

At the time of patient treatment and data collection, Richard L. Wasserman, Angela R. Hague, Deanna M. Pence, Robert W. Sugerman, Stacy K. Silvers, and Joanna G. Rolen were employed by Pediatric Allergy/Immunology Associates, Pa, and then Allergy Partners of North Texas, Dallas, Texas.

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REFERENCES

1. Wang J. Peanut oral immunotherapy: data from a real-world clinical practice. *J Allergy Clin Immunol Pract* 2019;7:427-8.
2. Wasserman RL, Hague AR, Pence DM, Sugerman RW, Silvers SK, Rolen JG, et al. Real-world experience with peanut oral immunotherapy: lessons learned from 270 patients. *J Allergy Clin Immunol Pract* 2019;7:418-26.
3. Wasserman RL, Jones DH, Windom HH. Oral immunotherapy for food allergy: the FAST perspective. *Ann Allergy Asthma Immunol* 2018;121:272-5.
4. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in peanut allergic children. *J Allergy Clin Immunol* 2009;124:286-91.
5. Bird JA, Feldman M, Arneson A, Dougherty I, Brown LS, Burk CM, et al. Modified peanut oral immunotherapy protocol safely and effectively induces desensitization. *J Allergy Clin Immunol Pract* 2015;3:433-5.

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Reply



To the Editor:

In the opening paragraph, Wasserman et al¹ state that my editorial “criticizes the report for not being the randomized, controlled trial that it was never intended to be.” I am surprised that they interpreted the editorial to be a criticism as I simply pointed out that “the authors acknowledge certain limitations given the retrospective nature of their data,”² which is a reiteration of Wasserman et al’s³ own words in the discussion of their original report, “As a retrospective study, there are potential biases.” As the authors already present their report as being from real-world practice, the editorial serves to point out to readers the similarities and differences, as well as advantages and limitations, when examining different approaches to peanut oral immunotherapy.

The correspondence takes issue with my statement about the lack of food challenges, which simply stated: “The authors acknowledge certain limitations...For example, baseline food challenges were not performed so the magnitude of efficacy remains uncertain.”² The authors themselves state in their original article that “clinicians modified patient treatment according to their judgment” and specifically say that “because all patients were not challenged before beginning POIT, we cannot be certain that they were all peanut allergic.”³ Therefore, it is merely a statement of fact on my part that baseline food challenges were not performed for the patients in their cohort, and not an implication of inferiority. However, I would not agree with Wasserman et al’s conclusion that “the only bias was the choice parents made in seeking care for their children” when we are discussing a retrospective review of an open treatment.

Wasserman et al¹ further question “would it have been ethical to challenge patients with known peanut allergy?” Although it is understandable why this “real-world” study decided not to routinely perform food challenges, I take issue with the comment that doing so is unethical. There are dozens of completed and ongoing clinical trials of peanut allergy that are sponsored by the National Institutes of Health, investigator-initiated or

pharmaceutical trials that include baseline food challenges for patients with known peanut allergy. These studies have all undergone review and received approval by different institutional review boards and Data Safety Monitoring Boards. The mandate of institutional review boards is to provide ethical and regulatory oversight of research that involves human subjects. Therefore, challenging patients with known peanut allergy has repeatedly been found to be an acceptable procedure to be included in peanut allergy studies.

Wasserman et al allege that the editorial is promoting a specific product. First, there is no mention of any specific product anywhere in the editorial.² Second, the word “product” is used as a generic term throughout the editorial, defined as “something that is marketed or sold as a commodity.”⁴ This term was chosen because there are different sources of peanut protein available (including peanut, peanut butter, peanut flour) that have been used for peanut oral immunotherapy (OIT). The authors also mistakenly interpret the editorial statement on allergic reactions due to OIT, erroneously assuming that it refers only to the use of nonstandardized peanut. The editorial notes that Wasserman et al’s report is in fact similar to other published reports in finding that allergic symptoms to OIT are common. The references I cite included 4 different studies that used different peanut sources/products, 3 of which used nonstandardized products (Blumchen et al⁵ used crushed roasted peanut and Anagnostou et al⁶ and Varshney et al⁷ used lightly roasted flour).

Another point related to safety brought up in the editorial to which Wasserman et al take offense is that switching between peanut protein sources during OIT could pose a potential safety concern. This concern was raised on the basis of data published by Filep et al⁸ and Hindley et al,⁹ which demonstrate variability in peanut protein content across different peanut foods. Following Wasserman et al’s suggestion to compare peanut OIT to subcutaneous immunotherapy for environmental allergies, I would point out that the practice parameter on allergen immunotherapy¹⁰ specifically states that:

“[A]n allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the allergen immunotherapy extract. These include changes in the lot, manufacturer, extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is potentially an increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient’s dose is not modified.”

As such, an analogous approach should not be unexpected for peanut OIT in that caution would be warranted when switching between peanut protein sources from different manufacturers, both standardized and nonstandardized. Although Wasserman et al³ did not report any problems when their patients switched between peanut products, these data from a single cohort are insufficient to deem this concern to be irrelevant, such that no caution is warranted for any patient.

