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The value of oral immunotherapy

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On July 10, 2019, the Institute for Clinical and Economic Review (ICER) published its final report on the effectiveness and value of AR101 and Viaskin® Peanut for peanut allergy¹. At a threshold of \$50,000 USD per quality-adjusted life-year (QALY), the report concludes that the limit of cost-effectiveness is reached at an annual cost of \$2,369 per year for ARA101 and \$1,508 for Viaskin® peanut, which is in line with recent estimates from Shaker and Greenhawt². While the premises for these calculations can be debated, it is important not to overshadow the report's general conclusion which is that food immunotherapy "is predicted to produce incremental benefit for people with peanut allergy relative to standard care (no desensitization treatment)" and that "these benefits are due to improved subjective quality of life despite the relative rarity with which serious events occur"¹.

This conclusion justly identifies the impact on patients' life as the true relevant outcome of oral immunotherapy (OIT). This shift in focus is a breath of fresh air considering the recent debate opposing the conclusions of two meta-analysis on the topic^{3,4}. The first meta-analysis, published in 2017 as a prelude to the first EAACI guidelines on OIT, concluded to the efficacy of OIT at increasing reaction threshold on oral food challenge (i.e. the primary outcome of included studies). The PACE study, published this winter, changed the primary outcome to the overall rate of allergic events and thus concluded to the detrimental effect of OIT compared to no desensitization. This was supposedly a more patient-oriented outcome, based on the idea that the motivation for OIT is to decrease the risk of reactions. In reality, neither of these outcomes really captures patients' priorities as identified by previous qualitative studies assessing patient's perspective⁵⁻⁸.

The main problem identified by patients with food allergy and their parents is the fear and anxiety^{5-7,9}, which has very little to do with actual rates of adverse events. It rather depends on patient's perception of risk of having a reaction, of it being severe or life-threatening and of their ability to cope with it, were it to happen⁸. The second major issue for patients is all the limitations and missed opportunities because of their food allergies^{5-7,9}. Finally, another major theme from qualitative literature research is that of uncertainty⁶⁻⁹. This includes intrinsic uncertainty regarding the true severity of their allergies and their capacity to react appropriately if needed, as well as

extrinsic uncertainty regarding the actual amount of allergen contained in food or the understanding that others have of this risk and of its seriousness.

For patients, OIT is often a game-changer for all three themes. While OIT increases the overall risk of reactions, most if not all of these will occur from taking the dose. They are expected and result from a conscious choice. As a trade-off, the risk of reactions with accidental exposure, which directly contribute to the feeling of lack of safety, is greatly decreased. Even if a full portion of the food is not completely reintegrated, protection against traces and cross-contamination alone will greatly reduce social limitations. Paradoxically, dosing reactions at home, which can be a source of anxiety, can also over time contribute to demystifying the allergy and convince the patient of his own ability to manage reactions, directly addressing intrinsic uncertainty¹⁰.

The recognition by ICER that the main benefit of OIT stems from quality of life should be a reminder that patient experience should be at the center of our discussions around the relevance and value of OIT.

One challenge with valuating quality of life is that the impact of food allergy differs from one patient to another (Figure 1)¹⁰. For example, an allergist suffering from food allergy may consider there is little to gain from OIT, considering he/she already has near perfect understanding of the disease, very concrete estimation of risk and complete confidence in his/her ability to manage reactions. To date, inter-patient differences can in great part be captured with available Food Allergy Quality of Life Questionnaires (FAQLQ), which specifically addresses many of the themes mentioned above¹¹. However, the weight of individual questions in these questionnaires and of each item on the answering scales is unknown, and therefore the results cannot currently be treated in a quantitative manner. This is a problem, considering that cost-utility calculations measure benefit in terms of a quantified amount of quality of life over a quantified period of time (i.e. QALY) (Figure 2)¹¹.

The lack of QALY data for food allergy is an admitted weakness of the ICER report. Prediction models were based on QALY estimates from a single study using a generic questionnaire (EQ-5D) in 144 food allergic patients on avoidance¹². A particular limit to the EQ-5D is that contrarily to other generic questionnaires (SF-6D, CHU-9D), it does not include the social dimension, which is

particularly relevant in the context of food allergy¹³. Moreover, the values currently derived from the different possible answers to the EQ-5D were never validated in the food allergic population. The study did not include patients on OIT and the expected gain in from treatment is therefore unknown. As an arbitrary solution, the authors chose to define the health state of desensitized patients as a 60% improvement between that of patients on avoidance and that of healthy population¹. The ideal solution would be to create utility value sets specific for allergic populations or alternatively to create conversion algorithms to translate current FAQLQ results directly into QALY.

