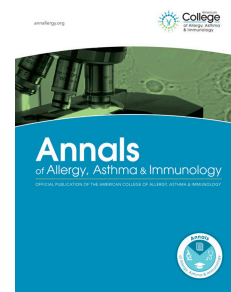


Journal Pre-proof

ICER report for peanut OIT comes up short

Thomas Eiwegger, MD, Katherine Anagnostou, MD, Stefania Arasi, MD, Philippe Bégin, MD, Moshe Ben-Shoshan, MD, Kirsten Beyer, MD, Katharina Blumchen, MD, Helen Brough, PhD, Jean-Christoph Caubet, MD, Edmond S. Chan, MD, Sharon Chinthrajah, MD, Carla M. Davis, MD, Anne Des Roches, MD, George Du Toit, M.B., B.Ch., Arnon Elizur, MD, Stephen J. Galli, MD, Geir Håland, MD, Karin Hoffmann-Sommergruber, PhD, Harold Kim, MD, Donald Y.M. Leung, MD, PhD, Antonella Muraro, MD, PhD, Ulugbek B. Nurmatov, MD, Giovanni B. Pajno, MD, Sayantani Sindher, MD, Zsolt Szepfalusi, MD, Maria Jose Torres, MD, PhD, Julia Upton, MD, Margitta Worm, MD, Kari Nadeau, MD, PhD



PII: S1081-1206(19)31056-7

DOI: <https://doi.org/10.1016/j.anai.2019.09.001>

Reference: ANAI 3014

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 13 August 2019

Accepted Date: 3 September 2019

Please cite this article as: Eiwegger T, Anagnostou K, Arasi S, Bégin P, Ben-Shoshan M, Beyer K, Blumchen K, Brough H, Caubet JC, Chan ES, Chinthrajah S, Davis CM, Roches AD, Du Toit G, Elizur A, Galli SJ, Håland G, Hoffmann-Sommergruber K, Kim H, Leung DYM, Muraro A, Nurmatov UB, Pajno GB, Sindher S, Szepfalusi Z, Torres MJ, Upton J, Worm M, Nadeau K, ICER report for peanut OIT comes up short, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.09.001>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ICER report for peanut OIT comes up short

Thomas Eiwegger, MD^{1,2,3}, Katherine Anagnostou, MD^{4,5}, Stefania Arasi, MD⁶, Philippe Bégin, MD^{7,8}, Moshe Ben-Shoshan, MD⁹, Kirsten Beyer, MD¹⁰, Katharina Blumchen, MD¹¹, Helen Brough, PhD, ^{12,13,14}, Jean-Christoph Caubet, MD¹⁵, Edmond S. Chan, MD¹⁶, Sharon Chinthrajah, MD^{17,18}, Carla M. Davis, MD^{4,5}, Anne Des Roches, MD⁷, George Du Toit, M.B., B.Ch.^{12,13,14}, Arnon Elizur, MD¹⁹, Stephen J. Galli, MD^{17, 20}, Geir Håland, MD²¹, Karin Hoffmann-Sommergruber, PhD²², Harold Kim, MD^{23,24}, Donald Y. M. Leung, MD, PhD²⁵, Antonella Muraro MD, PhD²⁶, Ulugbek B Nurmatov, MD²⁷, Giovanni B. Pajno, MD²⁸, Sayantani Sindher, MD^{17,18}, Zsolt Szepefalusi, MD²⁹, Maria Jose Torres, MD, PhD³⁰, Julia Upton, MD¹, Margitta Worm, MD³¹, Kari Nadeau, MD, PhD^{17,18, 32}

¹ Division of Immunology and Allergy, Food Allergy and Anaphylaxis Program, The Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada.

² Research Institute, The Hospital for Sick Children, Translational Medicine, Toronto, Canada.

³ Department of Immunology, The University of Toronto, Toronto, Canada.

⁴ Texas Children's Hospital, Department of Pediatrics, Section of Immunology, Allergy and Retrovirology, Houston, TX, USA.

⁵ Baylor College of Medicine, Houston, TX, USA.

⁶ Department of Pediatric Medicine, Pediatric Allergology Unit, Bambino Gesù Children's research Hospital (IRCCS), Rome, Italy.

⁷ Division of Immunology and Allergy, Department of Pediatrics, CHU Ste-Justine, Montreal, Canada.

⁸ Division of Immunology and Allergy, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, Canada.

⁹ Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, McGill University Health Center, Montreal, QC, Canada.

¹⁰ Department of Pediatric Pneumology, Immunology and Intensive Care, Charité Universitätsmedizin Berlin, Berlin, Germany.

¹¹ Dept. of Children and Adolescent Medicine, Division of Pneumology, Allergology and Cystic fibrosis, University Hospital Frankfurt, Frankfurt am Main, Germany.

¹² Department of Women and Children's Health (Pediatric Allergy), School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK.

¹³ Peter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, UK.

¹⁴ Children's Allergy Service, Evelina London, Guy's and St Thomas' Hospital, London, UK.

