Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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allergenis

ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
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This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.

- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate $\geq$ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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Treatable traits in the European U-BIOPRED adult asthma cohorts

To the Editor,

Improvements in asthma outcomes have stalled over the past decade,[1] which may be attributed to treating patients on the basis of a generic diagnostic label. The taxonomy "Treatable Traits" was proposed by Agusti et al (2016) as a precision medicine approach for the diagnosis and management of chronic airway diseases that is based on the identification of genetic, phenotypic and psychosocial characteristics for which therapeutic interventions are known to improve respiratory health.[2] The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project was set up to identify multidimensional phenotypes and endotypes in severe asthma.[3] Here, we aim to identify and quantify treatable traits within the severe and mild/moderate U-BIOPRED adult asthma cohorts[3] and across previously identified phenotypes.[4] We hypothesize that treatable traits will be more common in severe asthma and vary significantly across asthma phenotypes.

Data from the severe asthma and mild/moderate asthma cohorts of the U-BIOPRED project were included in this study. Full details of the study population and methodology have been presented elsewhere.[3] Criteria for treatable traits were based on Agusti et al[2] and presented in Table 1. Chi-squared tests were used to examine differences in the prevalence of each treatable trait between groups and independent sample t tests used to determine differences in the total number of traits between cohorts. No adjustment for multiple testing was applied as the analyses were considered exploratory; as this may inflate the type-1 error rate, individual *P* values are presented for each comparison. A post hoc power calculation shows our sample of 421 (severe smoking/ex-smoking vs severe nonsmoking) and 399 (severe nonsmoking vs mild/moderate) is sufficient to identify a difference in treatable trait prevalence between cohorts with a medium effect size (0.3) and a power close to 1.00. Data analysis was supported by IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA, with significance set at $P < 0.05$, unless otherwise stated.

1 | PREVALENCE OF TREATABLE TRAITS

Twenty-three treatable traits were identified, including seven pulmonary, 11 extra-pulmonary and five behavioural/psychosocial treatable traits (Table 2). Seven out of the ten most prevalent traits in severe asthma were classed as pulmonary treatable traits. The most prevalent extra-pulmonary traits were as follows: atopy, rhinosinusitis, obesity, reflux and obstructive sleep apnoea. Poor adherence to medication, anxiety and depression were the most common behavioural/psychosocial treatable traits in severe asthma.

2 | DIFFERENCES IN TREATABLE TRAITS ACROSS ASTHMA COHORTS

The severe smoking/ex-smoking asthma cohort displayed on average one more treatable trait than the severe nonsmoking asthma cohort (8 ± 3 vs 7 ± 2, $P = 0.007$). Differences in the prevalence of individual traits, all higher in the smoking/ex-smoking cohort, were seen in bronchodilator reversibility, fixed airflow limitation ($P = 0.050$), reflux, cardiovascular disease and psychiatric disease. Only atopy was higher in prevalence in the nonsmoking cohort.

Nonsmoking individuals with severe asthma have more treatable traits than nonsmoking individuals with mild/moderate asthma (7 ± 2 vs 5 ± 2, $P < 0.001$). Likewise, individual treatable traits were generally more common in nonsmoking severe asthma compared to the mild/moderate asthma cohort. Only in atopy and poor medication adherence was the prevalence of the treatable trait significantly higher in mild/moderate asthma. The prevalence of treatable traits across previously identified clusters[4] is presented and discussed on the Appendix S1.

3 | DISCUSSION

The identification of treatable traits facilitates a precision medicine strategy for the management of airways disease, that is free from the traditional diagnostic labels and based on the identification of pulmonary, extra-pulmonary and psychosocial characteristics, for which there are evidence-based therapeutic choices. This proposal was recently supported by the *Lancet* commission "After asthma: redefining airways disease"[5] and was a favoured strategy to move the field towards precision medicine at a research seminar, held at the European Respiratory Society's annual meeting.[6] Ours is the first study to apply the concept to a large asthma cohort, and we have identified a plethora of pulmonary, extra-pulmonary and behavioural / psychosocial treatable traits. The prevalence of treatable traits, both pulmonary and nonpulmonary, was generally higher in individuals with severe asthma compared to mild/moderate asthma. We also identified a difference in the prevalence of pulmonary treatable traits across clinical clusters of patients. Approximately 5%-10% of asthmatics remain poorly controlled, despite being prescribed the