The other gap of knowledge specifically mentioned in the conclusion of the ICER report was the lack of data on long-term effectiveness. For treatments to be cost-effective, we need to be able to stop them and reap the subsequent benefit on quality of life accumulating over time (Figure 2). This requires either A) evidence of sustained tolerance induction or B) the demonstration of the possibility to safely switch to native food alternatives to maintain desensitization without having to pay for expensive pharmaceutical products.

In conclusion, the ICER report rightly puts patients experience at the center of the OIT discussion. It serves to show how patient engagement is essential to contextualize findings from clinical trials. In this context, addressing current limits in the quantification of quality of life in food allergy should be made a priority^{13,14}. Until then, any recommendation on OIT should take into account patient perspective obtained from qualitative research, as uncontextualized and dehumanized statistics (e.g. adverse event rates, relative change in reaction threshold) will necessarily lead to erroneous estimates of treatment value.

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References

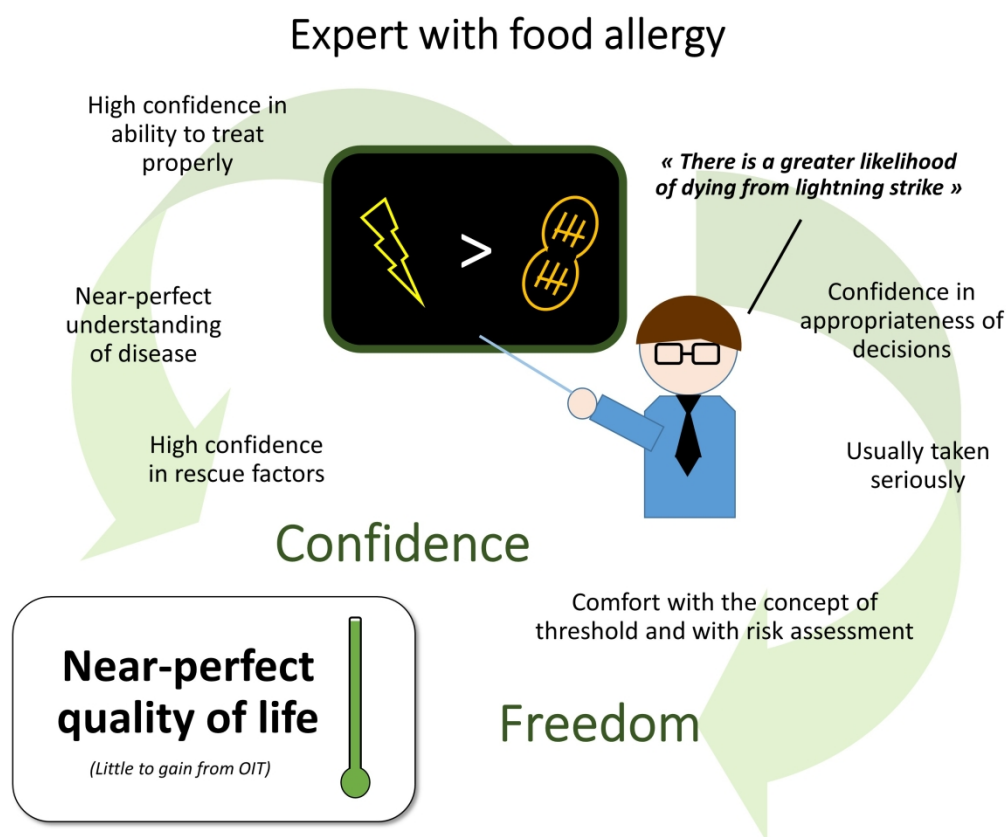
1. Institute for Clinical and Economic Review. *Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value*. 2019.
2. Shaker M, Greenhawt M. Estimation of Health and Economic Benefits of Commercial Peanut Immunotherapy Products: A Cost-effectiveness Analysis. *JAMA network open*. 2019;2(5):e193242-e193242.
3. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72(8):1133-1147.
4. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *The Lancet*. 2019;393(10187):2222-2232.
5. Begen FM, Barnett J, Barber M, Payne R, Gowland MH, Lucas JS. Parents' and caregivers' experiences and behaviours when eating out with children with a food hypersensitivity. *BMC public health*. 2018;18(1):38.
6. Rouf K, White L, Evans K. A qualitative investigation into the maternal experience of having a young child with severe food allergy. *Clinical child psychology and psychiatry*. 2012;17(1):49-64.
7. Pitchforth E, Weaver S, Willars J, Wawrzkowicz E, Luyt D, Dixon-Woods M. A qualitative study of families of a child with a nut allergy. *Chronic illness*. 2011;7(4):255-266.
8. Duca B, Patel N, Turner PJ. GRADE-ing the Benefit/Risk Equation in Food Immunotherapy. *Curr Allergy Asthma Rep*. 2019;19(6):30.
9. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy*. 2010;65(8):933-945.
10. Kansen HM, Le TM, Meijer Y, et al. The impact of oral food challenges for food allergy on quality of life: A systematic review. *Pediatr Allergy Immunol*. 2018;29(5):527-537.
11. 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(1):25.
12. Protudjer JL, Jansson S-A, Arnlin M, et al. Household costs associated with objectively diagnosed allergy to staple foods in children and adolescents. *The Journal of Allergy and Clinical Immunology: In Practice*. 2015;3(1):68-75.
13. Upton JEM, Poder TG, Begin P. Early introduction without screening is a good deal, if caregivers will buy it. *Allergy*. 2019;74(2):213-215.