Wasserman et al also take offense to the points made in my editorial about reasons why practices may find implementing OIT to be challenging. The reasons listed for physician concern are taken directly from the study by Greenhawt and Vickery¹¹ who conducted a survey of American Academy of Allergy, Asthma

& Immunology membership that included 442 respondents, of which 75.9% self-identified they were in private practice and 13.8% reported they were “providing OIT as a service or were studying OIT under a research protocol.” In this study, 381 providers who were not using OIT currently were asked to rate the relative importance of factors that would specifically motivate them to offer OIT in the future—91.9% stated availability of a standardized product and 86% would like a current procedural terminology (CPT) billing code. The report indicates that 74.3% are awaiting Food and Drug Administration approval before offering this therapy, and 4.5% identify that they did not have the resources at present to offer OIT. Thus, the reasons brought forth as challenging regarding OIT implementation are not a single person’s opinion, but rather the opinions of American Academy of Allergy, Asthma & Immunology members taking the survey. In fact, another one of Wasserman et al’s¹² publications specifically states that:

“[B]ecause FOIT [oral immunotherapy for food allergy] is not yet the standard of care, discussions about the process, the risks, and potential benefits are time consuming. Sourcing and preparing foods requires staff training. Food allergy patients may require 1 or more food challenges before FOIT. Only those allergy practices with extensive experience in performing food challenges should consider offering FOIT. Although all allergy offices should be prepared to manage anaphylaxis, this capability is especially important to an FOIT program.”

This direct quote from Wasserman et al’s first author publication clearly asserts that resources (including people and time) are required for practices choosing to provide OIT.

There is no implication in the editorial “that it is not possible to have a guideline or billing code without a commercial product” as the authors contend.¹ Wasserman et al misconstrue the statement, “the medicolegal implications associated with off-label OIT, a treatment that is currently not recommended by evidence-based guidelines, as well as lack of Current Procedural Terminology (CPT) billing code and insurance coverage are additional concerns for widespread adoption of OIT,”² which, again, are concerns brought forth by the results of Greenhawt and Vickery’s¹¹ survey. The editorial is simply stating the facts that OIT is not currently recommended by evidence-based US guidelines and there is currently no CPT billing code available.

Wasserman et al¹ raise the point that Bamba and peanut butters are included in prevention guidelines and suggest that use of such commercial peanut food products for OIT would be comparable with regard to treatment guidelines and billing codes. However, it is important to remember that early introduction of peanut into an infant’s diet is intended for those who are NOT allergic. Therefore, the discussion of foods used in infant feeding should not be conflated with discussions on products or protein sources to be used as medical therapy for treatment of patients who are known to be allergic and are at risk for reactions, including severe ones, with allergen exposure.

Wasserman et al claim that the editorial promotes a single pathway for OIT product development, which is a gross misinterpretation. The intention of the statement that “development of well-characterized products from GMP facilities [NOTE: the plural of “product” is used, indicating that this is not a promotion for a single product. Also, these words were

specifically chosen to not only refer to a pharmaceutical product, but also OIT products that are manufactured at different GMP facilities in academic centers or other locations] is ultimately worthwhile to allow more patients and practices to have access to this therapeutic approach”² is to leave open room for different OIT products to be used to increase access of this therapeutic option to more patients.

I hope that Wasserman et al can agree that I never criticized the report “for not being ...[a] randomized, controlled trial.” In fact, I emphasized the value of the information obtainable from this large “real-world” study in my editorial. But, I am confident Wasserman et al and others recognize the advantages of controlled trials. Wasserman et al³ state in their original article, “no study has yet demonstrated the ideal or even preferred food allergy immunotherapy algorithm,” indicating the need for further investigations to fully understand safety, efficacy, and how treatment should be provided. Under the principles of beneficence and nonmaleficence in medical ethics, a benefit-risk analysis is important before starting a medical therapy. As Wasserman et al³ also point out in their original report, there was an “apparently high frequency of epinephrine use” and a “rate of ELORS [eosinophilic esophagitis-like oral immunotherapy-related syndrome] within a range seen in other POIT reports.” These data support the need for assessments of risk and burden of treatment such as those discussed in the recent review by Soller et al¹³ that compare the rates of epinephrine administration using studies of peanut avoidance, peanut OIT in research, and peanut OIT in clinical practice. Soller et al point out that among those practicing peanut avoidance, there is a 10% annual rate of accidental reactions, with 1% to 2% requiring epinephrine or emergency department visits. This rate is lower than reported rates of epinephrine use in peanut OIT in research, which ranges up to 14%,¹⁴ and peanut OIT in clinical practice, which was reported to be 10%.¹⁵ To fully evaluate the risk/benefit, in this area that we agree remains in equipoise, I would argue in fact that randomized, placebo-controlled trials have a clear advantage in allowing us to compare the benefit of OIT versus allergen avoidance.

