Can artificial intelligence (AI) replace oral food challenge?

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Allergists are aware of the diversity of their patients' personal history of allergic disease(s), the potential complexity of their individual pathophysiology, and the variety of treatment interventions (comprising both immunotherapy and other suitable treatments) that can be attempted. One recent development, the possible applications of artificial intelligence (AI) to the broad field of allergic diseases, has been extensively reviewed by van Breugel et al.[1] As stated in the abstract of their review article,[1] "The field of medicine is witnessing an exponential growth of interest in AI, which enables new research questions and the analysis of larger and new types of data."

A long-standing goal in food allergy (FA) diagnostics is replacing oral food challenge (OFC), which is the current standard of FA assessment and involves the patient ingesting food allergens under the supervision of an experienced allergist. But OFC exposes patients to the risk of anaphylaxis, and it is time- and resource-intensive. Composite clinical symptom scores and many biomarkers could be used in place of OFCs for diagnosing FA; they including food-specific IgE, epitope-specific IgE, basophil activation tests (BATs), transcriptomics and other omics, and many more such items that are in development. Moreover, FA diagnosis often involves not only use of a binary classification (ie, allergic or nonallergic) but also assessment of the risk of severe reactions, potential cross-reactivity with other foods, and suitability for treatment.

With such a large parameter space, AI, which excels at extracting information from high-dimensional, unstructured, and diverse data sets that are too complex for traditional data analysis, is well suited for examining all available data to guide clinical decision making.

BUT COULD AI REPLACE OFCs?

Thus far, studies have demonstrated the power of AI for identifying IgE epitope biomarkers,[2] combining activation markers to enhance BAT diagnostic accuracy,[3] and evaluating microbiome profiles,[4] among others. There have also been efforts to combine data from multiple clinical instruments and biomarkers to predict the outcome[5] and severity of reactions in OFCs.[6] AI can also be used to generate threshold levels of "at-risk" food protein amounts that place an individual at risk of development of an allergic reaction and are personalized to match the needs of an individual with food allergy.

Nevertheless, as van Breugel et al suggested, "applications that go beyond proof of concepts and deliver clinical value remain rare, especially in the field of allergy."[1] For many patients who currently have allergic diseases, actionable AI-based interventions in disease management have not yet been realized or are not widely available. This raises the questions of why and what are we waiting for?

As for any new method, we need further validation of AI diagnostic algorithms in larger cohorts. There may also be "algorithm aversion"—a psychological reluctance to trust AI. For FA diagnostics, the limited availability of quality test data may also be limiting. For example, in the study by Chinthrajah et al,[6] basophil activation was identified as the strongest predictor of OFC severity among 94 available clinical, laboratory, and demographic features using a multistage machine learning model. However, the BAT is not yet broadly accessible. Currently, the standard BAT (which measures the activation of living basophils by a variety of potential allergens) must be done in specialized laboratories, and generally, blood must be obtained and tested within 24 hours to establish reactivity of basophils to challenge with various amounts of candidate allergens.[7,8] When performed properly, BATs can demonstrate allergic reactivity for many food allergens with high accuracy. Notably however, some patients may have basophils that are unresponsive to challenge with antigens that are demonstrably not tolerated by the patients.[7,8] Such "antigen-unreactive" basophils may occur in as many as 5% to 15% of all patients with FA.[7,8] If such results are obtained, the BAT is not useful, and a mast cell activation test using passive sensitization of the mast cells with only plasma from the patient may provide more conclusive results.[8]

Nevertheless, in the majority of patients with FA, BATs alone can give an accurate identification of the food allergens to which the patient is sensitive, providing approximately 95% accuracy for many food allergens as opposed to approximately 50% when standard assays of food allergen-reactive IgE are used.[7] Then why is the BAT not used more often for diagnosis of food allergies?

First, conventional BATs generally must be performed on freshly prepared blood, and ideally, the test must be completed within 24 hours of venipuncture. Although we have shown that this amount of time is sufficient for the overnight shipment of freshly obtained blood, the tests of basophil reactivity must be performed promptly thereafter.[7] Notably, Beckman Coulter is developing a BAT that stabilizes stimulated blood for 5 days before analysis.[9]