14. Muraro A, Dubois AE, DunnGalvin A, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. *Allergy*. 2014;69(7):845-853.

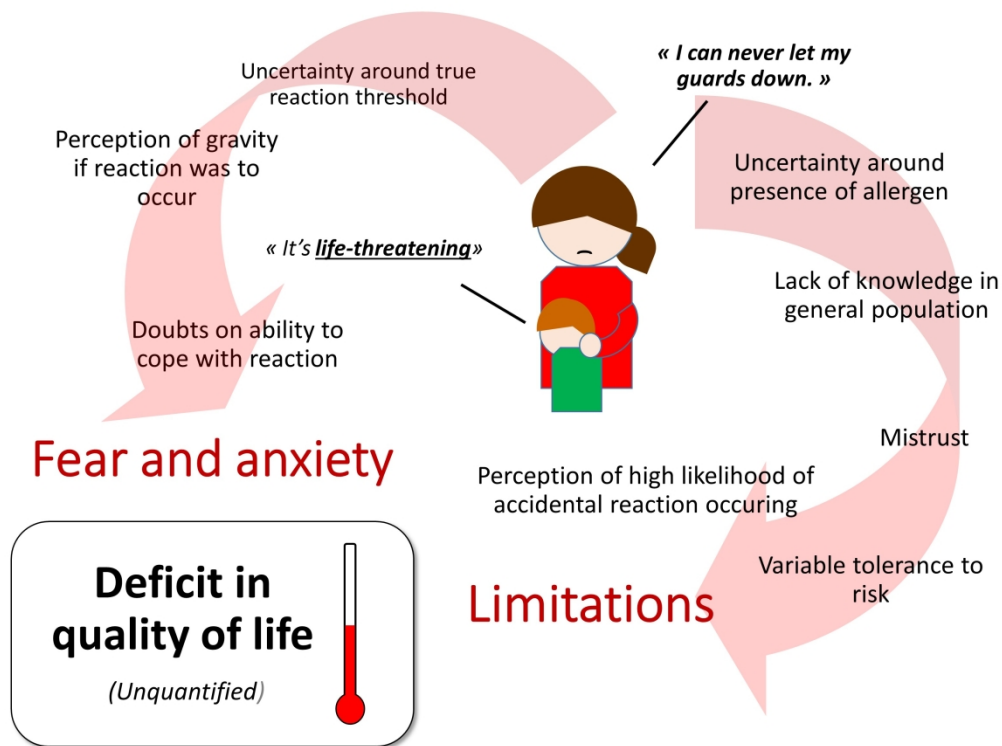
FIGURE LEGENDS

Figure 1. Impact of food allergy on quality of life. Qualitative research informs on the various aspects that modulate the impact of food allergy on patient's quality of life (panel A vs B). The expected benefit of oral immunotherapy on health-related quality of life is dependent on the deficit at baseline, which varies between patients (panel C). Current questionnaires help capture patients' reality, but cannot be used to measure this deficit in quantitative terms.

