMPACT trial suggest that initiation of peanut oral immunotherapy (pnOIT) before age 4 years can increase chances of achieving desensitization and remission.

**Objective:** We assessed sequential (linear) epitope-specific (es)-IgE and es-IgG<sub>4</sub> profiles over the course of pnOIT to determine whether they could predict desensitization and remission outcomes.

**Methods:** Participants in the IMPACT trial (NCT03345160) were randomized to pnOIT or placebo for 134 weeks.

Desensitization and remission end points were assessed by oral food challenges. There were 93 (96.9%) of 96 participants in the pnOIT group and 47 (94%) of 50 in the placebo group. Specific IgE and IgG<sub>4</sub> levels to peanut, component proteins, and 64 allergenic epitopes were measured. Machine learning was used to develop predictive models for desensitization and remission. **Results:** PnOIT was associated with an overall decrease in sequential es-IgE and increase in es-IgG<sub>4</sub> levels. Younger subjects (<2.3 years old) had lower baseline es-IgE binding and lower fold change in es-IgE and es-IgG<sub>4</sub> binding during pnOIT. Participants with desensitization had lower baseline es-IgE levels than those without desensitization. A machine learning model that included 9 es-IgE antibodies predicted remission with an overall performance as follows: accuracy 88.2%, area under the curve 88.2%, sensitivity 83.3%, and specificity 90.0%—comparable to, but not better than, models based on peanut IgE.

**Conclusions:** Baseline epitope IgE profiles can predict remission outcome for children undergoing pnOIT. Age and baseline peanut IgE remain important factors across models. (J Allergy Clin Immunol 2026;158:1018-31.)

## Abbreviations used

|                                 |                                                 |
|---------------------------------|-------------------------------------------------|
| AUC:                            | Area under the ROC curve                        |
| BBEA:                           | Bead-based epitope assay                        |
| D <sup>+</sup> R <sup>-</sup> : | Desensitized/nonremission                       |
| D <sup>+</sup> R <sup>+</sup> : | Desensitized/remission                          |
| DBPCFC:                         | Double-blind, placebo-controlled food challenge |
| D <sup>-</sup> R <sup>-</sup> : | Nondesensitized/nonremission                    |
| es-IgE:                         | Epitope-specific IgE                            |
| es-IgG <sub>4</sub> :           | Epitope-specific IgG <sub>4</sub>               |
| FDR:                            | False discovery rate                            |
| LMEM:                           | Linear mixed-effects model                      |
| MFI:                            | Median fluorescence intensity                   |
| ML:                             | Machine learning                                |
| OIT:                            | Oral immunotherapy                              |
| PA:                             | Peanut allergy                                  |
| pnOIT:                          | Peanut OIT                                      |
| ROC:                            | Receiver operating characteristic               |
| SCP:                            | Serum component protein                         |

**Key words:** Food allergy, peanut allergy, oral immunotherapy, desensitization, remission, epitopes, epitope-binding profiles

Peanut allergy (PA) affects 2-3% of children in the United States, which for most persists into adulthood, with only 20-30% of children developing natural resolution by adolescence.<sup>1-4</sup> Peanut oral immunotherapy (pnOIT) is one approach for managing PA, and multiple clinical trials have shown that pnOIT induces desensitization for most children. However, far fewer develop sustained nonresponsiveness after discontinuation of pnOIT.<sup>5-10</sup>

Results from the IMPACT trial, a randomized, double-blind, placebo-controlled trial of pnOIT in children aged 1 to 4 years with PA (NCT03345160), indicate that younger age at pnOIT initiation in this population is associated with higher rates of remission (defined as nonresponsiveness to a 5,000 mg oral challenge 6 months after discontinuation of pnOIT).<sup>7</sup> Across multiple trials of pnOIT, lower baseline peanut-specific IgE and Ara h 2-specific IgE, and higher baseline peanut-specific IgG<sub>4</sub> to peanut-specific IgE ratio have been associated with a greater likelihood of obtaining remission with pnOIT.<sup>11-13</sup> Changes from baseline in peanut-specific and peanut component IgE and IgG<sub>4</sub> during pnOIT have not been consistently reliable predictors of desensitization or remission outcomes.<sup>10,14,15</sup>

Peanut sequential (linear) epitope-specific (es)-IgE profiles have been shown to accurately diagnose PA and predict reaction thresholds for those with PA, and have been predictive of response to pnOIT.<sup>16-18</sup> In this study, using samples from the IMPACT trial, we assessed sequential es-IgE and es-IgG<sub>4</sub> over the course of

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**TABLE I.** Characteristics of cohort at study initiation by treatment assignment and age group

| Characteristic               | Cohort by treatment group |                       |                       |      | Cohort by age        |                       |       |
|------------------------------|---------------------------|-----------------------|-----------------------|------|----------------------|-----------------------|-------|
|                              | Overall cohort            | pnOIT                 | Placebo               | P    | Younger (<2.3 years) | Older (>2.3 years)    | P     |
| No. of participants          | 140                       | 93                    | 47                    |      | 65                   | 71                    |       |
| Age (years)                  | 2.30 [1.58, 2.73]         | 2.30 [1.60, 2.70]     | 2.30 [1.55, 2.75]     | .903 | 1.50 [1.00, 1.90]    | 2.70 [2.40, 2.90]     | <.001 |
| Male sex, no. (%)            | 93 (66.4)                 | 63 (67.7)             | 30 (63.8)             | .785 | 42 (64.6)            | 48 (67.6)             | .852  |
| Peanut SPT wheal             | 14.25 [11.50, 18.00]      | 14.00 [12.00, 17.50]  | 15.50 [10.00, 19.75]  | .93  | 14.00 [11.50, 18.00] | 15.00 [11.50, 18.50]  | .802  |
| Peanut IgE                   | 53.10 [27.68, 194.25]     | 54.30 [28.20, 189.00] | 45.10 [26.25, 238.50] | .93  | 38.60 [19.50, 85.60] | 68.00 [32.65, 227.00] | .024  |
| IgE Ara h 1                  | 4.52 [0.70, 26.68]        | 4.14 [0.69, 26.60]    | 4.87 [0.85, 23.55]    | .798 | 2.87 [0.71, 12.80]   | 8.76 [0.77, 33.45]    | .130  |
| IgE Ara h 2                  | 45.10 [21.68, 86.48]      | 45.20 [24.50, 83.40]  | 44.40 [16.10, 95.00]  | .898 | 31.00 [14.10, 79.10] | 60.00 [34.70, 91.80]  | .018  |
| IgE Ara h 3                  | 0.70 [0.22, 3.16]         | 0.73 [0.23, 3.16]     | 0.65 [0.22, 2.70]     | .881 | 0.65 [0.20, 1.87]    | 0.85 [0.26, 5.10]     | .134  |
| IgE Ara h 6                  | 33.25 [16.23, 63.70]      | 32.20 [16.00, 58.60]  | 35.10 [16.30, 67.80]  | .595 | 29.50 [13.20, 57.40] | 36.50 [17.15, 67.25]  | .281  |
| Peanut IgG <sub>4</sub>      | 0.58 [0.26, 1.69]         | 0.60 [0.29, 1.68]     | 0.49 [0.15, 1.72]     | .524 | 0.49 [0.18, 1.68]    | 0.62 [0.30, 1.74]     | .139  |
| IgG <sub>4</sub> Ara h 1     | 0.04 [0.04, 0.16]         | 0.04 [0.04, 0.16]     | 0.04 [0.04, 0.17]     | .879 | 0.04 [0.04, 0.16]    | 0.04 [0.04, 0.16]     | .441  |
| IgG <sub>4</sub> Ara h 2     | 0.22 [0.04, 0.42]         | 0.24 [0.11, 0.45]     | 0.19 [0.04, 0.39]     | .363 | 0.20 [0.04, 0.42]    | 0.21 [0.08, 0.39]     | .817  |
| IgG <sub>4</sub> Ara h 3     | 0.16 [0.04, 0.70]         | 0.15 [0.04, 0.47]     | 0.16 [0.04, 0.91]     | .598 | 0.13 [0.04, 0.31]    | 0.20 [0.07, 0.82]     | .035  |
| IgG <sub>4</sub> Ara h 6     | 0.17 [0.04, 0.32]         | 0.17 [0.04, 0.31]     | 0.16 [0.04, 0.34]     | .475 | 0.16 [0.04, 0.38]    | 0.15 [0.04, 0.27]     | .600  |
| es-IgE diversity for Ara h 1 | 0.53 [0.26, 0.83]         | 0.53 [0.32, 0.85]     | 0.56 [0.22, 0.82]     | .359 | 0.41 [0.21, 0.71]    | 0.71 [0.37, 0.94]     | .001  |
| es-IgE diversity for Ara h 2 | 0.56 [0.36, 0.75]         | 0.56 [0.38, 0.75]     | 0.56 [0.25, 0.75]     | .46  | 0.50 [0.25, 0.62]    | 0.69 [0.38, 0.88]     | .001  |
| es-IgE diversity for Ara h 3 | 0.50 [0.21, 1.00]         | 0.57 [0.29, 1.00]     | 0.36 [0.18, 0.93]     | .185 | 0.36 [0.14, 0.64]    | 0.79 [0.36, 1.00]     | <.001 |

Data are presented as medians [IQRs] unless otherwise indicated.

SPT, Skin prick test.

pnOIT and placebo OIT to determine whether epitope profiles can predict desensitization and remission outcomes. We specifically examined whether the inclusion of es-IgE and es-IgG<sub>4</sub> can enhance the prediction of clinical outcomes over whole and component peanut IgE and IgG<sub>4</sub>.

## METHODS

### Study design and participants

Detailed study design and main outcomes of the IMPACT trial have been described previously.<sup>7</sup> In brief, this was a randomized, double-blind, placebo-controlled study conducted at 5 academic medical centers in the United States. Participants included children aged 12 to under 48 months with PA confirmed by double-blind, placebo-controlled food challenge (DBPCFC). Participants were randomly assigned to receive pnOIT or placebo (oat flour). Those in the pnOIT group underwent dose escalation to a maximal daily maintenance dose of 2,000 mg peanut protein (0-30 weeks) and maintained this dose for 24 months (30-134 weeks). DBPCFCs to demonstrate desensitization and remission were performed at weeks 134 and 160, respectively, to a cumulative dose of 5,000 mg of peanut protein. Per protocol, all patients discontinued therapy at week 134 and then underwent remission DBPCFC at week 160, regardless of the week 134 DBPCFC outcome. Treatment outcome groups were defined as desensitized/remission ( $D^+R^+$ ), desensitized/nonremission ( $D^+R^-$ ), and nondesensitized/nonremission ( $D^-R^-$ ).