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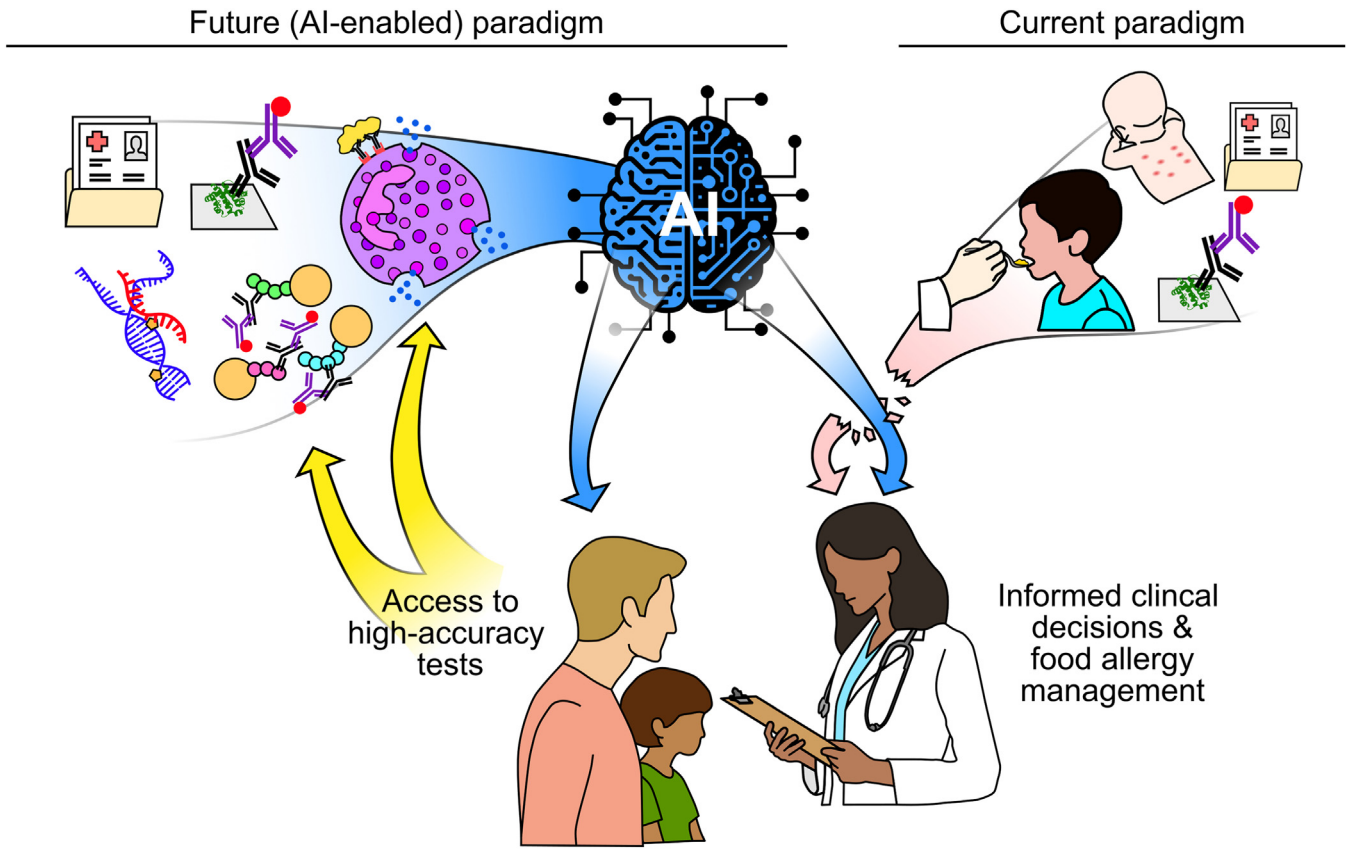

FIG 1. The current paradigm of FA diagnostics relies on OFCs (the criterion standard), skin prick tests, specific IgE tests, and medical history, but all of these approaches are either inaccurate, unsafe, or impractical for frequent use. The future of FA diagnostics, if freed from *in vivo* challenges, may consist of various AI-enabled tests, each contributing some biologic insight. BATs, epitope mapping, and omics methods, along with sIgE tests and medical history, will be used to generate rich, high-dimensional data sets. AI will synthesize these comprehensive data to build patient-specific models, guiding doctors and patients in selecting optimal FA management strategies. This future (AI-enabled) paradigm has the *potential* to make routine use of OFCs and skin prick tests obsolete. And with the continued development of accurate diagnostic tests, their accessibility will increase—and their use will, it is hoped, become part of common clinical practice.

Second, the blood must be analyzed by technicians who are highly competent in flow cytometry analysis of the basophils after stimulation with candidate allergens and suitable controls. As a result, although there is abundant evidence of the utility of BAT for allergy diagnosis, its use has been restricted to specialized centers.

Our group has been attempting to make the BAT much more accessible.[10] If successful, our approach will permit widespread adoption of the BAT for the more precise diagnosis of FAs. Clearly, there are many other promising avenues of research on developing improved FA diagnostics, some of which are reported in other articles in this issue of the *Journal of Allergy and Clinical Immunology*.

AI algorithms can be and have been developed to use multiple clinical features and conventional (but individually less accurate) FA tests (ie, skin prick tests and IgE tests) *without* the BAT or advanced diagnostics for FA assessment. However, one must consider the trade-off in costs and interpretability between performing many less accurate tests and a single highly accurate test (or small number of highly accurate tests). We think that the availability of high-quality diagnostics should go hand in hand with the development of AI in the future of FA diagnostics.

We envision a time when FA diagnoses based on conventional assays of IgE alone or even OFCs have been replaced by much more powerful and widely available tests that are complemented by AI (Fig 1). It will be of great interest to see which of the new research directions will yield successful approaches to substantially improve methods for the diagnosis of FAs (to eventually replace OFC), as well as for the treatment of FAs and other allergic disorders.

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