¹⁵ Division of Pediatric Allergy, Department of Pediatrics, University Hospitals of Geneva, Geneva, Switzerland.

¹⁶ Division of Allergy and Immunology, Department of Pediatrics, University of British Columbia, BC Children's Hospital, Vancouver, British Columbia, Canada.

¹⁷ Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford University, Stanford, CA, USA.

¹⁸ Division of Pulmonary and Critical Care Medicine, Stanford University, Stanford, CA, USA.

¹⁹ The Institute of Allergy, Immunology and Pediatric Pulmonology, Yitzhak Shamir Medical Center and Department of Pediatrics, Sackler Faculty of Medicine, Tel Aviv University, Israel.

²⁰ Department of Pathology and Department of Microbiology and Immunology, Stanford University, Stanford, CA, USA.

²¹ Department of Paediatric Allergy and Pulmonology, Oslo University Hospital, Oslo, Norway.

²² Department of Pathophysiology and Allergy Research, Medical University of Vienna, Austria.

²³ Division of Clinical Immunology and Allergy, Department of Medicine, Western University, London, Canada.

²⁴ Division of Clinical Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, Canada.

²⁵ Department of Pediatrics, National Jewish Health, Denver, and the Department of Pediatrics, University of Colorado at Denver Health Sciences Center, Aurora, Colorado, USA.

²⁶ Food Allergy Centre -Veneto Region, Department of Woman and Child Health , Padua University Hospital, Padua, Italy.

²⁷ Division of Population Medicine, School of Medicine, The National Centre for Population Health and Wellbeing Research, Wales, UK.

²⁸ Department of Pediatrics, Allergy Unit, University of Messina, Messina, Italy.

²⁹ Division of Ped. Pulmonology, Allergy and Endocrinology, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria.

³⁰ Allergy Unit, National Network ARADyAL, IBIMA-Regional University Hospital of Malaga-UMA, Malaga, Spain.

³¹ Division of Allergy and Immunology, Department of Dermatology, Allergy and Venerology, Charité Universitätsmedizin Berlin, Germany.

³² Division of Allergy, Immunology and Rheumatology, Stanford University, Stanford, CA, USA.

69

70 **Corresponding Author:** Kari C. Nadeau, MD, PhD, Director, Sean N. Parker Center for
71 Allergy and Asthma Research at Stanford University, 269 Campus Drive, CCSR 3215, MC
72 5366, Stanford, CA 94305-5101, USA. E-mail: knadeau@stanford.edu.

73

74 **CONFLICT OF INTEREST**

- 75 1. Thomas Eiwegger: Received funding or has research contracts with DBV Technologies,
76 ALK, Food Allergy and Anaphylaxis Program SickKids, Innovation Funds Denmark, and
77 contributing to investigator initiated OIT studies.
- 78 2. Katherine Anagnostou: Research contracts with Aimmune Therapeutics Inc and receives
79 honoraria from ACAAI, and Colorado Allergy and Asthma Society (CAAS).
- 80 3. Stefania Arasi: Nothing to disclose.
- 81 4. Philippe Bégin: Grants from Fonds de Recherche en Santé du Québec, Canadian Allergy,
82 Asthma and Immunology Foundation, DBV Technologies, Sanofi Genzyme, Merck and
83 Regeneron and personal fees from Aralez, Novartis and ALK outside the submitted work.
- 84 5. Moshe Ben-Shoshan: Co-investigator for Aimmune and currently involved in OIT studies.
- 85 6. Kirsten Beyer reports outside the submitted work grants and personal fees from Aimmune,
86 Danone, Infectopharm, personal fees from Bencard, Hycor, Mabyon AG, Mylan, Nestle and
87 grants from ALK, DBV Technologies, Hipp.
- 88 7. Katharina Blumchen: Personal fees and nonfinancial support from Novartis; personal fees
89 from HAL Allergy, ThermoFisher, Bencard Allergie, Allergopharma, ALK, DBV, Nestle,
90 Nutricia; and grants and personal fees from Aimmune Therapeutics, grant from Hipp.

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.
15. Arnon Elizur: Nothing to disclose.