The concluding paragraph of my editorials states that “advancing OIT into routine clinical practice will require a balance between rigorous placebo-controlled studies and large retrospective studies of this kind,”² which in fact reads no different than Wasserman et al’s³ original conclusion that “careful observations of clinical experiences can supplement information from controlled clinical trials to improve the treatment of peanut allergic patients.” As in other areas of medicine, there will be a place for various approaches to treatment and as we move the field forward, it “will be essential to weigh the benefits versus risks of this therapy in a precision medicine approach.”²

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REFERENCES

1. Wasserman RL, Hague AR, Pence DM, Sugerman RW, Silvers SK, Rolen JG, et al. The real world is not standardized. *J Allergy Clin Immunol Pract* 2019;7:2098-9.
2. Wang J. Peanut oral immunotherapy: data from a real-world clinical practice. *J Allergy Clin Immunol Pract* 2019;7:427-8.
3. Wasserman RL, Hague AR, Pence DM, Sugerman RW, Silvers SK, Rolen JG, et al. Real world experience with peanut oral immunotherapy: lessons learned from 270 patients. *J Allergy Clin Immunol Pract* 2019;7:418-26.e4.
4. Merriam-Webster. Dictionary by Merriam-Webster: America's most trusted online dictionary. Available from: <https://www.merriam-webster.com/>. Accessed March 20, 2019.
5. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschoner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126:83-91.e1.
6. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014;383:1297-304.
7. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011;127:654-60.
8. Filep S, Block DS, Smith BRE, King EM, Commins S, Kulis M, et al. Specific allergen profiles of peanut foods and diagnostic or therapeutic allergenic products. *J Allergy Clin Immunol* 2018;141:626-31.e7.
9. Hindley JP, Filep S, Block DS, King EM, Chapman MD. Dose of allergens in a peanut snack (Bamba) associated with prevention of peanut allergy. *J Allergy Clin Immunol* 2018;141:780-2.
10. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127:S1-S55.
11. Greenhawt MJ, Vickery BP. Allergist-reported trends in the practice of food allergen oral immunotherapy. *J Allergy Clin Immunol Pract* 2015;3:33-8.
12. Wasserman RL, Jones DH, Windom HH. Oral immunotherapy for food allergy: the FAST perspective. *Ann Allergy Asthma Immunol* 2018;121:272-5.
13. Soller L, Abrams EM, Chan ES. An update on the controversy around offering oral immunotherapy to peanut-allergic children outside of research. *Ann Allergy Asthma Immunol* 2019;122:559-62.
14. Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, Hourihane JO, et al. AR101 Oral immunotherapy for peanut allergy. *N Engl J Med* 2018;379:1991-2001.
15. Wasserman RL, Factor JM, Baker JW, Mansfield LE, Katz Y, Hague AR, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. *J Allergy Clin Immunol Pract* 2014;2:91-6.

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Closing the door on social determinants of health and asthma disparities: Not so fast



To the Editor:

We read with interest the article by Guilbert et al,¹ which aims to address the important question of whether racial and ethnic asthma disparities are caused by differences in social determinants of health. Although asthma disparities research is critically important, particularly because we have made little progress in reducing these disparities, there are some methodologic limitations and overinterpretation of the results, which call for a reevaluation of the study's conclusions and implications.

Because the statistically significant differences in measures of asthma burden between black and white children were not eliminated by including various factors in statistical models, the authors concluded that the study “extends the finding of an increase in asthma burden in black compared with white children to a phenotype with severe or difficult-to-treat asthma.” The results of the analyses, however, suggest that a substantial proportion of differences observed between black and white children were in fact explained by fairly simplistic measures of

socioeconomic status (SES). For example, adjustment for residence in an urban area, health insurance type, and median income in the zip code of residence reduced differences in the exacerbation score by approximately 40%, suggesting that addressing poverty- and neighborhood-associated factors would reduce the exacerbation disparity by this amount. This degree of reduction would dwarf the advances in reducing disparities that have been made over more than 3 decades!

A second concern is that the measures of SES and environmental differences were unlikely to capture all relevant variation by race that has resulted from multigenerational policies of segregation and racial discrimination. On the one hand, the experience of what it means to live in an urban core or neighborhood with a particular level of SES can be quite different for black and white families, with important implications for health outcomes.² And, on the other hand, the measures fail to capture multiple aspects of SES.³ For example, even when comparing blacks and whites with similar incomes, blacks experience much greater financial and social hardship, and one study found that these differences in hardship explained approximately 40% of differences in asthma readmission rates between black and white children.⁴ Not only were measures of financial and social hardship not captured in the Guilbert et al study, other factors such as wealth, health literacy, and direct measures of a host of environmental exposures were also not captured. The authors acknowledge this limitation, but the magnitude of this limitation warrants a reevaluation of the conclusions.

A final important point is the framing of racial and ethnic differences in the burden of asthma as being *confounded* by SES and other factors rather than what *mediates* racial and ethnic differences. Focusing on *mediation* enables us to pay critical attention to the role that race—including a broad range of historical antecedents, contemporary policies, and everyday experiences—plays in the distribution of these factors, which may in turn catalyze poorer outcomes.⁵

Although we can all agree with their conclusion that there is a “high unmet need for this population” and “on the importance of improving outcomes for black patients with pediatric asthma,” focus on the biologic factors that underlie disparities in asthma outcomes obscures the modifiable factors that help us understand and address a large portion of these disparities.

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