

allergic diseases potentially attributable to GM foods when regulated by rational guidelines. The 21st century will likely be remembered as the period when humans mastered the manipulation of the genome to control the variety of extant biology. Urbanization makes us dwell in the paradox of alternating between biologically sterile homes and an atmosphere of tire particles and exhaust fumes. With increasing globalization, it is common to spend the formative years of our immune system in an environment very different from the rest of our life. In a few decades, we are likely to live in a world where the transition between natural and synthetic biology is seamless. Against that backdrop, the effect of GM foods on allergic disease is just one of the plethora of influences on the immune system to be considered.

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## Genetically modified products and food allergy Beliefs, evidence, and opportunity



The effect of genetically modified (GM) products on human health is a timely and important topic. This month's CME Review does an excellent job providing background on this technology, outlining potential health concerns as they relate to food allergy, and summarizing evidence on this topic.<sup>1</sup> The article addresses 2 issues that practicing physicians face. First is the increasing disconnect between scientific evidence and popularized fixed health care beliefs and concerns. The second is the many questions we face for which evidence is lacking. Recognizing both these aspects of care is important to provide proactive, engaged, and collaborative care to our patients.

The concern about increased or novel allergenicity related to GM products dates back more than 20 years and was prominently documented in a *New England Journal of Medicine* study that found that the introduction of Brazil nut protein into soybeans resulted in specific IgE binding of that protein in vitro and positive skin test results in sensitive individuals.<sup>2</sup> In addition, in the early 2000s, cases of anaphylaxis were reported after suspected exposure to Starlink corn.<sup>3</sup> Starlink corn was not developed for human consumption but found its way into the human food supply nonetheless. These reports led to a Centers for Disease Control and Prevention (CDC) study that relieved this concern through in vitro testing and oral food challenges.

The disconnect between public discourse and scientific evidence is apparent in the concern over the safety of GM products. Despite the CDC study and reassurance from the scientific community, media reports still presented the findings with skepticism, with one report stating, "If Starlink didn't make them sick, what did?"<sup>4</sup> For allergists, this question seems rhetorical. In daily clinical practice, allergists routinely encounter patients with allergic symptom for which allergens are not identified. For many patients, particularly those with chronic idiopathic urticaria, not identifying

an external trigger for their symptoms is a difficult concept to internalize.

Effectively communicating this concept can be difficult, and patients sometimes are unreceptive to the practitioners' estimation of their situation. Fixed health care beliefs often present challenges in delivering optimal care. Perhaps the most notable example is the ongoing vaccine controversy. Despite strong evidence supporting the safety of vaccines, many parents continue to believe that vaccines present intolerable risks for their children. In the case of GM products, public concern over the safety of these products, even if not routed in evidence, can be difficult to overcome. At the bedside, patient concerns about GM products driving allergic symptoms may need to be addressed with the understanding that physician and patient belief in the evidence may not be aligned.

Another challenge that clinicians and patients often face is the lack of evidence. The authors' findings point out that the question of whether GM products will lead to increased allergy development has not been fully evaluated. Patients regularly ask their physicians questions for which evidence-based answers are unavailable. In allergy/immunology, our practice parameters contain a perhaps surprising number of recommendations based on low-level evidence.<sup>5</sup> When faced with evidentiary uncertainty, clinicians are well served to apply shared decision-making techniques to ensure our patients are given the opportunity to accommodate ambiguity into their choices.<sup>6</sup>

These discussions with our patients can serve as fertile ground for practitioners to connect with the communities we serve and work toward a shared and integrated understanding of health. An example of a program that attends to patient and population health with the community is Rooted Community Health, a program of Vanderbilt University's Center for Biomedical Ethics and Society. Focusing on engaging the community's concerns about food supply, agricultural production, and distribution methods as they intersect with health care, Rooted

Community Health is an interdisciplinary collaborative that brings together farmers, clinicians, community leaders, and patients to investigate how food sources affect the health of Nashville and the surrounding area.<sup>7</sup> As we engage with the key stakeholders, we have seen that GM products have become an ever present consideration in farming. Drawing on the resources within the medical center and the community encourages a rich collaboration that can help patients navigate complex decisions pertaining to their health in light of the ambiguity endemic to environmental and technological changes.