Blood samples were collected at baseline (week 0), at end of pnOIT dose escalation (week 30), during maintenance dosing (weeks 30 and 82), at desensitization DBPCFC (week 134), and at remission DBPCFC (week 160). Samples were measured for IgE and IgG<sub>4</sub> to whole peanut protein (peanut IgE and peanut IgG<sub>4</sub>), peanut serum component proteins (SCP) (ie, Ara h 1, 2, 3, 6), and Ara h 1, 2, and 3 epitopes.

### Bead-based epitope assay and signal processing

We used the bead-based epitope assay (BBEA) protocol focusing on sixty-four 15-mer epitopes derived from key peanut allergens: 34 from Ara h 1, 16 from Ara h 2, and 14 from Ara h 3.<sup>19</sup> These epitopes, synthesized by CS Bio (Menlo Park, Calif), were chosen on the basis of a comprehensive screening of overlapping 15-mer peptides covering the entirety of Ara h 1, 2, and 3 sequences.

The assay was performed following established methods, outlined here in brief.<sup>19</sup> Epitope-coupled xMAP microspheres (Luminex, Austin, Tex) were prepared in PBS-TBN buffer and formed into aliquots placed into 96-well filter plates (100  $\mu$ L per well). After a washing step with PBS-TBN, plates were incubated with 10-fold diluted plasma samples (100  $\mu$ L per well) in triplicate, shaking at 300 rpm for 2 hours at ambient temperature. Subsequent washes preceded a 30-minute incubation with either mouse anti-human IgE-phycoerythrin (2  $\mu$ g/mL; Thermo Fisher Scientific, Waltham, Mass) or IgG<sub>4</sub>-phycoerythrin (0.25  $\mu$ g/mL; Southern Biotech, Birmingham, Ala) secondary antibodies. After a final wash, PBS-TBN was added, and microspheres were relocated to fixed-bottom plates for median fluorescence intensity (MFI) analysis by xPONENT software on a Luminex200 instrument. To assess nonspecific signals, control wells containing only PBS-TBN buffer were included on each plate. The peanut-BBEA assay has been previously described<sup>19</sup> and validated for its high reproducibility and sensitivity.

### Statistical analysis

All data processing, quality control, and analyses were performed by R v4.2.2 (R Foundation, Vienna, Austria; [www.r-project.org](http://www.r-project.org)) by the 'pvca,' 'bbaR,'<sup>20</sup> and 'limma' packages.<sup>21</sup> Unless otherwise specified, results were considered statistically significant if the 2-sided *P* value was less than .05 after adjusting for multiple comparisons via false discovery rate (FDR).

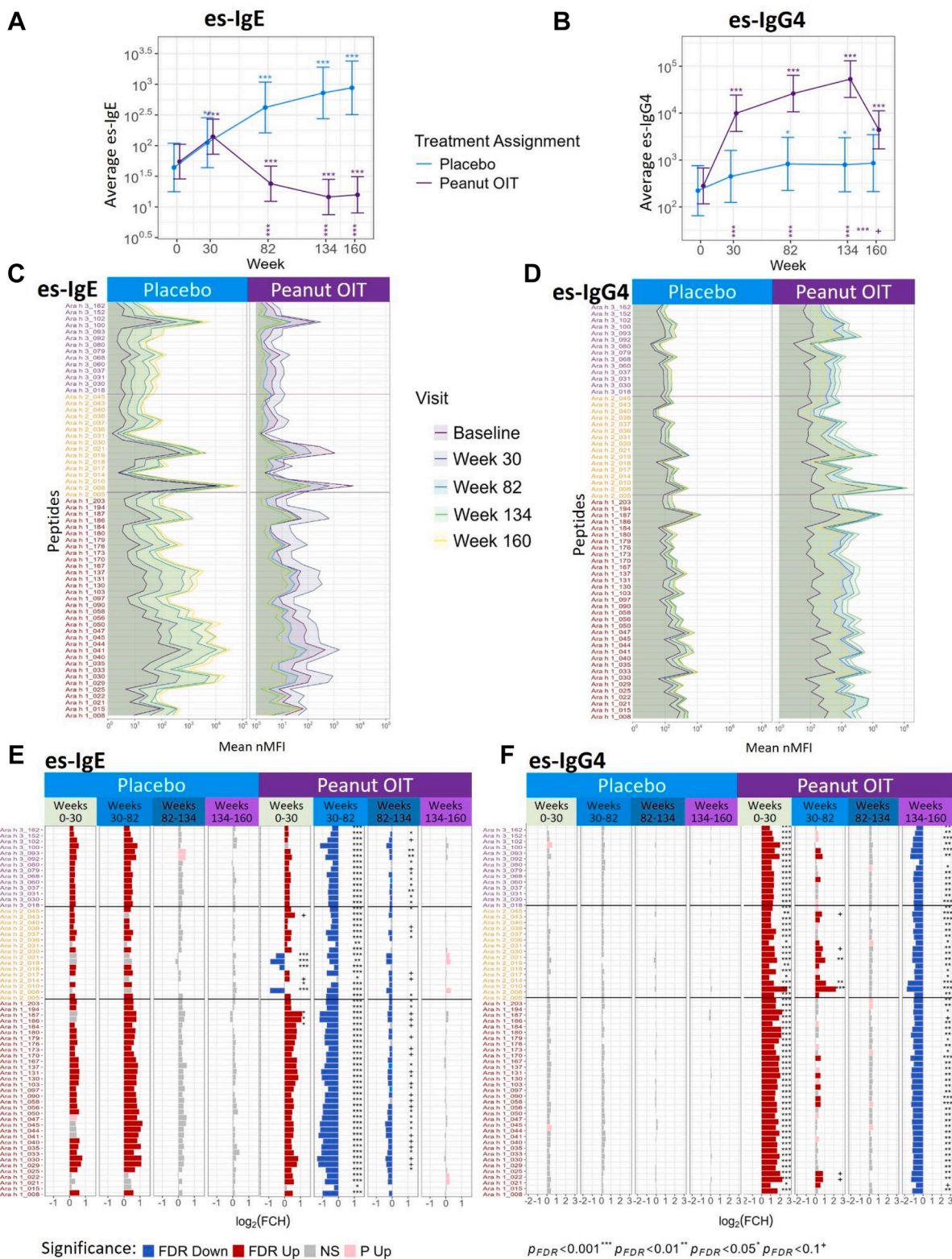


**FIG 1.** Epitope expansion over time by treatment for each immunoglobulin from IMPACT trial. (**A** and **B**) Longitudinal trajectories derived from LMEMs assessing interaction of time  $\times$  treatment, adjusted for age, for es-IgE (*left*) and es-IgG<sub>4</sub> (*right*). Stars above confidence intervals mark within-group changes from baseline (week 0): + $P_{FDR} < .1$ , \* $P_{FDR} < .05$ , \*\* $P_{FDR} < .01$ , \*\*\* $P_{FDR} < .001$ . Vertical stars below es-IgE curves show treatment effect (pNIT – placebo) at each time point. Horizontal stars along bottom between weeks 134 and 160 reflect within-group changes after treatment discontinuation. (**C** and **D**) Ridge plots illustrating average binding (normalized MFI [nMFI]) across all epitopes and time points for es-IgE (*left*) and

## Quantification, quality control, and adjustment for technical confounders

MFIs obtained from the BBEA platform were first normalized and transformed into normalized MFI values, which were then converted to antigen-specific binding scores. Agreement across technical replicates was evaluated by coefficients of variation and intraclass correlation coefficients, with a 2-way intraclass correlation coefficient model applied to quantify consistency across triplicates. Because samples were distributed across multiple microplates, potential plate effects were assessed by principal component analysis and graphical inspection. While replicate consistency was high (intraclass correlation coefficients of >0.925 for es-IgE and >0.95 for es-IgG<sub>4</sub>), principal component analysis revealed nontrivial plate effects.

To further account for technical and biological confounders, we implemented principal variance component analysis with a principal component threshold of 0.8.<sup>19</sup> This analytic framework evaluated contributions of experimental factors (age, treatment assignment, study visit, treatment-by-visit interaction, and participant). Adjustments were then applied by linear mixed-effects models within the ‘lme4’ framework,<sup>22</sup> and corrected values were carried forward for downstream analyses. Finally, composite scores were generated for each sample by averaging *z* scores across triplicate measures of all 64 epitopes for es-IgE and es-IgG<sub>4</sub>.

Quality BBEA data were available for 140 participants, with 136 at baseline (97.1%), 124 (88.6%) at week 30, 118 (84.3%) at week 82, 114 (81.4%) at week 134, and 92 (65.5%) at week 160 after treatment discontinuation.

## Longitudinal models

Linear mixed-effects models (LMEMs) were applied to data from all 64 epitopes by the ‘lme4’ package to assess the effects of pNOIT, treatment response, and age-related treatment effects over time. To evaluate the longitudinal effect of pNOIT, LMEMs were constructed with a random intercept to account for within-subject correlation and fixed effects for age, treatment arm, study visit, and treatment-by-visit interaction. To allow for heteroscedasticity across time points, models were specified with time-dependent residual variances. This modeling framework was also applied to summary outcomes, including average *z* scores, diversity indexes, and other secondary end points. These models were fitted by the ‘nlme’ package in R, which allows for flexible variance structures in repeated-measures data.

For the evaluation of treatment response, LMEMs included a random intercept and fixed effects for age, treatment arm, study visit, treatment response group (defined as a combination of treatment assignment and clinical tolerance status), and the interaction between study visit and treatment response group.

Finally, to assess the effect of early initiation of pNOIT based on age at enrollment (<2.3 years vs >2.3 years), the LMEM was fitted with a random intercept to account for within-subject correlation and fixed effects for treatment arm, study visit, and age-at-enrollment

category. The age group categories were split according to the cohort’s median age.

## Machine learning

We developed a machine learning (ML) pipeline to predict desensitization and remission in peanut-allergic children who underwent pNOIT, which was based on DBPCFCs that occurred at weeks 134 and 160. Following the intention-to-treat principle, the 12 participants who were not desensitized at week 134 were classified as D<sup>−</sup>R<sup>−</sup> in the ML analysis (see Fig E8 in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)).

Models incorporated baseline age, peanut IgE, peanut IgG<sub>4</sub>, SCP IgE and IgG<sub>4</sub>, and es-IgE and es-IgG<sub>4</sub>. After removing highly correlated features and applying a Boruta algorithm for feature selection,<sup>23</sup> an elastic net logistic regression with stochastic gradient descent was trained by stratified 5-fold cross-validation with an 80:20 split, oversampling, and scaling methods that were based on the area under the receiver operating characteristic curve (AUC). Given the limited sample size, we used a Monte Carlo approach where the split in training and testing described above was repeated 100 times, producing robust estimates of the testing performance. Overall testing performance was estimated by average performance metrics, including accuracy, AUC, area under the precision-recall curve, positive predictive value, and F1 scores, as well as sensitivity and specificity.

## RESULTS

Of the 146 subjects from the original IMPACT cohort, we analyzed BBEA profiles for 140 participants (96%) with available samples, with 93 (96.9%) of 96 participants with samples available from the pNOIT group and 47 (94%) of 50 in the placebo group.

### Baseline characteristics and pNOIT outcomes

Table I lists the baseline characteristics of the pNOIT and placebo groups. Overall, participants were predominantly male (66%) with a median age of 2.3 years. There were no significant baseline differences between the pNOIT and placebo groups for peanut skin prick test wheal diameter, median peanut IgE and peanut IgG<sub>4</sub>, and median SCP IgE and SCP IgG<sub>4</sub> to Ara h 1, 2, 3, and 6.

Of the 93 subjects included in this study from the pNOIT group, 76 subjects underwent desensitization DBPCFC in week 134. Of those who underwent DBPCFC, 64 (84%; see Fig E7 in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)) experienced desensitization. Among the desensitized subjects, 56 underwent a remission DBPCFC at week 160; 18 of those who underwent DBPCFC experienced remission (32%; Fig E7). Of the 12 participants (16%) who did not experience desensitization, 10 participants (83%) returned for the remission DBPCFC at week 160, and 1 participant (10%) completed this challenge with no dose-limiting symptoms.

es-IgG<sub>4</sub> (right). (E and F) Bar plots illustrating sequential mean FCH (log<sub>2</sub>[FCH], x-axis) in es-IgE (E) and es-IgG<sub>4</sub> (F), shown separately for placebo (left) and pNOIT (right), derived from LMEMs evaluating time × treatment interaction and adjusted for age. Bar colors denote significance level based on FDR (dark red or blue) or nominal *P* values (light blue, pink, or gray). Black stars indicate significant sequential differences between placebo and pNOIT. Individual peptides appear on y-axis in order of their position across Ara h 1 to Ara h 3 proteins. FCH, Fold change.

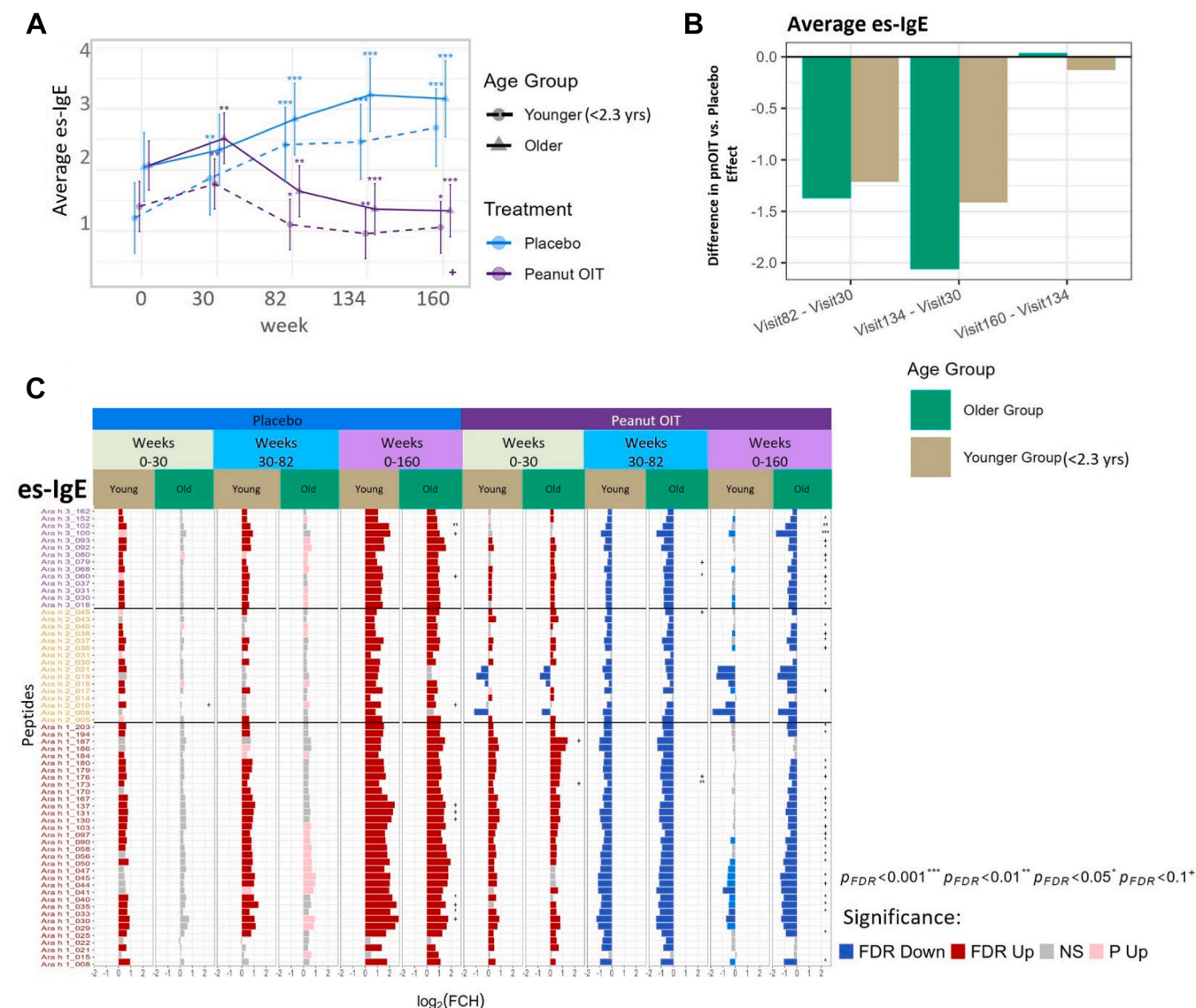


**FIG 2.** Age-stratified es-IgE dynamics over time by treatment. **(A)** Longitudinal trajectories from LMEM, assessing interaction of time  $\times$  treatment  $\times$  age group, for average es-IgE for placebo (blue) and pNOIT (purple), stratified by younger and older participants (dashed lines denote younger participants). Stars above confidence intervals mark within-group changes from baseline (week 0):  $+P_{FDR} < .1$ ;  $*P_{FDR} < .05$ ,  $**P_{FDR} < .01$ ,  $***P_{FDR} < .001$ . **(B)** Bar plots of differences between pNOIT and placebo relative to week 30 for both younger (<2.3 years) and older (>2.3 years) participants. **(C)** Bar plots illustrating mean FCH ( $\log_2[FCH]$ , x-axis) at selected weeks in es-IgE derived from LMEM assessing interaction of time  $\times$  treatment  $\times$  age group, shown for placebo (left) and pNOIT (right), stratified by age group. Bar color reflects magnitude of increase based on FDR (dark red or blue) or nominal  $P$  values (light blue, pink, or gray). Black stars denote significant differences between younger and older participants within each treatment arm and at each time-point comparison. Individual peptides appear on y-axis in order of their position across Ara h 1 to Ara h 3 proteins. FCH, Fold change.

Younger children (<2.3 years old) had significantly lower baseline peanut IgE, Ara h 2 IgE, and es-IgE diversity for Ara h 1, 2, and 3 epitopes (Table I). Rates of desensitization and remission differed significantly between younger and older children (Fisher exact test,  $P < .0001$ ).

### pnOIT alters epitope binding and diversity

**pnOIT decreases es-IgE.** The longitudinal trajectory of average es-IgE is shown in Fig 1, A. There was a significant

increase in average es-IgE for the placebo group over the entire time frame of the study. In comparison, the pnOIT group had an initial increase during dose escalation week 0 to week 30, a significant decline during pnOIT maintenance, and then an increase in es-IgE between weeks 134 and 160 after pnOIT was discontinued.

Longitudinal changes in diversity, the proportion of unique epitope-specific antibodies present in each sample, estimated through a LMEM, mirrored the results of average es-IgE. While es-IgE diversity increased in the placebo group over time (see Fig

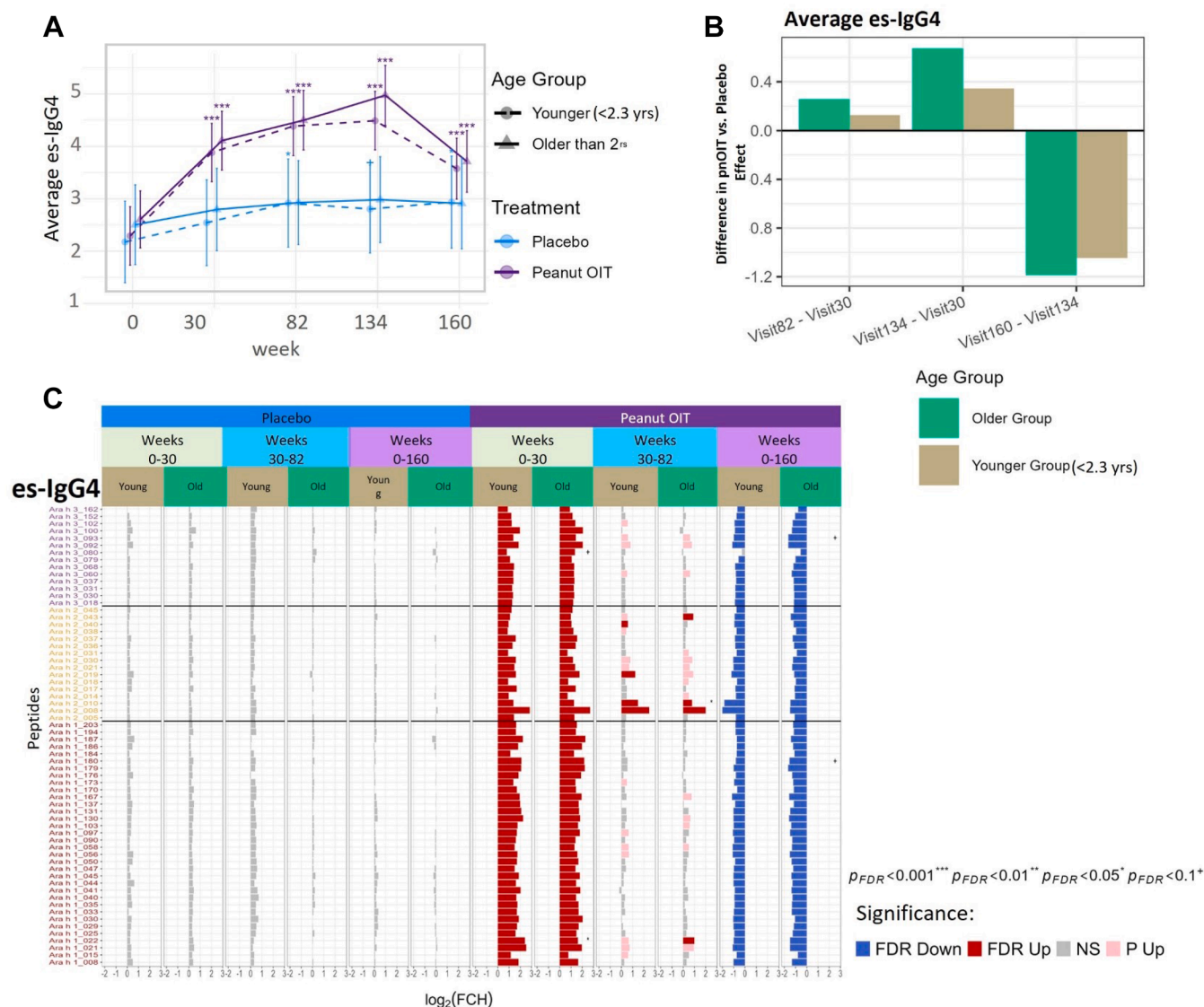


**FIG 3.** Age-stratified es-IgG<sub>4</sub> dynamics over time by treatment. **(A)** Longitudinal trajectories from LMEM, assessing interaction of time  $\times$  treatment  $\times$  age group, for average es-IgG<sub>4</sub> for placebo (blue) and pNOIT (purple), stratified by younger and older participants (dashed lines denote younger participants). Stars above confidence intervals mark within-group changes from baseline (week 0, +  $P_{FDR} < .1$ , \*  $P_{FDR} < .05$ , \*\*  $P_{FDR} < .01$ , \*\*\*  $P_{FDR} < .001$ ). **(B)** Bar plots of differences between pNOIT and placebo relative to week 30 for both younger (<2.3 years) and older (>2.3 years) participants. **(C)** Bar plots illustrating mean FCH (log<sub>2</sub>[FCH], x-axis) at selected weeks in es-IgG<sub>4</sub> derived from LMEM assessing interaction of time  $\times$  treatment  $\times$  age group, shown for placebo (left) and pNOIT (right), stratified by age group. Bar color reflects magnitude of increase based on FDR (dark red or blue) or nominal  $P$  values (light blue, pink, or gray). Black stars denote significant differences between younger and older participants within each treatment arm and at each time-point comparison. Individual peptides appear on y-axis in order of their position across Ara h 1 to Ara h 3 proteins. FCH, Fold change.

E1, A, in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)), there was an overall decrease in es-IgE diversity in the pNOIT group during treatment that was maintained after pNOIT was discontinued.

Mean changes in es-IgE's binding to individual epitopes from baseline to each study visit time point were examined (Fig 1, C and E). The es-IgE expansion occurred in the placebo group for all epitopes throughout the trial. Trajectories for average es-IgE to individual epitopes varied in the pNOIT group: For the majority of epitopes, there was an increase in es-IgE during dose escalation

during weeks 0-30 before a steady decline during maintenance pNOIT (eg, Ara h 1\_030, Ara h 3\_100; see Fig E2, A, in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)). However, there was a different trajectory for 4 epitopes in Ara h 2 (Ara h 2\_008, Ara h 2\_018, Ara h 2\_019, and Ara h 2\_021; Fig 1, E, and see Table E1 in the Online Repository). For these epitopes, there was no initial increase but rather a continuous decline in es-IgE throughout the entire duration of pNOIT (Fig E2, A).

**pNOIT increases es-IgG<sub>4</sub>.** The pNOIT group had a significant increase in average es-IgG<sub>4</sub> during treatment and a decline

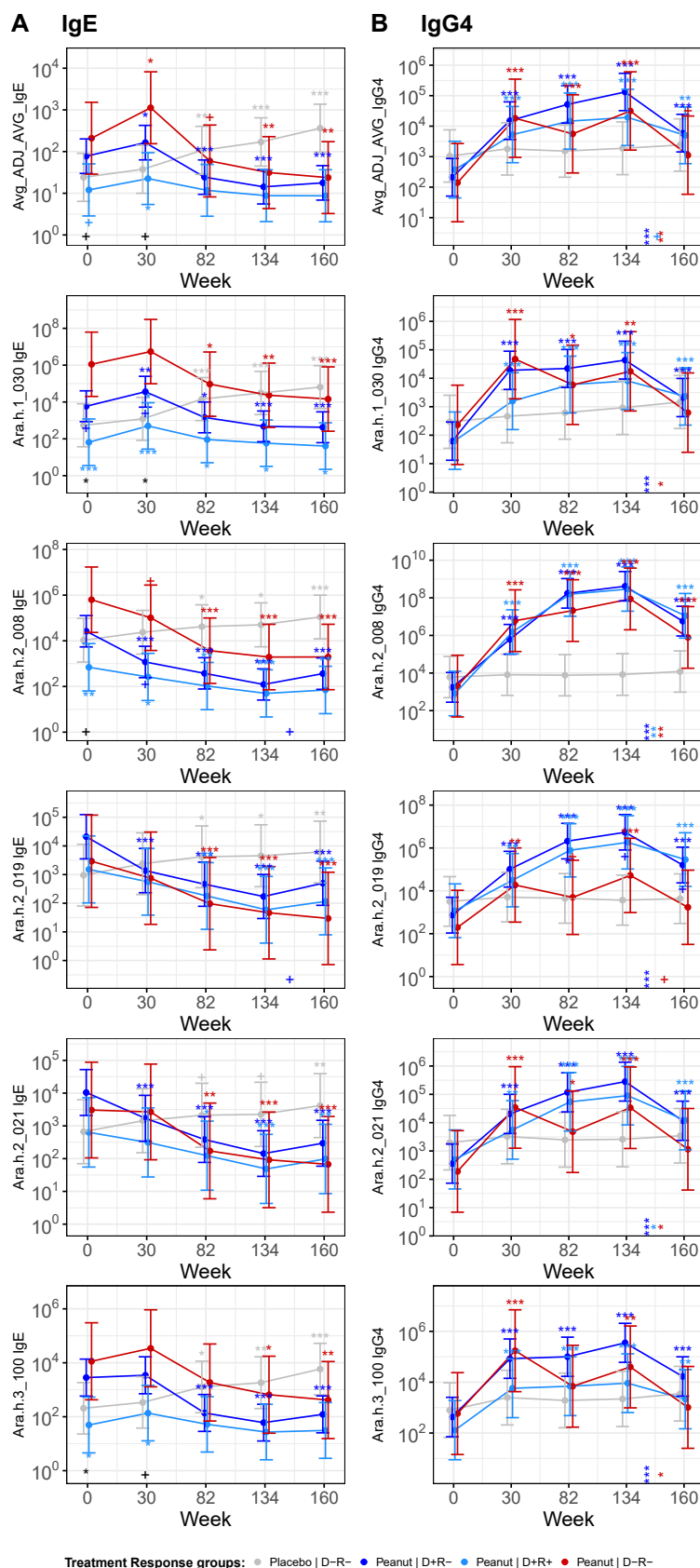


**FIG 4.** Es-IgE and es-IgG<sub>4</sub> trajectories over time by treatment response group. Longitudinal trajectories from LMEMs of treatment response for average es-IgE (left) and es-IgG<sub>4</sub> (right) across epitopes of interest (Ara h 1\_030, Ara h 2\_008, Ara h 2\_019, Ara h 2\_021, and Ara h 3\_100). Stars above confidence intervals indicate

in average es-IgG<sub>4</sub> once treatment was discontinued at week 134 (Fig 1, B). In terms of es-IgG<sub>4</sub> to individual epitopes, es-IgG<sub>4</sub> antibodies were uniformly increased during pNOIT dose escalation (weeks 0-30) compared to placebo (Fig 1, D and F, and Table E1). After dose escalation, the increases in es-IgG<sub>4</sub> slowed such that no significant changes were seen across all epitopes during the maintenance phase of pNOIT (weeks 82-134). Significant decline in es-IgG<sub>4</sub> across all epitopes occurred when pNOIT was discontinued (weeks 134-160). No appreciable changes in es-IgG<sub>4</sub> were seen in the placebo group. Patterns for es-IgG<sub>4</sub> diversity mirrored those of average es-IgG<sub>4</sub> (see Figs E3 and E4 in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)).

### Older children on pNOIT have greater changes in epitope binding profiles compared to younger children

Younger children in the IMPACT cohort (<2.3 years at pNOIT initiation) had lower initial levels in average es-IgE binding to peanut epitopes than the older children (Fig 2, A and B). Overall, older participants had a higher change in individual es-IgE levels compared to younger participants while receiving pNOIT, particularly during dose escalation (weeks 0-30) and the early maintenance phase (weeks 30-82) (Fig 2, C, and Table E1).

Similarly, younger children had lower initial levels and less change in average es-IgG<sub>4</sub> binding to peanut epitopes than older children (Fig 3, A and B), although both groups had increases in es-IgG<sub>4</sub> across individual epitopes during pNOIT. After discontinuation of pNOIT, older children had greater decreases across all es-IgG<sub>4</sub> (Fig 3, C, and Table E1).

### Epitope binding by treatment outcomes

Average es-IgE and es-IgG<sub>4</sub> were compared by treatment outcome (Fig 4; Table E1; and see Figs E4 to E6 in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)). Overall, there were no significant differences in es-IgE trajectories between the D<sup>+</sup>R<sup>+</sup> versus D<sup>+</sup>R<sup>-</sup> groups during pNOIT (Fig 4, A, top). Those who underwent pNOIT but did not experience desensitization (D<sup>-</sup>R<sup>-</sup>) started with higher baseline es-IgE that remained higher throughout the course of the study. For those who experienced desensitization, there was a difference in baseline es-IgE between those who experienced remission versus those who did not. (D<sup>+</sup>R<sup>-</sup> started with higher average es-IgE than D<sup>+</sup>R<sup>+</sup>).

While there were no significant differences in es-IgG<sub>4</sub> trajectories between the D<sup>+</sup>R<sup>+</sup> compared to D<sup>+</sup>R<sup>-</sup> group during pNOIT, a larger decline in es-IgG<sub>4</sub> was observed in the D<sup>+</sup>R<sup>-</sup> group after pNOIT was discontinued (Fig 4, B, top). No significant differences were seen for baseline es-IgG<sub>4</sub> between those who were desensitized (D<sup>+</sup>R<sup>+</sup> and D<sup>+</sup>R<sup>-</sup>) versus those who were

not desensitized (D<sup>-</sup>R<sup>-</sup>). Trajectories of es-IgG<sub>4</sub> were similar across the pNOIT groups, regardless of clinical outcome.

Trajectories of individual es-IgE and es-IgG<sub>4</sub> (Ara h 1\_030, Ara h 2\_008, Ara h 2\_019, Ara h 2\_021, and Ara h 3\_100) were generally similar across treatment outcomes (Fig 4).

### ML/predictive models for pNOIT desensitization and remission

Supervised ML models to predict pNOIT-induced desensitization (at week 134) and remission (at week 160) were developed using IgE epitope binding profiles at baseline (week 0) and weeks 30 and 82 (see Fig E5 in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)).

Table II shows the baseline characteristics stratified by treatment outcome. Of the 64 participants who were desensitized, 56 completed the week 160 DBPCFC, and among them, 18 (32%) experienced remission and were categorized as D<sup>+</sup>R<sup>+</sup>, and 38 were categorized as D<sup>+</sup>R<sup>-</sup>. Those who experienced desensitization and remission (n = 18) were younger (median age, 1.55 years) and had lower peanut IgE, lower SCP IgE, and less IgE diversity compared to those in the D<sup>+</sup>R<sup>-</sup> and D<sup>-</sup>R<sup>-</sup> groups.

### Predictive importance of SCP and epitope profiles

We applied the Boruta algorithm<sup>23</sup> to identify the most important predictors of desensitization and remission among established biomarkers and epitope profiles (Fig 5; see the Methods section in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)). Baseline levels of IgE Ara h 6 were the most important marker for desensitization (Fig 5, A), followed by peanut IgE and Ara h 2 IgE. During OIT dose escalation (weeks 0-30), Ara h 2 IgE was most important for desensitization prediction, and Ara h 3 IgG<sub>4</sub> emerged as important at week 82. For remission, Ara h 2 IgE was a consistently important predictor across all time points (Fig 5, B). Peanut IgE was only an important predictor for remission at baseline.

We also compared the relative contributions of es-IgE and es-IgG<sub>4</sub> for desensitization and remission (Fig 5, C and D). IgE epitopes were significantly ( $P < .001$ , LMEM) more important than IgG<sub>4</sub> in predicting both desensitization and remission. IgG<sub>4</sub> epitopes only played a role at week 134 and so were excluded from the ML models. On the basis of overall feature importance across time points for both desensitization and remission, the ML models considered Ara h 6 IgE, peanut IgE, Ara h 2 IgE, Ara h 3 IgG<sub>4</sub>, and es-IgE epitopes as well as peanut IgG<sub>4</sub>.

### Performance of ML models for pNOIT outcomes

A simulation-based Monte Carlo experiment was conducted to make the best use of the limited trial sample. Within participants

within-group changes relative to baseline (week 0): +  $P_{FDR} < .1$ , \*  $P_{FDR} < .05$ , \*\*  $P_{FDR} < .01$ , \*\*\*  $P_{FDR} < .001$ . Vertical stars between weeks 130 and 160 at bottom indicate within-group changes after treatment discontinuation. Star color corresponds to specific response group: gray indicates placebo (not desensitized (D<sup>-</sup>) and no remission (R<sup>-</sup>); dark blue indicates pNOIT with desensitization (D<sup>+</sup>) but no remission (R<sup>-</sup>); light blue indicates pNOIT with both desensitization (D<sup>+</sup>) and remission (R<sup>+</sup>); and red indicates pNOIT without desensitization (D<sup>-</sup>) and without remission (R<sup>-</sup>). Stars at lower confidence intervals indicate significant differences between not-desensitized/no-remission (D<sup>-</sup>R<sup>-</sup>) group and desensitized groups, both with and without remission (D<sup>+</sup>R<sup>-</sup> and D<sup>+</sup>R<sup>+</sup>). Black stars at bottom indicate significant differences between desensitized groups with and without remission at that time point (D<sup>+</sup>R<sup>+</sup> and D<sup>+</sup>R<sup>-</sup>).

**TABLE II.** Characteristics of pnOIT cohort at study initiation by treatment response

| Characteristic           | pnOIT                         |                               |                               | Placebo                       | P    |
|--------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|------|
|                          | D <sup>+</sup> R <sup>+</sup> | D <sup>+</sup> R <sup>-</sup> | D <sup>-</sup> R <sup>-</sup> | D <sup>-</sup> R <sup>-</sup> |      |
| No. of samples           | 18                            | 38                            | 9                             | 20                            |      |
| Age (years)              | 1.55 [0.95, 2.25]             | 2.35 [1.92, 2.90]             | 2.40 [2.00, 2.40]             | 2.30 [1.68, 2.68]             | .018 |
| Male sex, no. (%)        | 12 (66.7)                     | 27 (71.1)                     | 6 (66.7)                      | 13 (65.0)                     | .966 |
| Peanut SPT wheal         | 13.50 [11.12, 17.88]          | 13.75 [12.00, 17.00]          | 15.00 [12.00, 19.50]          | 12.50 [9.50, 17.50]           | .561 |
| Peanut IgE               | 16.40 [8.92, 46.70]           | 72.80 [38.98, 208.25]         | 76.80 [44.6, 295]             | 36.95 [19.75, 209]            | .002 |
| IgE Ara h 1              | 0.64 [0.16, 3.45]             | 7.30 [1.26, 39.78]            | 16.20 [4.85, 39.80]           | 3.99 [0.45, 17.30]            | .006 |
| IgE Ara h 2              | 12.75 [7.91, 32.12]           | 71.80 [38.38, 86.70]          | 86.70 [43.50, 111]            | 35.40 [14.32, 66.38]          | .001 |
| IgE Ara h 3              | 0.22 [0.06, 0.69]             | 1.05 [0.32, 4.20]             | 4.11 [0.62, 11.00]            | 0.37 [0.14, 1.34]             | .027 |
| IgE Ara h 6              | 14.55 [9.45, 36.08]           | 38.50 [20.95, 62.90]          | 50.60 [27.30, 98.70]          | 25.30 [10.88, 62.58]          | .017 |
| Peanut sIgG <sub>4</sub> | 0.72 [0.11, 2.65]             | 0.49 [0.32, 1.50]             | 0.92 [0.29, 1.23]             | 0.62 [0.36, 2.32]             | .873 |
| IgG <sub>4</sub> Ara h 1 | 0.04 [0.04, 0.16]             | 0.04 [0.04, 0.08]             | 0.04 [0.04, 0.13]             | 0.04 [0.04, 0.21]             | .656 |
| IgG <sub>4</sub> Ara h 2 | 0.26 [0.04, 0.47]             | 0.26 [0.13, 0.40]             | 0.23 [0.11, 0.32]             | 0.17 [0.04, 0.40]             | .985 |
| IgG <sub>4</sub> Ara h 3 | 0.15 [0.06, 0.56]             | 0.14 [0.04, 0.34]             | 0.19 [0.12, 0.41]             | 0.24 [0.09, 1.05]             | .337 |
| IgG <sub>4</sub> Ara h 6 | 0.14 [0.04, 0.52]             | 0.16 [0.05, 0.27]             | 0.19 [0.04, 0.38]             | 0.13 [0.04, 0.37]             | .985 |
| Diversity Ara h 1 IgE    | 0.38 [0.24, 0.50]             | 0.72 [0.37, 0.91]             | 0.71 [0.29, 0.94]             | 0.44 [0.23, 0.71]             | .065 |
| Diversity Ara h 2 IgE    | 0.31 [0.19, 0.50]             | 0.66 [0.44, 0.80]             | 0.75 [0.50, 0.94]             | 0.56 [0.25, 0.69]             | .011 |
| Diversity Ara h 3 IgE    | 0.36 [0.21, 0.48]             | 0.64 [0.38, 1.00]             | 1.00 [0.29, 1.00]             | 0.36 [0.21, 0.75]             | .021 |

Data are presented as medians [IQRs] unless otherwise indicated.  
SPT, Skin prick test.

who had an observed outcome, we addressed class imbalance (minority-class proportions of  $\approx 16\%$  for desensitization and  $\approx 26\%$  for remission) by using resampling. Participants without a determined outcome ( $\approx 18\%$  and  $\approx 27\%$ , respectively) were not included in the corresponding analyses (Table III and Fig E7). The average performance across 100 iterations in training and testing for the best model (selected to maximize AUC) for each time point is presented in Table III, along with selected performance metrics. In a previous report, a logistic regression model that was based on peanut IgE predicted remission with 80.72% AUC.<sup>7</sup> However, those estimates were over all the samples and may be biased; as such, we also obtained performance estimates via the Monte Carlo approach for peanut IgE.

### Predictive models for pnOIT desensitization

At baseline, we found that a model combining peanut IgE, peanut IgG<sub>4</sub>, and SCP markers (Ara h 2 IgE, Ara h 6 IgE, and Ara h 3 IgG<sub>4</sub>) demonstrated an average AUC of 80% in training and 72.7% in testing (Table III). This model showed no loss of sensitivity compared to peanut IgE alone but substantially improved specificity, from an average of 42.0% to 64.1% in the training set (+53.7% improvement) and from 41.8% to 58.3% in the test set (+39.5% improvement). ML models based on es-IgE profiles did not yield more parsimonious algorithms with better performance at baseline.

At week 30, a model that used 5 es-IgE markers (Ara h 1\_056, Ara h 2\_005, Ara h 2\_008, Ara h 2\_019, and Ara h 2\_037) predicted desensitization with an average AUC of 84.9% in the training set and 71.7% in the testing set, improving the specificity of peanut IgE alone by 60.5% on average (Table III). The next-best performing model combined peanut IgE, peanut IgG<sub>4</sub>, and SCP and demonstrated slightly lower performance (average AUC 78.9% in the training set and 70.4% in the testing set).

By week 82, the model that included peanut IgE and 6 es-IgE markers (Ara h 1\_029, Ara h 1\_030, Ara h 1\_035, Ara h 2\_008, Ara h 2\_019, and Ara h 2\_021) achieved AUC of 85% in the training set and 72% in the testing set, significantly outperforming

peanut IgE alone at week 82 (AUC 70.2% in the training set and 67.7% in the testing set; data not shown) and the combined peanut IgE + peanut IgG<sub>4</sub> + SCP model (AUC 81.3% in the training set and 68.9% in the testing set; Table III).

### Predictive models for pnOIT remission

The highest-performing models for predicting remission were based on baseline biomarker profiles (Table III). In contrast to the desensitization models, predictive performance for remission did not improve with the inclusion of postbaseline epitope-specific measurements. In Monte Carlo cross-validation experiments, the peanut IgE + peanut IgG<sub>4</sub> + SCP model achieved a mean AUC of 89.6% in the training set and 84.1% in the test set, whereas the 9 es-IgE marker panel (Ara h 1\_029, Ara h 1\_030, Ara h 1\_041, Ara h 1\_045, Ara h 2\_008, Ara h 2\_018, Ara h 2\_019, Ara h 2\_021, and Ara h 2\_038) demonstrated a mean AUC of 89.4% in the training set and 78.2% in the testing set. Both models demonstrated improved specificity compared to peanut IgE alone, with mean increases of 20 percentage points for peanut IgE + peanut IgG<sub>4</sub> + SCP and 14 percentage points for the 9 es-IgE model. Across all 3 models evaluated, the mean sensitivity was 83.4%. In terms of specificity, the peanut IgE + peanut IgG<sub>4</sub> + SCP model reached 88.3% in training and 84.9% in testing, and the 9 es-IgE model reached 87.2% and 80.7%, respectively. Of note, similar performance could be obtained without including SCP IgE Ara h 6 (see Table E2 in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)).

### Diagnostic models for oral food challenge outcome

We applied a ML pipeline to assess the diagnostic performance of peanut IgE, peanut IgG<sub>4</sub>, SCP, and es-IgE profiles in predicting the outcome of DBPCFCs (week 134 desensitization and week 160 remission challenges). These biomarkers were measured from samples collected at the same time points as the corresponding food challenges. As summarized in Table E2, incorporating peanut IgE alone yielded modest diagnostic performance, characterized

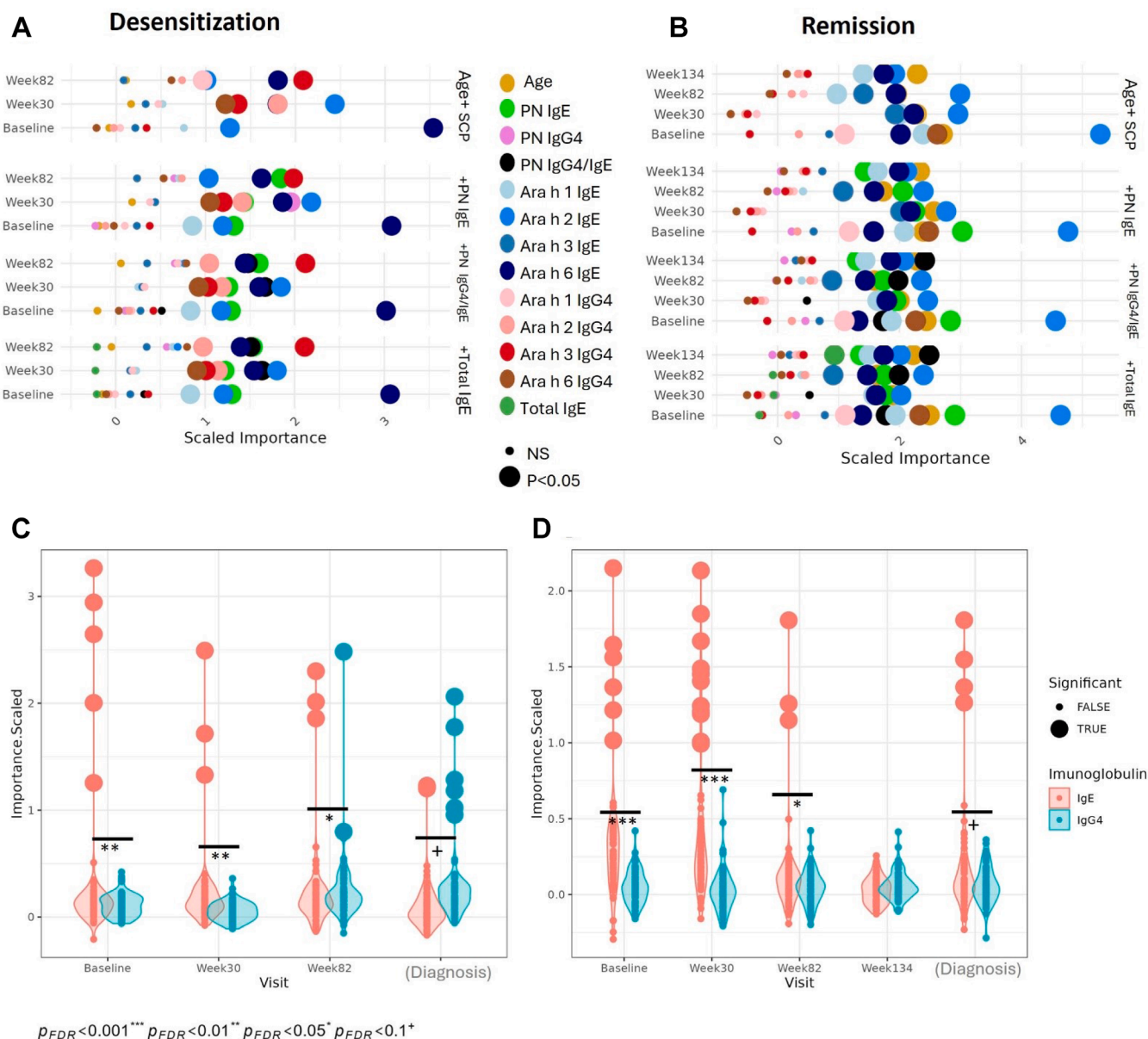


**FIG 5.** Boruta feature importance results across visits. **(A)** Scaled feature importance, based on z score, shown by visit and individual feature for desensitization prediction. At each time point, *larger circles* denote features that reached significance. **(B)** Scaled feature importance, based on z score, shown by visit and individual feature for remission prediction. At each time point, *larger circles* denote features that reached significance. **(C)** Scaled importance of es-IgE and es-IgG4 epitopes for desensitization prediction across visits. Circle size reflects feature importance, with *larger circles* marking features that reached significance at each time point. *Black stars* denote statistically significant differences between IgE and IgG4 epitopes at corresponding time point. **(D)** Scaled feature importance of es-IgE and es-IgG4 epitopes for predicting remission at each time point. Circle size is proportional to importance, with *larger circles* denoting features that reached significance at given visit. *Black stars* indicate significant differences between IgE and IgG4 epitopes at each time point.

by acceptable sensitivity (ie, ~80%) but relatively low specificity in the training and testing sets. However, the addition of peanut IgG<sub>4</sub> and SCP markedly improved diagnostic accuracy, increasing specificity to 85.1% and 83.2% across cross-validation folds in the training and testing sets, while preserving sensitivity at 80.4% in the training set. These gains were obtained by using a compact feature set consisting of only 5 variables and a logistic regression model, emphasizing the efficiency of the approach.

While es-IgE alone performed poorly, combining es-IgE with peanut IgE, peanut IgG<sub>4</sub>, and SCP maintained the overall sensitivity at 80% and increased the overall specificity of this model to 90.8% from 45.5% in es-IgE alone and 85.1% in peanut IgE + peanut IgG<sub>4</sub> + SCP models. Nevertheless, Monte Carlo simulations indicated that this improvement may not be broadly generalizable in external cohorts, as average specificity in the simulations declined slightly (88.9% vs 81.6% in the training and testing sets,

**TABLE III.** Monte Carlo analysis of prediction marker performance for OIT desensitization at week 134 and remission at week 160

| Characteristic                                                                                            | Desensitization (week 134)                          |                                                                                                                                                                                                                 |                                                                                                                                                                                                     |                                                                                                                                                           |                                                                                                                                                                                                           |
|-----------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                           | Baseline                                            | Baseline                                                                                                                                                                                                        | Baseline                                                                                                                                                                                            | Week 30                                                                                                                                                   | Week 30                                                                                                                                                                                                   |
| No. (desensitized/<br>not desensitized)<br>or (remission/<br>no remission)                                | 64/12                                               | 64/12                                                                                                                                                                                                           | 64/12                                                                                                                                                                                               | 65/12*                                                                                                                                                    | 65/12*                                                                                                                                                                                                    |
| Predictors                                                                                                | PN IgE                                              | 5 es-IgE‡                                                                                                                                                                                                       | PN IgE +<br>PN IgG <sub>4</sub> + SCP§                                                                                                                                                              | 5 es-IgE‡                                                                                                                                                 | PN IgE +<br>PN IgG <sub>4</sub> + SCP§                                                                                                                                                                    |
| Monte Carlo<br>performance<br>in training/<br>testing (% change<br>vs PN IgE model<br>at same time point) |                                                     |                                                                                                                                                                                                                 |                                                                                                                                                                                                     |                                                                                                                                                           |                                                                                                                                                                                                           |
| Accuracy                                                                                                  | 74.4/72.7                                           | 79.3/68.8 (6.6/−5.4)                                                                                                                                                                                            | 77.9/74.1 (4.7/1.9)                                                                                                                                                                                 | 79.1/70.2 (0.4/0.1)                                                                                                                                       | 76.9/71.2 (6.4/1.6)                                                                                                                                                                                       |
| AUPRC                                                                                                     | 94.1/93.7                                           | 96.6/89.3 (2.7/−4.7)                                                                                                                                                                                            | 95.4/92.5 (1.4/−1.3)                                                                                                                                                                                | 96.9/93.8 (5.0/2.3)                                                                                                                                       | 94.5/92.3 (2.4/0.7)                                                                                                                                                                                       |
| F1                                                                                                        | 84.1/82.4                                           | 86.7/79.5 (3.1/−3.5)                                                                                                                                                                                            | 86/82.7 (2.3/0.4)                                                                                                                                                                                   | 86.6/80.2 (4.3/−0.9)                                                                                                                                      | 85.4/80.9 (2.9/0)                                                                                                                                                                                         |
| PPV                                                                                                       | 88.1/87.8                                           | 94.1/86.6 (6.8/−1.4)                                                                                                                                                                                            | 92.3/91 (4.8/3.6)                                                                                                                                                                                   | 93.5/88.2 (9.4/3.6)                                                                                                                                       | 90.8/87.9 (6.2/3.3)                                                                                                                                                                                       |
| ROC AUC                                                                                                   | 73.6/72.2                                           | 85.7/60.8 (16.4/−15.8)                                                                                                                                                                                          | 80/72.7 (8.7/0.7)                                                                                                                                                                                   | 84.9/71.7 (27.7/10.8)                                                                                                                                     | 78.9/70.4 (18.6/8.8)                                                                                                                                                                                      |
| Sensitivity                                                                                               | 80.5/78.5                                           | 80.5/74.6 (0/−5)                                                                                                                                                                                                | 80.5/77 (0/−1.9)                                                                                                                                                                                    | 80.7/74.8 (0/−4.1)                                                                                                                                        | 80.7/76.4 (0/−2.1)                                                                                                                                                                                        |
| Specificity                                                                                               | 42/41.8                                             | 73/38.3 (73.8/−8.4)                                                                                                                                                                                             | 64.1/58.3 (52.6/39.5)                                                                                                                                                                               | 71/46.7 (143.2/60.5)                                                                                                                                      | 57.3/44.4 (96.2/52.6)                                                                                                                                                                                     |
| Overall performance                                                                                       |                                                     |                                                                                                                                                                                                                 |                                                                                                                                                                                                     |                                                                                                                                                           |                                                                                                                                                                                                           |
| Accuracy                                                                                                  | 75.0                                                | 0.789                                                                                                                                                                                                           | 78.9                                                                                                                                                                                                | 74.3                                                                                                                                                      | 74.3                                                                                                                                                                                                      |
| AUPRC                                                                                                     | 94.2                                                | 0.96                                                                                                                                                                                                            | 95.3                                                                                                                                                                                                | 95.8                                                                                                                                                      | 94.4                                                                                                                                                                                                      |
| F1                                                                                                        | 84.6                                                | 0.867                                                                                                                                                                                                           | 86.7                                                                                                                                                                                                | 84.0                                                                                                                                                      | 84.0                                                                                                                                                                                                      |
| PPV                                                                                                       | 88.1                                                | 0.929                                                                                                                                                                                                           | 92.9                                                                                                                                                                                                | 87.7                                                                                                                                                      | 87.7                                                                                                                                                                                                      |
| ROC AUC                                                                                                   | 73.8                                                | 0.833                                                                                                                                                                                                           | 79.2                                                                                                                                                                                                | 79.2                                                                                                                                                      | 76.7                                                                                                                                                                                                      |
| Sensitivity                                                                                               | 81.2                                                | 0.812                                                                                                                                                                                                           | 81.2                                                                                                                                                                                                | 80.6                                                                                                                                                      | 80.6                                                                                                                                                                                                      |
| Specificity                                                                                               | 41.7                                                | 0.667                                                                                                                                                                                                           | 66.7                                                                                                                                                                                                | 41.7                                                                                                                                                      | 41.7                                                                                                                                                                                                      |
| Model details (equation)                                                                                  | DS = −2.3798<br>× Peanut IgE<br>− Age; DS < −5.0588 | DS = 0.8495<br>× Ara h 1_029<br>+ 0.1938 × Ara h 1_041<br>− 1.3234 × Ara h 2_005<br>− 0.1982 × Ara h 2_008<br>+ 0.8796 × Ara h 2_019<br>− 0.1910 × Ara h 2_021<br>− 0.9415 × Ara h 2_038<br>− Age; DS < −4.0943 | DS = −0.4828<br>× Peanut IgE<br>+ 0.8951 × Peanut IgG <sub>4</sub><br>+ 0.0169 × SCPIgE<br>Ara h 2 − 0.0409<br>× SCPIgE<br>Ara h 6 + 0.1146<br>× SCPIgG <sub>4</sub> Ara h 3<br>− Age; DS < −4.9233 | DS = −0.1451 × Ara h 1_056<br>− 1.7309 × Ara h 2_005<br>− 1.0112 × Ara h 2_008<br>+ 2.3236 × Ara h 2_019<br>+ 1.3768 × Ara h 2_037<br>− Age; DS < −0.7513 | DS = −1.3348<br>× Peanut IgE<br>+ 1.0715<br>× Peanut IgG <sub>4</sub><br>− 0.0192 × SCPIgE<br>Ara h 2<br>+ 0.0205 × SCPIgE<br>Ara h 6<br>+ 0.3613 × SCPIgG <sub>4</sub><br>Ara h 3 − Age;<br>DS < −3.6135 |

Values represent mean performance across classification metrics. For Monte Carlo study, results reflect averages over 100 iterations of 5-fold cross-validation.

AUPRC, Area under the precision-recall curve; PN, peanut; PPV, positive predictive value.

\*There are more subjects in week 30 because 1 subject was missed at baseline visit.

†There are more subjects in baseline because 2 subjects missed week 82 visit.

‡Ara h 1-056 IgE, Ara h 2-005 IgE, Ara h 2-008 IgE, Ara h 2-019 IgE, Ara h 2-037 IgE.

§SCP: IgE Ara h 2, IgE Ara h 6, and IgG<sub>4</sub> Ara h 3.

¶Ara h 1-029 IgE, Ara h 1-030 IgE, Ara h 1-035 IgE, Ara h 2-008 IgE, Ara h 2-019 IgE, Ara h 2-021 IgE.

||SCP: IgE Ara h 6, and IgG<sub>4</sub> Ara h 3.

#Ara h 1\_029 IgE, Ara h 1\_030 IgE, Ara h 1\_041 IgE, Ara h 1\_045 IgE, Ara h 2\_008 IgE, Ara h 2\_018 IgE, Ara h 2\_019 IgE, Ara h 2\_021 IgE, Ara h 2\_038 IgE.

respectively); there was no clear superiority from the peanut IgE + peanut IgG<sub>4</sub> + SCP model in the testing set (Table E2).

## DISCUSSION

To our knowledge, this is the first study to evaluate epitope-specific binding profiles of children younger than 48 months who underwent pOIT. By mapping these epitope profiles at baseline and over the trajectory of pOIT, we were able to identify the key epitopes associated with the diagnosis of PA and, separately, response to pOIT. We were then able to use a ML approach to develop prediction models of desensitization and remission that were based on these unique epitope profiles.

This cohort of young children with PA enrolled onto the IMPACT trial had a baseline profile similar to the children in the

LEAP trial who developed PA early in life.<sup>19</sup> Young children in LEAP with early persistent PA had significantly greater es-IgE to Ara h 2\_008, Ara h 2\_019, and Ara h 2\_021, which are also prominent epitopes in this IMPACT cohort. Children in the IMPACT placebo group had a similar epitope progression as the LEAP avoider group, with significant increases in es-IgE over time and minimal changes in es-IgG<sub>4</sub>.<sup>19</sup>

Further, the trajectory of peanut-specific IgE and IgG<sub>4</sub> over the course of pOIT was consistent with findings from other pOIT studies.<sup>5,6</sup> The IMPACT participants who underwent pOIT had a general decline of peanut-specific IgE and expansion of peanut-specific IgG<sub>4</sub> over the course of treatment. As with the epitope analyses from the POISED trial,<sup>18</sup> the IMPACT cohort had similar broad suppression of IgE, with an overall decrease in es-IgE binding and diversity that continued through the maintenance phase.

| Desensitization (week 134)                                                                                                                                                                                  |                                                                                                                                                      | Remission (week 160)                                   |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Week 82                                                                                                                                                                                                     | Week 82                                                                                                                                              | Baseline                                               | Baseline                                                                                                                                                                                   | Baseline                                                                                                                                                                                                                                                         |
| 62/12†                                                                                                                                                                                                      | 62/12†                                                                                                                                               | 18/50                                                  | 18/50                                                                                                                                                                                      | 18/50                                                                                                                                                                                                                                                            |
| PN IgE + 6 es-IgE¶                                                                                                                                                                                          | PN IgE + PN IgG <sub>4</sub> + SCP                                                                                                                   | PN IgE                                                 | PN IgE + PN IgG <sub>4</sub> + SCP§                                                                                                                                                        | 9 es-IgE#                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                             |                                                                                                                                                      |                                                        |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                  |
| 79.8/71.1 (7.1/−1.8)                                                                                                                                                                                        | 77.3/70.4 (3.8/−2.8)                                                                                                                                 | 74.7/72.8                                              | 87/81.2 (16.5/11.5)                                                                                                                                                                        | 86.2/76.8 (15.4/5.5)                                                                                                                                                                                                                                             |
| 97.1/93.9 (4.1/1.5)                                                                                                                                                                                         | 96.2/93.1 (3.1/0.6)                                                                                                                                  | 70.1/72.1                                              | 76/68.4 (8.4/−5.1)                                                                                                                                                                         | 74.3/59.4 (6/−17.6)                                                                                                                                                                                                                                              |
| 87/80.8 (3.4/−1.7)                                                                                                                                                                                          | 85.6/80.5 (1.8/−2.1)                                                                                                                                 | 64.9/59.6                                              | 77.7/65.3 (19.7/9.6)                                                                                                                                                                       | 76.4/57.9 (17.7/−2.9)                                                                                                                                                                                                                                            |
| 94.5/88.7 (7.4/1.4)                                                                                                                                                                                         | 91.3/87.4 (3.8/−0.1)                                                                                                                                 | 54.7/52.9                                              | 73.8/66.9 (34.9/26.5)                                                                                                                                                                      | 71.1/55.9 (30/5.7)                                                                                                                                                                                                                                               |
| 85/72 (21.1/6.4)                                                                                                                                                                                            | 81.3/68.9 (15.8/1.8)                                                                                                                                 | 85.4/84                                                | 89.6/84.1 (4.9/−0.1)                                                                                                                                                                       | 89.4/78.2 (4.7/−7.1)                                                                                                                                                                                                                                             |
| 80.7/75.5 (0/−3.7)                                                                                                                                                                                          | 80.7/76 (0/−3.1)                                                                                                                                     | 83.4/77.5                                              | 83.4/70.2 (0/−9.4)                                                                                                                                                                         | 83.4/65.3 (0/−15.7)                                                                                                                                                                                                                                              |
| 75.3/47.8 (75.9/15.7)                                                                                                                                                                                       | 60/40.6 (40.2/−1.7)                                                                                                                                  | 71.7/70.8                                              | 88.3/84.9 (23.2/19.9)                                                                                                                                                                      | 87.2/80.7 (21.6/14)                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                             |                                                                                                                                                      |                                                        |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                  |
| 79.7                                                                                                                                                                                                        | 78.4                                                                                                                                                 | 69.1                                                   | 85.3                                                                                                                                                                                       | 88.2                                                                                                                                                                                                                                                             |
| 97.0                                                                                                                                                                                                        | 96.1                                                                                                                                                 | 70.5                                                   | 72.2                                                                                                                                                                                       | 71.2                                                                                                                                                                                                                                                             |
| 87.0                                                                                                                                                                                                        | 86.2                                                                                                                                                 | 58.8                                                   | 75.0                                                                                                                                                                                       | 78.9                                                                                                                                                                                                                                                             |
| 94.3                                                                                                                                                                                                        | 92.6                                                                                                                                                 | 45.5                                                   | 68.2                                                                                                                                                                                       | 75.0                                                                                                                                                                                                                                                             |
| 84.3                                                                                                                                                                                                        | 80.4                                                                                                                                                 | 85.4                                                   | 89.4                                                                                                                                                                                       | 88.2                                                                                                                                                                                                                                                             |
| 80.6                                                                                                                                                                                                        | 80.6                                                                                                                                                 | 83.3                                                   | 83.3                                                                                                                                                                                       | 83.3                                                                                                                                                                                                                                                             |
| 75.0                                                                                                                                                                                                        | 66.7                                                                                                                                                 | 64.0                                                   | 86.0                                                                                                                                                                                       | 90.0                                                                                                                                                                                                                                                             |
| DS = 0.6390 × Ara h 1_029<br>+ 0.2713 × Ara h 1_030<br>− 1.3676 × Ara h 1_035<br>− 1.1209 × Ara h 2_008<br>+ 4.5133 × Ara h 2_019<br>− 0.6259 × Ara h 2_021<br>− 3.3370 × Peanut IgE<br>− Age; DS < −4.8852 | DS = −1.5196 × Peanut IgE<br>+ 0.8275 × SCPIgE Ara h 2<br>+ 0.1723 × SCPIgE Ara h 6<br>+ 2.5138 × SCPIgG <sub>4</sub><br>Ara h 3 − Age; DS < −4.8870 | DS = −2.0147<br>× Peanut IgE<br>− Age;<br>RS < −4.2070 | DS = −0.8243 × Peanut IgE<br>+ 0.5471 × Peanut IgG <sub>4</sub><br>− 0.0308 × SCPIgE Ara h 2<br>+ 0.0143 × SCPIgE Ara h 6<br>+ 0.1150 × SCPIgG <sub>4</sub><br>Ara h 3 − Age; RS < −4.1734 | DS = 0.3605 × Ara h 1_029<br>− 0.5098 × Ara h 1_030<br>− 0.6255 × Ara h 1_041<br>+ 0.4094 × Ara h 1_045<br>− 0.1899 × Ara h 2_008<br>− 0.4189 × Ara h 2_018<br>+ 0.4384 × Ara h 2_019<br>− 0.3419 × Ara h 2_021<br>− 0.2889 × Ara h 2_038<br>− Age; RS < −2.9195 |

Differences in epitope binding by treatment outcome were observed. Younger participants had lower es-IgE at baseline compared to older participants, but baseline es-IgG<sub>4</sub> was similar between the age groups. Overall, older participants had larger changes in es-IgE and es-IgG<sub>4</sub> compared to younger participants while receiving pNOIT. In terms of treatment outcomes, participants who experienced desensitization started with lower average es-IgE compared to pNOIT treatment participants who did not experience desensitization. Among those desensitized, average es-IgE level at baseline was lower for participants who experienced remission compared to those who did not. After discontinuation of pNOIT, the no-remission group (D<sup>+</sup>R<sup>−</sup>) had an increase in es-IgE and a more significant decrease in es-IgG<sub>4</sub> compared to the D<sup>+</sup>R<sup>+</sup> group. These baseline differences are consistent with previous work demonstrating younger

age and lower baseline IgE are favorable predictors of pNOIT effect.

Notably, the longitudinal trajectory of IgE to individual peanut epitopes during OIT is not uniform, and a few informative epitopes have consistent fold change decreases throughout the OIT process, without an initial increase. Specifically, IgE binding to epitopes Ara h 2\_008, Ara h 2\_018, Ara h 2\_019, and Ara h 2\_021 had the largest decrease with pNOIT. These informative epitopes were also noted to be some of the epitopes that had the greatest increase in es-IgE after the first year of life for children avoiding peanut who became peanut allergic in the LEAP cohort<sup>19</sup> and have been shown to be highly correlated with PA,<sup>16,18</sup> suggesting that they are important drivers of symptomatic PA. In the recent analysis of the LEAP cohort, those who developed PA early (both persistent and resolving) had more binding

es-IgE to Ara h 1\_041,<sup>24</sup> and this epitope was noted to be a key predictive feature in the ML model for predicting remission to pnOIT in IMPACT. This suggests that peanut proteins other than Ara h 2 deserve further exploration.

These epitopes may not only be key drivers in the immunopathophysiology of PA but may also be potential targets for therapeutics and useful biomarkers to monitor response to treatments. These informative IgE epitopes (Ara h 2\_008, Ara h 2\_019, and Ara h 2\_021), along with a few other epitopes in Ara h 1, were identified as important predictive features in the ML models for predicting desensitization and remission, particularly when measured during maintenance pnOIT (here, at week 82 of therapy). Similar results have been seen in older children and adults in the POISED pnOIT trial.<sup>18</sup> ML models that used baseline epitopes (week 0) to predict remission in both POISED and IMPACT cohorts identified Ara h 2\_008 as a key epitope. Keswani et al<sup>25</sup> reported that neutralizing IgG<sub>4</sub> to conformational epitopes masking the region around Ara h 2\_008 is found in patients who experienced remission with pnOIT, further supporting the hypothesis that this is not only a critical region correlating with PA<sup>19</sup> but also predictive of optimal treatment outcomes, as demonstrated previously for POISED<sup>18</sup> and now in the IMPACT trial. It is interesting to note that IgG<sub>4</sub> binding to linear epitopes does not seem to play a role in pnOIT treatment response, as no IgG<sub>4</sub> epitopes were identified as features predictive of pnOIT outcome in IMPACT.

ML was used to assess the diagnostic performance of peanut IgE, peanut IgG<sub>4</sub>, Ara h 1, 2, and 3 IgE and IgG<sub>4</sub>, and es-IgE profiles in predicting the outcome of desensitization and remission challenges. Models that used epitope profiles alone or in combination with the other parameters did not have clear superiority over the models that did not include epitopes, which is in contrast to previously published data.<sup>16</sup> This is likely because the previously published study<sup>16</sup> used pooled data from diagnostic food challenges (participants in LEAP and CoFAR2 did not receive therapeutic interventions, and POISED data included only baseline challenges) whereas in this study, desensitization and remission food challenge data were used. These results suggest that prediction models for posttherapy food challenge results may need to be developed independently from diagnostic food challenges.

Limitations of our study include a small sample size and the lack of demographic variability, as well as the lack of a validation set for our ML analysis. Models had consistent performance on training and testing across metrics for the two groups of models—desensitization/remission and diagnostic models—but there was a consistent drop in specificity from training to testing at different time points for the desensitization/remission models. The diagnostic model included more samples but also may not be broadly generalizable in external cohorts, as average specificity in the simulations declined slightly. Larger-scale studies using independent cohorts of peanut-allergic patients are needed to validate our models.

Our findings demonstrate that the dynamic changes in peanut-specific epitopes in young children receiving OIT provide predictive insight into desensitization outcomes and clinically relevant biomarkers for monitoring treatment response. ML approaches allowed the use of only a few key epitopes (ie, Ara h 2\_008, Ara h 2\_019, Ara h 2\_021, and Ara h 1\_041), along with age, to predict OIT outcomes with high accuracy. Future work is needed to determine if these epitopes may represent novel therapeutic targets for intervention and to validate these observations in larger, independent cohorts.

## DISCLOSURE STATEMENT

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**Clinical implication: Baseline es-IgE profiles predict remission in young children undergoing pnOIT and may help identify those most likely to benefit, though performance is comparable to standard peanut testing.**

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