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ICER report for peanut OIT comes up short

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Recently, a policy decision by ICER (the Institute for Clinical and Economic Research) on the grading of risk-benefit trade offs of investigational peanut immunotherapy regimens was demoted to a "D" (https://icer-review.org/announcements/peanut_evidence_report/), meaning a negative evaluation of the therapy. The report was issued to the public on July 10, 2019.

This decision to downgrade to a "D" was reported by ICER (please see slide presentation by ICER https://www.youtube.com/watch?v=Ur5f63jN0xU&feature=youtube) based on a recent article published by Chu *et al.* entitled "Oral immunotherapy (OIT) for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety".[1] The authors and ICER concluded that OIT provides little benefit for patients with peanut allergy because it results in a higher rate of allergic reaction as compared to allergen avoidance. We feel that the ICER conclusion needs further interpretation and is therefore premature. We are writing this commentary to encourage a balanced interpretation of peanut OIT by expressing the following concerns regarding the ICER decision.

A major concern relates to the review by Chu *et al*, which strongly influenced the ICER decision. First, their interpretation of the data differs from a recent European Academy of Allergy and Clinical Immunology (EAACI) initiated meta-analysis,[2] which forms the basis of formal guidelines on OIT.[3] Both studies demonstrated that participants in clinical trials are more likely to have an allergic reaction during peanut OIT vs. placebo. The interpretations of the data by these two studies likely differ due to differences in the order of the research questions. Nurmatov *et al.*[2] used desensitization as the primary outcome with allergic reaction as secondary outcome (i.e., side effects) whereas Chu *et al.* treated allergic reactions as the primary outcome with desensitization as a secondary outcome. In summary, the EAACI guideline-endorsed meta-analysis concludes that OIT is effective, although there are allergic side-effects.

Secondly, the ICER decision (based in part by Chu *et al.*) does not distinguish between adverse events during induction/initial maintenance vs. long-term treatment. The ICER group did not discuss that participants starting OIT provided informed consent, were aware of side effects during induction/initial maintenance, and were willing to tolerate exposure-related side effects for the potential of an overall future benefit. Moreover, the short follow-up used in ICER's analysis does not allow appropriate assessment of long-term outcome. Peanut allergy represents a lifelong condition for the majority of patients. In addition, several key studies, which did not meet the criteria for inclusion in the meta-analsis of PACE, including a recent real-life observational study of OIT, have proven that a high degree of safety can be achieved with OIT.[4, 5]

Before initiating OIT, standard practice involves the provision of detailed information on the risks of allergic reactions (including the likely increased frequency of allergic reactions during the updosing phase) and the need to carry emergency medications at

all times. This meets the general guidelines of ICER for joint decision making. In our experience, many participants are strongly motivated to increase their reactivity-threshold to a given food allergen. ICER's decision was strongly criticized by the patient community (see public comments Appendix F ICER report https://icer-review.org/wp-content/uploads/2018/12/ICER_PeanutAllergy_Final_Report_071019.pdf). It is the accidental rather than the obvious protocol-determined encounter of allergens in the course of an OIT study that most frequently causes situational anxiety and fear. Similar to the systematic review by Chu, the decision by ICER was not based on the differences between "expected" adverse allergic reactions vs "unexpected" allergic reactions (i.e. accidental ingestions); although the authors identified that this comparison was needed. We acknowledge the need for such comparisions, but we also think that the ICER Report could delay the access to OIT as an informed and reimbursed option for years despite the presence of phase 3 trials with significant efficacy and known but manageable symptoms during the first year of peanut OIT.

Accordingly, we feel that ICER's claim that there is no improvement in QoL is premature. Positive effects of OIT on QoL (in particular, after reaching maintenance therapy) have been published but were not considered.[6–9] Most participants summarized in PACE had no QoL assessments and, for the relatively few who did, the QoL was performed in the first year of OIT rather than during the entire period of therapy. This period – the first year of OIT – is known to have the highest rate of side effects; OIT typically occurs over a few years, during which the side effects decrease substantially.[5, 9] Most reactions are mild and managed well. Further, epinephrine can successfully treat rare severe reactions during dosing. The fact that "even when patients react to their doses, very few elect to discontinue therapy" [3] supports the assumption that protection against accidental ingestion may be "the" key outcome of interest to patients.

For the first time, we are able to offer therapeutic options in clinical trials (OIT, skin patch, sublingual immunotherapy, vaccines, biological therapies). We acknowledge that the safety margin of these new therapies need improvement, however, we would like to stress the need to make newly-approved treatments available first for those who most need them.

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CONFLICT OF INTEREST

1. Thomas Eiwegger: Received funding or has research contracts with DBV Technologies, ALK, Food Allergy and Anaphylaxis Program SickKids, Innovation Funds Denmark, and contributing to investigator initiated OIT studies.

2. Katherine Anagnostou: Research contracts with Aimmune Therapeutics Inc and receives honoraria from ACAAI, and Colorado Allergy and Asthma Society (CAAS).

3. Stefania Arasi: Nothing to disclose.

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5. Moshe Ben-Shoshan: Co-investigator for Aimmune and currently involved in OIT studies.

6. Kirsten Beyer reports outside the submitted work grants and personal fees from Aimmune, Danone, Infectopharm, personal fees from Bencard, Hycor, Mabylon AG, Mylan, Nestle and grants from ALK, DBV Technologies, Hipp.

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8. Helen Brough: UK Advisory Board for DBV Technologies and has received research support from ThermoScientific.

9. Jean-Christoph Caubet: Nothing to disclose.

10. Edmond Chan: Received research support from DBV Technologies, has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, and Kaleo, is a member of the scientific advisory board for Food Allergy Canada, and was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Guidelines for Peanut Allergy Prevention.

11. Sharon Chinthrajah: Dr. Receives grant support from CoFAR NIAID, Aimmune, DBV Technologies, Astellas, AnaptysBio, Novartis, Regeneron, Stallergenes-Greer, and Boehringer Ingelheim, and is a scientific advisory board member for Alladapt Immunotherapeutics.

12. Carla M. Davis: Co-investigator and contracts from Aimmune Therapeutics,Inc, DBV Technologies, Regeneron, Allakos, Inc, Scientific advisory board for DBV technologies.

13. Anne Des Roches: Grants from ALK and personal fees from Novartis and ALK outside the submitted work.

14. George Du Toit: Scientific Advisory Board member Aimmune, co-investigator on Aimmune funded peanut Immunotherapy trials, UK Advisory Board for DBV Technologies, holds equity in DBV technologies, and Lecturer at Allergy Symposia supported by Pharma companies, including Mylan and Aimmune.

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26. Maria Jose Torres: Collaboration with ALK-Abello.

27. Julia Upton: Current or prior investigator for DBV Technologies, Aimmune, Regeneron, and investigator lead OIT studies (Food Allergy and Anaphylaxis Program SickKids), advisory board Kaleo, Food Allergy and Anaphylaxis Chair CSACI, member of the scientific advisory board for Food Allergy Canada.

28. Margitta Worm: Reports outside the submitted work grants and personal fees from Aimmune, Mylan, ALK, DBV Technologies, Allergopharma, Regenron, Sanofi, EliLilly, Stallergene, Bencard, HAL and Novartis

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ABBEVIATIONS/ACRONYMS

EAACI	European Academy of Allergy and Clinical Immunology
ICER	The Institute for Clinical and Economic Research
OIT	Oral immunotherapy
QoL	Quality of Life

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