TABLE 1 Treatable traits and defining criteria

Treatable trait category	Treatable trait	Defining criteria
Pulmonary	Fixed airflow limitation	Postbronchodilator FEV_1/FVC < 0.7
	Bronchodilator reversibility	Postbronchodilator increase in FEV_1 AND/OR FVC ≥12% AND ≥200 ml
	Type 2 inflammation	Sputum eosinophil count ≥ 2% AND/OR blood eosinophils ≥ 450 cells per ul AND/OR FeNO > 50 ppb
	Neutrophilic inflammation	Sputum neutrophil count > 60%
	Cough	Asthma Quality of Life Questionnaire (AQLQ) Question 12 score ≤ 4 AND/OR Sino-Nasal Outcomes Test (SNOT-20) Question score 4 ≥ 3
	Exercise-induced respiratory symptoms	Medical history finding of “routine physical activity and/or physical exercise as asthma trigger”
	Bronchitis	Medical history finding of “Current AND/OR chronic bronchitis”
Extra-pulmonary	Rhinosinusitis	Medical history finding of “Allergic/Non-allergic rhinitis active AND/OR sinusitis active”
	Nasal polyps	Medical history finding of “Nasal polyps active”
	Obese	BMI > 30
	Underweight	BMI < 18.5
	Obstructive sleep apnoea	Epworth sleepiness scale score ≥ 11
	Reflux	Medical history finding of “Reflux active”
	Vocal cord dysfunction	Medical history finding of “Vocal Cord Dysfunction active”
	Osteoporosis	Medical history finding of “Osteoporosis active”
	Cardiovascular disease	Medical history finding of “Coronary disease active”
	Eczema	Medical history finding of “Eczema active”
	Atopic	Positive skin prick test AND/OR blood IgE result
Behavioural/psychosocial	Smoking	Medical history finding of “Current smoker”
	Poor medication adherence	Medication Adherence Rating Scale (MARS) mean score <4.5
	Psychiatric disease	Medical history finding of “Psychiatric disease active”
	Depression	Hospital Anxiety and Depression (HADS) depression domain score ≥ 11
	Anxiety	Hospital Anxiety and Depression (HADS) anxiety domain score ≥ 11

Treatable traits presented here are based on that of Agusti et al.[2] BMI, body mass index; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

maximum dose of therapy.[7] Our data suggest individuals with severe asthma, who remain symptomatic despite receiving a high dose ICS, display on average seven treatable traits, and therefore present multiple treatment opportunities beyond the traditional stepwise approach.

Perhaps unsurprisingly, pulmonary traits accounted for seven of the ten most prevalent treatable traits in our asthma cohorts and were generally more common in severe asthma. Interestingly, however, we also observed an increased prevalence of extra-pulmonary and behavioural/psychosocial traits in severe asthma suggesting an association with asthma severity, which may reflect the impact of living with severe chronic respiratory conditions. Our data highlight that multiple treatment opportunities exist beyond the pulmonary system, and a holistic management strategy, such as the treatable trait approach, may be beneficial to both physical and mental well-being.

This is the first study to apply the concept of treatable traits to a large asthma cohort. Several limitations are worthy of discussion; firstly, we utilized the original paper on treatable traits,[2] treatment guidelines and clinical experience to determine the classification criteria for our treatable traits. We acknowledge that our list of traits is not exhaustive and that the selected criteria for some traits could be contentious. Prospective studies would benefit from additional paraclinical investigations to determine the prevalence of additional treatable traits, for example ventilation heterogeneity and small airway disease. Finally, we acknowledge that some traits may not be mutually exclusive and some maybe modified by asthma treatment. Associations between traits were not explored here but have been discussed elsewhere.[8]

In conclusion, the label-free, precision medicine approach provided by the treatable traits construct allowed for the identification of multiple treatment opportunities for patients with asthma, beyond the traditional stepwise approach. We eagerly await the results of prospective, longitudinal, clinical trials to determine whether this translates to improved clinical outcomes for individuals with respiratory disease.

TABLE 2 Frequency of treatable traits in severe and mild/moderate asthma, ordered by trait category and then trait frequency in severe asthma cohort

Trait category	Treatable trait	Severe asthma (combined)	Severe smoking/ex-smoking asthma	Severe nonsmoking asthma	Mild/moderate nonsmoking asthma	Severe smoking/ex-smoking vs severe nonsmoking asthma	Mild/moderate vs severe nonsmoking
	Subjects, n	421	110	311	88		
Pulmonary	Exercise-induced respiratory symptoms, n (%)	352/421 (84)	91/110 (83)	261/311 (84)	56/88 (64)	$P = 0.085$	$P < 0.001$
	Cough, n (%)	246/387 (64)	65/98 (66)	181/289 (63)	19/87 (22)	$P = 0.511$	$P < 0.001$
	Fixed airflow limitation, n (%)	245/415 (59)	73/109 (67)	172/306 (56)	17/85 (20)	$P = 0.050$	$P < 0.001$
	Bronchodilator reversibility, n (%)	244/415 (59)	74/109 (68)	170/306 (56)	33/85 (39)	$P = 0.025$	$P = 0.006$
	Bronchitis, n (%)	214/421 (51)	57/110 (52)	157/311 (51)	16/88 (18)	$P = 0.810$	$P < 0.001$
	Type 2 inflammation, n (%)	184/421 (44)	50/110 (45)	134/311 (43)	30/88 (34)	$P = 0.667$	$P = 0.130$
	Neutrophilic inflammation, n (%)	73/181 (40)	20/53 (38)	53/128 (41)	13/43 (30)	$P = 0.647$	$P = 0.193$
Extra-pulmonary	Atopic, n (%)	298/421 (71)	68/110 (62)	230/311 (74)	79/88 (90)	$P = 0.016$	$P = 0.002$
	Rhinosinusitis, n (%)	204/421 (48)	48/110 (44)	156/311 (50)	35/88 (40)	$P = 0.239$	$P = 0.085$
	Obese, n (%)	164/421 (39)	44/110 (40)	120/311 (39)	16/88 (18)	$P = 0.794$	$P < 0.001$
	Reflux, n (%)	152/421 (36)	50/110 (46)	102/311 (33)	10/88 (11)	$P = 0.018$	$P < 0.001$
	Obstructive sleep apnoea, n (%)	95/372 (26)	26/95 (27)	69/277 (25)	9/85 (11)	$P = 0.635$	$P = 0.005$
	Osteoporosis, n (%)	94/421 (22)	24/110 (22)	70/311 (23)	3/88 (3)	$P = 0.881$	$P < 0.001$
	Eczema, n (%)	76/421 (18)	19/110 (17)	57/311 (18)	10/88 (11)	$P = 0.805$	$P = 0.123$
	Nasal polyps, n (%)	58/421 (14)	14/110 (13)	44/311 (14)	1/88 (1)	$P = 0.710$	$P = 0.001$
	Vocal cord dysfunction, n (%)	17/421 (4)	5/110 (5)	12/311 (4)	1/88 (1)	$P = 0.753$	$P = 0.204$
	Cardiovascular disease, n (%)	9/421 (2)	5/110 (5)	4/311 (1)	0/88 (0)	$P = 0.042$	$P = 0.285$
	Underweight, n (%)	2/421 (1)	0/110 (0)	2/311 (1)	2/88(2)	$P = 0.399$	$P = 0.175$
Behavioural/psychosocial	Poor medication adherence, n (%)	147/372 (40)	38/94 (40)	109/278 (39)	44/84 (52)	$P = 0.835$	$P = 0.032$
	Anxiety, n (%)	65/295 (22)	16/72 (22)	49/223 (22)	4/70 (6)	$P = 0.965$	$P = 0.002$
	Depression, n (%)	39/295 (13)	13/72 (18)	26/223 (12)	2/70 (3)	$P = 0.164$	$P = 0.029$
	Smoking, n (%)	42/421 (10)	42/110 (38)	-	-	-	-
	Psychiatric disease, n (%)	32/421 (8)	14/110 (13)	18/311 (6)	0/88 (0)	$P = 0.018$	$P = 0.021$

Data are expressed as n/N (%). Differences between cohorts determined using Chi-squared test.

CONFLICT OF INTEREST

Dr Simpson has nothing to disclose; Dr. Hekking has nothing to disclose; Dr Shaw reports advisory board fees from GSK, Novartis and AZ and travel fees from TEVA and AZ; Dr. Fleming reports personal fees from Vectura, personal fees from Novartis, personal fees from Boehringer Ingelheim, outside the submitted work; Dr. Roberts reports grants to University of Southampton during the conduct of the study; Dr. Riley reports he is employed by and holds shares in GlaxoSmithKline. Dr. Bates reports he is employed by and holds shares in GlaxoSmithKline. Dr. Sousa has nothing to disclose. Dr. Bansal has nothing to disclose. Dr. Pandis has nothing to disclose. Dr. Sun has nothing to disclose. Dr P Bakke has nothing to disclose. Dr. Caruso has nothing to disclose. Dr. B Dahlén reports personal fees from Advisory Board membership, personal fees from Payments for lectures, outside the submitted work; Dr. S-E Dahlén reports personal fees from AZ, GSK, Merck, Novartis, RSPR AB, Teva, outside the submitted work; Dr. Horvath reports personal fees from AstraZeneca, Boehringer-Ingelheim, GSK, Novartis, CSL Behring, Roche, Sandoz, Chiesi, Sager Pharma, Orion, Affidea and Teva, outside the submitted work. Dr. Krug reports grants from IMI, during the conduct of the study; Dr. Montuschi reports personal fees from AstraZeneca, outside the submitted work; Dr. Sandstrom reports personal fees from AstraZeneca, personal fees from GSK, personal fees from Boehringer Ingelheim, personal fees from Novartin, personal fees from Teva, outside the submitted work; Dr. Singer has nothing to disclose; Dr. Adcock reports grants from EU-IMI, during the conduct of the study; Dr. Wagers reports grants from Innovative Medicines Initiative, other from Roche, grants from European respiratory society, during the conduct of the study, other from GSK, other from European Respiratory Society, outside the submitted work; Dr. Chung reports personal fees from Advisory Board membership, grants for research, personal fees from payments for lectures, outside the submitted work; Dr. Sterk reports grants from Innovative Medicines Initiative (IMI), during the conduct of the study; Dr. Fowler has nothing to disclose.

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The details of U-BIOPRED Study Group are given in Appendix.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

APPENDIX

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American Academy of Allergy, Asthma and Immunology response to the EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of Urticaria 2017 revision

The most recent EAACI/GA²LEN/EDF/WAO Guideline update on Urticaria was published in the July 2018 issue of ALLERGY.[1] This guideline has been endorsed by 42 national and international societies including the American Academy of Allergy, Asthma and Immunology (AAAAI). Several aspects of this revised guideline are notable and praiseworthy including the rigorous approach to an