An allergist's purview directly connects our patient's health and the changing environment.<sup>8</sup> As changes and technology affect human health, our patients are left with the challenging task of sifting through what information they will internalize. Identifying fixed health care beliefs, areas of lacking evidence, and proactive approaches to form bridges to common goals are essential to effectively advocate for our patient's health. Although there is limited evidence that GM products are negatively affecting human health in terms of food allergy, this concern is an important opportunity to directly attend to our patient's nutritional needs and acknowledge the inextricable interconnectedness of environmental concerns, nutrition, and health.

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## Penicillin skin testing

### The devil is in the details

Although approximately 10% of the population carries a label of penicillin allergy, the vast majority of these individuals turn out to be tolerant of penicillins. The rate of positive penicillin skin test reactions in patients with a history of penicillin allergy seems to have been decreasing in the past 2 decades.<sup>1,2</sup> For example, Jost et al<sup>1</sup> reported a skin test positive rate of 6% from 1993 through 2003 compared with 27% from 1979 through 1992 in consecutive pediatric patients using the same full set of penicillin skin test reagents. The type of penicillin reaction history influences how many patients have positive skin test reactions. Patients with more recent penicillin reaction histories are more likely to have positive skin test reactions, because penicillin-specific immunoglobulin E wanes over time.<sup>3</sup> In addition, patients with convincing reaction histories are more likely to have positive skin test reactions than those with vague reactions, because the latter probably include more individuals who were mislabeled as allergic at time of their original reactions (hence, were never allergic at all).<sup>4</sup> Some studies have shown that hospitalized patients also might have a higher rate of positive skin test reactions compared with those undergoing evaluation as outpatients.<sup>5</sup>

In this issue of *Annals of Allergy, Asthma and Immunology*, Geng et al<sup>6</sup> present a retrospective chart review of all inpatient penicillin skin tests performed at a tertiary medical center over a 5-year period. Twenty percent of patients (107 of 528) had positive skin test reactions to penicillin. This value is higher than in most recent published studies and is likely related to the characteristics of the patient sample. Geng et al surmised that, compared with other

publications, the included subjects had a higher pretest probability of allergy mediated by immunoglobulin E from more recent or convincing reactions. However, there are no data presented on the specific reaction histories or time elapsed since their reactions. It also is not clear whether patients with vague reaction histories were preferentially excluded, because the decision to refer for penicillin skin testing was presumably at the discretion of the non-allergist hospital staff. Patients with vague or distant penicillin reaction histories might have been given  $\beta$ -lactams in a graded challenge (without prior penicillin skin testing), and penicillin skin testing consultation might have been reserved for those with more convincing or recent reactions.

The choice of penicillin skin test reagents also can affect the positive skin test reaction rate. Geng et al used a complete set of major and minor allergenic determinants including penicilloyl polylysine (PPL), penicillin G, penicilloate, penilloate, and amoxicillin. Among the findings were observations that 26% of patients with positive skin test reactions reacted solely to penicilloate or penilloate and 8% reacted only to amoxicillin. Therefore, exclusion of these skin test reagents (ie, testing with only PPL and penicillin G) would have missed these patients. In contrast, most US large-scale studies of penicillin skin testing, using a similar set of skin test reagents, found that approximately 10% of subjects showed positivity to only penicilloate or penilloate and 3% to 15% showed positivity only to amoxicillin.<sup>7</sup> Geng et al did not document antibiotic treatment after penicillin skin testing; hence, it is unknown how many patients with negative skin test reactions were given penicillins and whether they experienced allergic reactions.

Previous research demonstrated that penicillin skin testing has a very high negative predictive value.<sup>8,9</sup> This was true whether only PPL and penicillin G were used or all major and minor determinants

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