Reply

To the Editor:

The concerns raised by Wasserman[1] and Modena et al[2] regarding the article by Randhawa and Marsteller[3] target 3 areas: breadth of the data presented, structure of the database and machine learning model, and replication of the Tolerance Induction Program (TIP) outcomes. Both Wasserman[1] and Modena et al[2] raise specific serum marker values as either missing or not indicative of anaphylaxis risk. Our article[3] provides all descriptive serum marker data for patients in the cohort. As all patients met the criteria of a 3-mm or larger skin prick test response to cow's milk and a grade 2 or higher anaphylactic reaction to cow's milk within 12 months of study entry, the persistence of milk allergy in the cohort is highly likely. Regarding adverse events, more than 50,000 at-home doses and more than 1,000 oral food challenges were conducted during the study. At an adverse event rate of only 1.3%, the distribution of these events across different types of mammalian milk was not statistically significant. Historically, we do see slightly greater adverse events during sheep milk protein cycles.

The comments in the correspondence from Wasserman[1] and Modena et al[2] on machine learning reflect pedestrian experience in data science. Database development is paramount in machine learning models. When starting TIP, patients first undergo the following assays: skin prick test, interleukin panel, complete blood count with differential, immunoglobulin level testing (IgG subclasses, IgE), and expansive laboratory-developed diagnostics tests to measure levels of specific IgE to food proteins and environmental proteins. All assays are run in the diagnostic laboratory at TPIRC, which is fully regulated as a Clinical Laboratory Improvement Amendments–approved level 3 high-complexity laboratory. The data collected from this process are entered into our proprietary machine learning software system, which produces a patient-specific treatment program for the patient. The patient then receives the appropriate treatment cycles of protein from our manufacturing facility. Every 7 to 8 weeks, the patient returns for clinical food challenge to advance along his or her treatment program. During this time, clinical data during reported adverse events are collected in our 24/7 on-call center. Dose vector adjustments are made on the basis of the machine learning model specific to that patient. The patient then undergoes the same assays noted from the beginning of the program at 12-month intervals. These data are entered into machine learning software to assess the efficacy of the current treatment vectors for the specific patient. The process repeats itself until the final challenge of treatment. The same assay testing continues on an annual basis into remission. The total testing data utilized in TIP machine learning and artificial intelligence (AI) are summative, chronologic, and boosted for optimal performance. Unfortunately, Wasserman[1] and Modena et al[2] did not read our AI article describing the details of our machine learning process in detail.[4] In fact, the Food Allergy Institute shared its data and machine learning code publicly in the article (under accessible data).

The final concern regarding reproducibility of TIP reveals a complex truth. For nearly 2 decades, we have built large databases of immunobiology, protein biology, and evolutionary protein data. The years of clinical interventions and applied mathematics led to machine learning models in 2009. The subsequent treatment of what now amounts to more than 16,000 patients to a state of unlimited allergen consumption on a weekly to monthly basis continues to train our machine learning and AI systems. The sheer volume of these data and the nexus of dozens of machine learning systems have yielded incomparable results. The success of the TIP is an example of applied mathematics solving clinical disease to a state of remission. This truth is complex and will require the joint effort of computer engineers, basic scientists, and clinicians to replicate our work. In short, we welcome it. In fact, the future of life science research and health care will move in this direction. Indeed, some institutions are replicating our work in machine learning.[5]

A final note on trust: the Food Allergy Institute has been publishing its work in peer-reviewed journals in molecular science, clinical outcomes, and machine learning for the past decade.[3,4,6,7] The organization operates under federal and state regulatory agencies in laboratory, data, and research science. The only concern regarding trust arises from a few OIT practitioners. The greatest trust that we maintain is with the more than 16,000 patients and families in TIP. As we expand our facilities and outreach, we invite our allergy colleagues to learn more about TIP, as we anticipate offering the treatment regionally in allergists' offices.

DISCLOSURE STATEMENT

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