

Suddenly Steakless: A Gastroenterologist's Guide to Managing Alpha-Gal Allergy

Sarah K. McGill, MD, MSc, FACG¹, Robert D. Richards Jr, MD² and Scott P. Commins, MD, PhD³

Am J Gastroenterol 2022;117:822–826. <https://doi.org/10.14309/ajg.000000000001765>; published online April 8, 2022

Alpha-gal allergy is an emerging clinical syndrome, first described in the 2000s, that can cause gastrointestinal (GI) distress, hives, angioedema, and anaphylaxis hours after ingestion of pork, beef, and other mammalian meat or meat-derived products (1). Various publications in the allergy, GI, and general medicine literature have described patients with the allergy who present with GI-isolated symptoms without typical allergic symptoms such as angioedema or hives (2–8). Here, we aim to inform gastroenterologists on how to diagnose and manage alpha-gal allergy.

CASE 1

A 58-year-old woman with no medical history presented to our GI clinic in 2018 with 2 months of abdominal bloating, diarrhea, mucous in the stools, and urgency to have bowel movements. She had no rash, difficulty in breathing, or dizziness. Stool studies for fecal pathogens and fecal calprotectin were normal. Serum alpha-gal immunoglobulin (Ig)E was 1.27 kU/L (upper limit of normal <0.35 kU/L). She was instructed to stop eating mammalian meat. Her symptoms improved but not immediately, and she also stopped taking dairy. At 2 months after initiation of the avoidance

diet, she canceled her planned colonoscopy because her symptoms had resolved. At the 2-year follow-up later, she reported daily formed bowel movements without GI distress. She strictly avoided mammalian meat and only ate small amounts of dairy. On 3 occasions at her work site, she had inhaled bacon that was frying and had developed urgency to defecate and mucous in the stools that lasted less than a day.

ALPHA-GAL ALLERGY: THE BASICS

The reaction is caused by hypersensitivity to the mammalian sugar galactose-alpha-1,3-galactose (alpha-gal), and affected individuals typically have elevated IgE antibodies to alpha-gal in the serum. Initially reported only in 2009, research on alpha-gal allergy is evolving, and the information presented here is based on current knowledge. In the United States, bites from the lone star tick (*Amblyomma americanum*) have been implicated as the cause of IgE sensitization to alpha-gal. Thus, people living in the Southeastern and Midwestern United States are most at risk, particularly those who spend time in the outdoors. The most common GI symptoms include diarrhea, abdominal pain, nausea, and vomiting, and the most common skin symptom is urticaria.

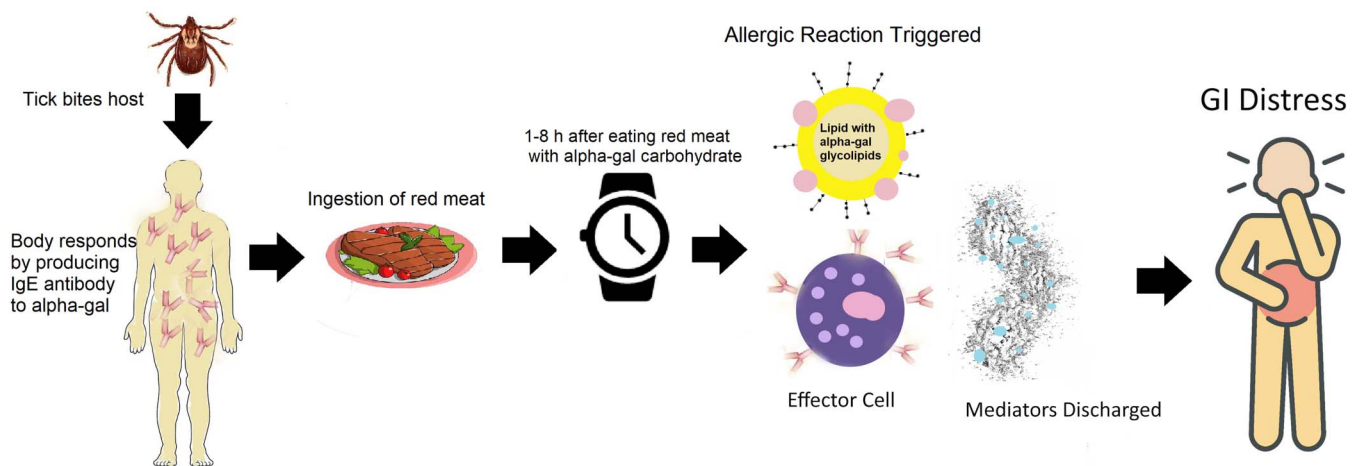


Figure 1. Representation of the proposed pathophysiology of alpha-gal allergy. A tick bites the host, injecting the mammalian cells of a prior host, which elicits the formation of IgE antibodies to alpha-gal in the human. Hours after the ingestion of a meal of mammalian meat, the individual develops allergic reaction, which may manifest as gastrointestinal (GI) distress, rash, and anaphylaxis.

¹Division of Gastroenterology and Hepatology, Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA;

²Gastroenterology Associates of Central Virginia, