TABLE I. Impact of including nonreactor patients when evaluating the diagnostic utility of different biomarkers to predicting the occurrence of life-threatening reactions to peanut in the LEAP and Peanut Allergy Sensitization studies

Parameter	Diagnostic cutoff		AUC	Sensitivity (%)	Specificity (%)	LR
BAT (% CD63 basophils)	48	Incl nonreactors	0.98	100 (100-100)	97 (95-98)	33.3
		Reactors only	**0.88**	**100 (76-100)**	**75 (64 to 0.84)**	**4**
IgE to Ara h 2	1.4 kU/L	Incl nonreactors	0.98	100 (100-100)	93 (91-98)	14.3
		Reactors only	**0.83**	**100 (73-100)**	**46 (32-60)**	**1.8**
IgE to peanut	5 kU/L	Incl nonreactors	0.98	100 (100-100)	90 (87-98)	10
		Reactors only	**0.86**	**100 (76-100)**	**53 (41-64)**	**2.1**
Peanut SPT	8mm	Incl nonreactors	0.96	100 (100-100)	92 (89-94)	12.5
		Reactors only	**0.66**	**100 (76 to 100)**	**34 (24-46)**	**1.5**

AUC, Area under the receiver operating characteristic curve; *Incl*, including; *LR*, likelihood ratio; *SPT*, skin prick test.
Diagnostic cutoffs as reported by Santos et al.[1]

lowered the likelihood ratio from 33 to 4 (a "good" likelihood ratio is typically quoted as ≥10).

In summary, the model used by Santos et al[1] may be predictive of life-threatening reactions in children aged 5 to 6 years whose peanut allergy status is *unknown* - and in whom the vast majority - 86% in the combined cohort of Santos et al - are *not* allergic to peanut. However, the more common clinical scenario is one in which clinicians wish to predict the risk of reaction in patients with *known* allergy or at least with IgE-sensitization to peanut. For this analysis, one must exclude nonreactors, as the research question is whether these tests predict severity rather than clinical reactivity. Unfortunately, others have also undertaken similar misleading analyses (including nonreactors as "nonsevere" reactors), resulting in a similar overestimation of predictive utility.[3] Notably, although IgE to Ara h 2 had better diagnostic utility in differentiating individuals with true peanut allergy from those with asymptomatic sensitization,[1] among patients with true peanut allergy it was not significantly better than specific IgE to (whole) peanut at predicting severity, which is consistent with other reports.[2,4]

We therefore urge caution when extrapolating the data presented in this and other reports[1,3] to clinical practice. Individuals with peanut allergy and a history of anaphylaxis do tend to have higher levels of IgE sensitization than those without[2] peanut allergy; however, the overlap is so extensive that in practice, these biomarkers are not helpful in predicting life-threatening allergic reactions. The risk is that patients with low levels of specific IgE might be falsely reassured that they cannot have anaphylaxis, whereas those with high levels are wrongly counseled that they are at high risk of severe reactions. More work is needed to address this very significant knowledge gap, as was recently acknowledged in an expert consensus report.[5]

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Reply

To the Editor:

The risk of severe allergic reactions from accidental exposure to peanut and during double-blind placebo-controlled food challenge (DBPCFC) has motivated the search for biomarkers able to reduce the need for DBPCFC and to be prognostic of risk. Turner and Custovic[1] raise several points about our findings on biomarkers of the severity of allergic reactions during peanut challenges, which were previously published in the *Journal of Allergy and Clinical Immunology.*[2] First, Turner and Custovic[1] state that our findings contrast with those of most published studies; however, there is currently no consensus regarding the role of the skin prick test and level of specific IgE to peanut and to Ara h 2 in predicting severe reactions. Similar numbers of reports show them as predictive and not predictive, and this has been recently reviewed.[3,4] Second, Turner and Custovic[1] question whether our analysis population properly reflected our research question and suggested that only subjects with peanut allergy be included in the analysis. We would like to highlight that the statistical methodology that we implemented reflects the *continuum* ranging from no reaction to death and allows us to provide probability estimates of our 3 observed categories of interest (no reaction, moderate reaction, and severe reaction) in a single model. Although we do include nonreactors in our analyses, the model provides probability estimates directly comparing moderate reactors with severe reactors. Probability estimates have previously been argued to be more suitable for clinical risk assessment in other areas of medicine,[5] and they can inform decisions regarding the likelihood of peanut allergy and the risk of severe allergic reactions.

TABLE I. Optimal cutoffs and diagnostic performance metrics to classify subjects at high risk of developing severe allergic reactions during oral peanut challenge when only reactors are considered

Parameter	BAT (% $CD63^+$ basophils)	Ara h 2–specific IgE level (kU/L)	Peanut-specific IgE level (kU/L)	Peanut SPT result (mm)
AUC	0.88 (0.80-0.96)	0.83 (0.71-0.96)	0.86 (0.76-0.95)	0.66 (0.50-0.81)
Threshold	48	4.2	22	8
Sensitivity	100 (92-100)	90 (60-90)	92 (75-92)	100 (42-100)
Specificity	75 (65-76)	67 (46-73)	74 (51-75)	34 (24-37)
PPV	41 (33-43)	30 (23-35)	38 (27-39)	21 (19-22)
NPV	100 (98-100)	98 (94-98)	98 (95-98)	100 (90-100)
Positive LR	4.00	2.70	3.46	1.51
Negative LR	0.00	0.15	0.11	0.00

Ara h 2, *Archis hypogaea* 2; *NPV*, negative predictive value; *PPV*, positive predictive value; *SPT*, skin prick test.

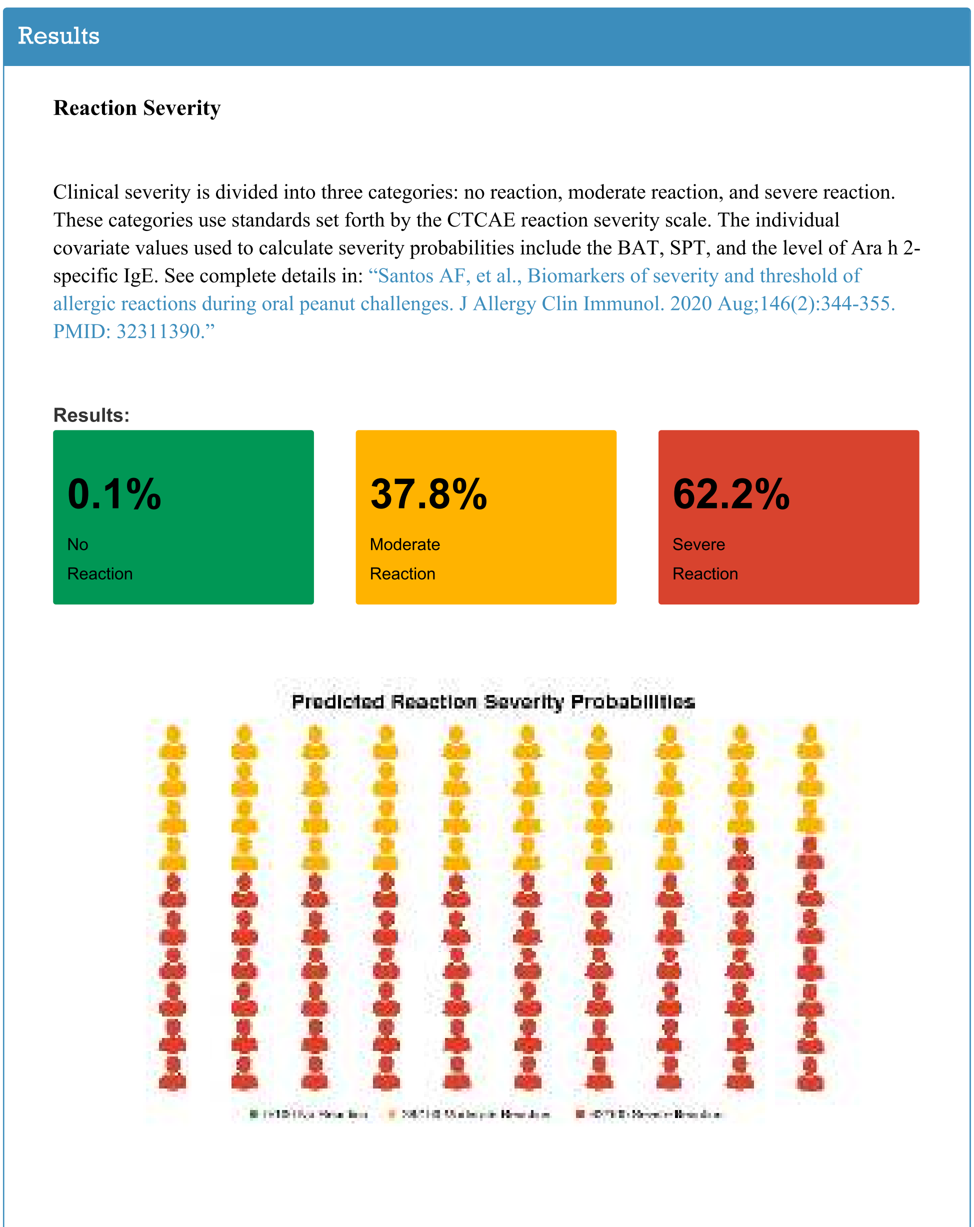

FIG 1. Example of model predictions from a child with a skin prick test (SPT) result of 13 mm, a BAT result of 86% $CD63^+$ basophils, and an *Arachis hypogaea* 2 (Ara h 2)-specific IgE level of 119 kU/L. The predicted probabilities for no reaction, a moderate reaction, and a severe reaction were obtained by using the online tool available to health care professionals at https://benaroyaresearch.shinyapps.io/peanutallergytool/.

Even if one were to have used a binary model focusing on those children with confirmed peanut allergy, which is the approach suggested by Turner and Custovic,[1] new optimal diagnostic thresholds would need to have been derived using this smaller data set. Instead, Turner and Custovic[1] applied the optimal cutoff that we had generated from the complete data set. If one considers that the ideal study population for assessment of severity is the reactors, one needs to define cutoffs specific for this population. We have done this and present these new results in Table I. When this approach is used, the areas under the receiver operating characteristic curves are still impressively large for the various tests (except for the skin prick test), and we can still differentiate all children with severe reactions with 100% sensitivity by using the basophil activation test (BAT) despite the loss in specificity. Turner and Custovic[1] comment that by including the entire cohort in our analysis we may have overestimated the specificity for severity. The inclusion of nonreactors does provide higher specificity because of more cases of true negatives (TNs) (ie, Specificity = TNs/(TNs + False positives [FPs])). However, we would argue that sensitivity (True positives [TPs]/(TPs + False negatives [FNs])) is the more germane metric in this scenario. Specificity does not consider FNs in its calculation, whereas sensitivity does. We believe the FN rate to be a more important metric to consider relative to the FP rate. Specifically, falsely predicting the absence of risk of a severe reaction could give a false sense of security, whereas FPs ostensibly cause less harm by increasing the motivation to adhere to the advised risk mitigation strategies. Similarly, Turner and Custovic[1] claim that our chosen analysis cohort decreases the positive likelihood ratio (LR) to a value that is below 10 or the "good" designation of a biomarker. We believe that this threshold of 10 is subjective and *circumstantial*; nevertheless, a positive LR can decrease for 2 reasons, namely, because of a decrease in either sensitivity or specificity (Positive LR = Sensitivity/(1 – Specificity)). In our case, sensitivity is held constant at 100% between the analysis populations, whereas specificity drops to 75% with use of the restricted binary analysis that we have argued against. Nevertheless, in this restricted binary model, the decrease in positive LR results from a decrease in specificity, which is the metric that is less important in predicting severity of allergic reactions.

We believe, however, that rather than the binary yes/no classification, a more appropriate risk assessment would be probability estimates from a multivariable ordinal logistic regression model utilizing the entire study population. Such a model moves beyond simple binary classifications from individual predictors and toward more granular and precise predictions. To facilitate risk assessment in the clinic by using this statistical methodology, we have created an online web-based application (which can be found at the hyperlink https://benaroyaresearch.shinyapps.io/peanutallergytool/).[6] The integration of multiple biomarkers allows probabilities to be given for each category, as shown in Fig 1. The model output illustrates how the algorithm can be used to identify those subjects who are very likely to have peanut allergy, should not undergo DBPCFC, and should carry adrenaline autoinjectors while implementing risk mitigation strategies to stringently avoid accidental exposure to peanut. Such patients could arguably also be considered as more appropriate for allergen-specific immunotherapy.

In summary, we have demonstrated that a variety of biomarkers, especially the BAT, can be useful in predicting severity of reactions. We would encourage prospective studies using the BAT and these other markers to test this predictive model.

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Epithelial repair in asthma: Defect or exaggerated?

To the Editor:

The epithelial cell culture study by Jin et al[1] examining IL-13–induced effects on closure of denuded areas features defect repair in asthma and reinforces the notion of a defective bronchial-epithelial barrier in asthma.[2,3] Reflecting the low priority and low availability of exploratory research using physiologically well-controlled and airway-specific *in vivo* methods, bench biology data have dominated this research field for decades.[1-3] Hence, it seems timely to ask whether bedside observations and *in vivo* studies in human disease–like conditions fully support the notion of epithelial defect repair in asthma.

Consistent with hundreds of Creola bodies in the sputum,[4,5] epithelial loss in asthma and preasthma, may be extensive and patchy (requiring whole mount histology preparations for proper detection).[5] If epithelial loss were associated with defect repair,