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Conflicts of interest
The authors disclose no conflicts.

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Reply. We agree with Philpott et al, that the mechanism for eosinophilic esophagitis (EoE) remains unclear, and that IgE antibodies are usually present and could play an important role, particularly in the early stages of the disease. However, one must clearly distinguish causal mechanisms from disease markers. Immunity is complex, with many seemingly redundant pathways. The only way to prove that a mechanism induces an immune response is to block it and see what happens. IgE depletion by omalizumab had no effect on symptoms or tissue eosinophil counts in our trial of mostly adult subjects. Philpott et al, correctly note that this is in agreement with the Rocha et al study,[1] which we cited.[2] However, our double-blind placebo-controlled trial of 30 subjects (which was called for by Rocha et al) is stronger evidence than an open-label, uncontrolled study of 2 subjects.

We also agree with Philpott et al, that showing esophageal mast cell IgE depletion is a crucial confirmation of treatment effect. Contrary to their statement, we did it! (See Supplementary Figure 2 of our article.[2]) We agree that the failure of omalizumab might not apply to pediatric or recent onset EoE, and that occasional IgG4-negative, IgE-mediated adult cases might happen, as stated in our discussion.

We do not "boldly contend" that adult EoE is mediated by IgG4 antibodies. We stated: "Although IgG4 immune complexes could be causal, we have no evidence to support that over other potential mechanisms." It remains highly plausible that EoE is entirely T-cell mediated. Also, as hypothesized for IgG4-related disease,[3] activated B cells could activate or promote the survival of pathogenic target-food-directed memory Th2 cells.

Oral immunotherapy for food allergies, in which the goal is a tolerance-inducing IgG4 immune response, causes EoE in 2.7% of patients.[4] While inconclusive, this certainly hints that IgG4, or the inflammatory pattern that induces IgG4 plasma cells, could play a role in EoE.

That IgE is not directly causal in most adults with EoE would not preclude the possibility that it could be a useful marker indicating the trigger foods. However, results of allergy-test-directed food elimination diets have varied widely; a recent meta-analysis found allergy-test-directed food elimination diets inferior to six-food elimination and elemental diets, with 45.5%, 72%, and 91% overall response rates, respectively.[5] More work is needed to accurately predict the trigger foods for an individual patient. It is plausible, although unproven, that IgG4 serology might be useful in addition to or in place of IgE.

We agree with Philpott et al, and so state in our paper, that our IgG4 serology findings must be interpreted cautiously and do not prove any practical clinical utility for such testing. IgG4 food reactivity is present even in some normal controls; false positives among atopic patients will likely be problematic. However, regardless of the control results, the presence of food-immunoreactive IgG4 in EoE has two implications: (1) IgG4 blocking antibodies are often present and might help explain the false negative allergy skin testing for trigger foods that is common in adult EoE, and (2) combined with particulate IgG4 immunostaining, it suggests that IgG4 immune complexes might be present, potentially activating cells (like eosinophils) lacking the inhibitory FcγR2b receptor. As stated above, the clinical significance of this hypothetical pathway is unproven.

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Conflicts of interest
The authors disclose no conflicts.

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