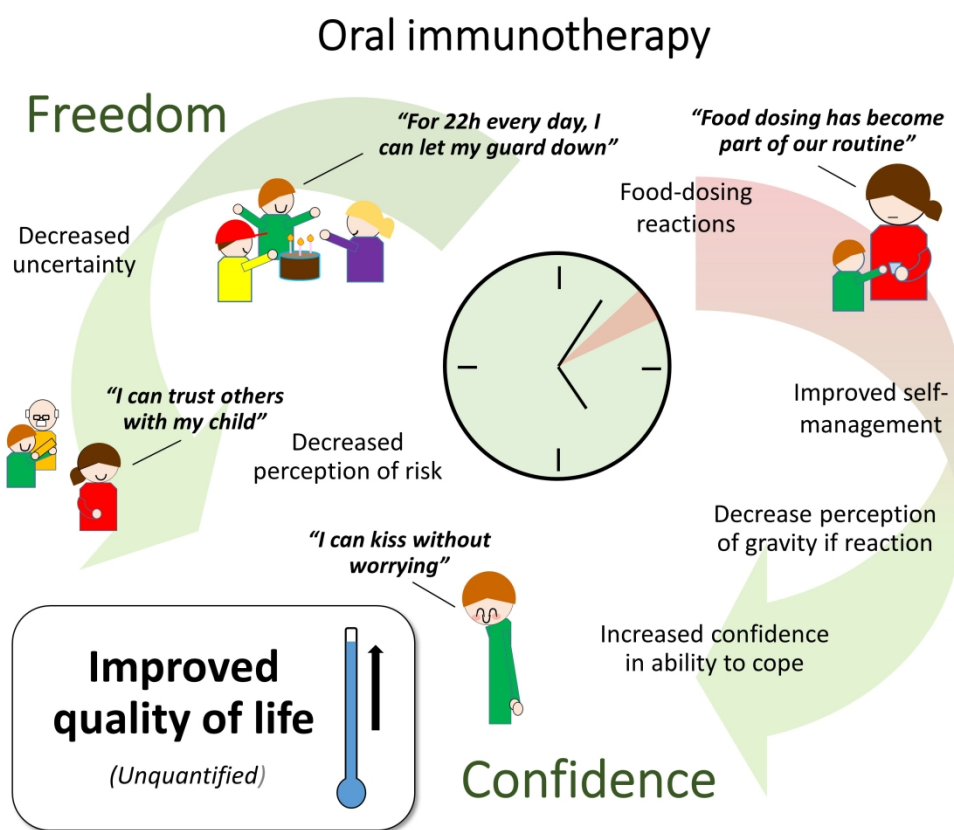
Figure 2. Gain in quality-adjusted life-years with intervention. Validated estimates of food allergy health state utility values at baseline and with treatment would allow precise quantification of the expected gain in quality of life following a given intervention. The amount of quality-adjusted life-years generated following this intervention could then be valued in monetary terms to justify allocation of resources in a fair manner.



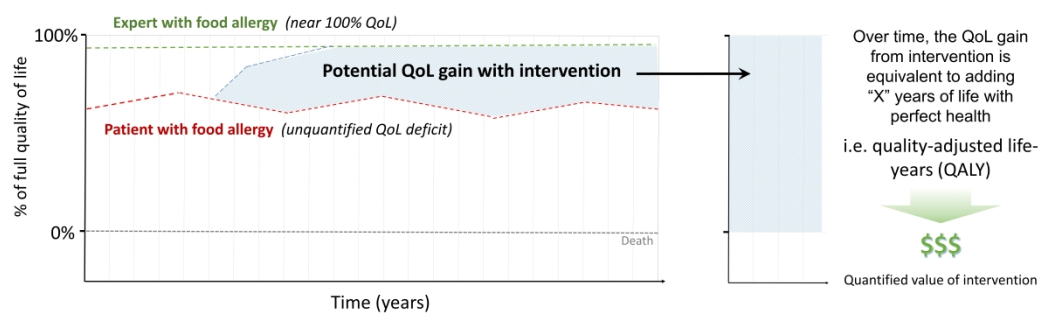
Non-expert with food allergy



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