- 112 16. Stephen J. Galli: Funding from NIH grants NIH/NIAID U19AI104209, NIH/NIAMS R01
113 AR067145, NIH/NIAID R01 AI125567, and NIH/NIAID R01 AI32494 and the United
114 States-Israel Binational Foundation (Grant 2017182).
- 115 17. Geir Haland: Nothing to disclose
- 116 18. Karin Hoffmann-Sommergruber: Grants from Austrian Science Fund and Horizon 2020
117 (Cost action) and honoraria from Nutricia; travel reimbursement from EAACI.
- 118 19. Harold Kim: Served as peaker and/or advisor for ALK, Aralez, Astrazeneca, CSL Behring,
119 Shire, Novartis, Pediapharm, Stallergenes, Kaleo, Sanofi, Pfizer, and Mylan.
- 120 20. Donald Y.M. Leung: Chairman of Aimmune Therapeutics, Inc DSMC; receives funding
121 from NIH grants NIH/NIAMS R01 AR41256, NIH/NIAID U19 AI117673, NIH/NCRR
122 UL1RR025780, NIH/NIAID UM1AI130780 and NIH/NIAID 1UM2AI130836 and consulted
123 for Sanofi, Regeneron, Demira, and Novartis.
- 124 21. Antonella Muraro: Speaker's fee for DBV Technologies, Aimmune , Chair of the EAACI
125 Food Allergy and Anaphylaxis Guidelines
- 126 22. Ulugbek Nurmatov: Nothing to disclose
- 127 23. Giovanni Battista Pajno: Nothing to disclose.
- 128 24. Sayantani Sindher: Sponsored research for clinical trials from Aimmune, DBV Technologies,
129 Sanofi, and Regeneron.
- 130 25. Zsolt Szepefalusi: Honoraria from ThermoFisher, Milupa, Allergopharma, Shire, Bencard,
131 Novartis, Meda, Vertex
- 132 26. Maria Jose Torres: Collaboration with ALK-Abello.
- 133 27. Julia Upton: Current or prior investigator for DBV Technologies, Aimmune, Regeneron, and
134 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, Regeneron, Sanofi, EliLilly, Stallergene, Bencard, HAL and Novartis
29. Kari Nadeau: Receives grant support from NIAID, Food Allergy Research & Education, End Allergies Together, Allergenics, Ukko; Personal Fees from Regeneron, AstraZeneca, ImmuneWorks, Cour; Sponsored research from Novartis, Sanofi, Astellas, Nestle; Sponsored research for clinical trials from Genentech, Aimmune Therapeutics, DBV Technologies, AnaptysBio, Stallergenes-Greer, Regeneron, and Adare Pharmaceuticals; Data and Safety Monitoring Board member at Novartis and NHLBI; Co-founded Before Brands, Alladapt Immunotherapeutics, and ForTra; Grant awardee for NIAID, NHLBI, NIEHS, and EPA; Director for Food Allergy Research & Education and WAO Center of Excellence.

FUNDING

None

KEYWORDS

Food allergy, oral immunotherapy, peanut, desensitization, safety, efficacy

ABBREVIATIONS/ACRONYMS

EAACI: European Academy of Allergy and Clinical Immunology

157 ICER: The Institute for Clinical and Economic Research

158 OIT: Oral immunotherapy

159 QoL: Quality of Life

160 **WORD COUNT**

161 830

162 **FIGURES**

163 **None**

164 **TABLES**

165 **None**

166

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

5
6 This decision to downgrade to a “D” was reported by ICER (please see slide presentation by
7 ICER <https://www.youtube.com/watch?v=Ur5f63jN0xU&feature=youtube>) based on a recent
8 article published by Chu *et al.* entitled “Oral immunotherapy (OIT) for peanut allergy (PACE): a
9 systematic review and meta-analysis of efficacy and safety”.¹ The authors and ICER concluded
10 that OIT provides little benefit for patients with peanut allergy because it results in a higher rate
11 of allergic reaction as compared to allergen avoidance. We feel that the ICER conclusion needs
12 further interpretation and is therefore premature. We are writing this commentary to encourage a
13 balanced interpretation of peanut OIT by expressing the following concerns regarding the ICER
14 decision.

15
16 A major concern relates to the review by Chu *et al.*, which strongly influenced the ICER decision.
17 First, their interpretation of the data differs from a recent European Academy of Allergy and
18 Clinical Immunology (EAACI) initiated meta-analysis,² which forms the basis of formal
19 guidelines on OIT.³ Both studies demonstrated that participants in clinical trials are more likely
20 to have an allergic reaction during peanut OIT vs. placebo. The interpretations of the data by
21 these two studies likely differ due to differences in the order of the research questions. Nurmatov
22 *et al.*² used desensitization as the primary outcome with allergic reaction as secondary outcome
23 (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-analysis 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

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 up dosing 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 comparisons, 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.

REFERENCES

1. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet*. 2019;393:2222-2232.
2. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72:1133-1147.
3. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73:799-815.
4. Soller L, Abrams EM, Carr S, et al. First Real-World Safety Analysis of Preschool Peanut Oral Immunotherapy. *J Allergy Clin Immunol Pract*. 2019.
5. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139:173-181 e178.
6. Epstein-Rigbi N, Goldberg MR, Levy MB, Nachshon L, Elizur A. Quality of Life of Food-Allergic Patients Before, During, and After Oral Immunotherapy. *J Allergy Clin Immunol Pract*. 2019;7:429-436.e422.
7. Otani IM, Begin P, Kearney C, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. *Allergy Asthma Clin Immunol*. 2014;10:25.
8. Arasi S, Otani IM, Klingbeil E, et al. Two year effects of food allergen immunotherapy on quality of life in caregivers of children with food allergies. *Allergy Asthma Clin Immunol*. 2014;10:57.
9. Blumchen K, Trendelenburg V, Ahrens F, et al. Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral

- 24 Immunotherapy in Children with Peanut Allergy. J Allergy Clin Immunol Pract.
25 2019;7:479-491 e410.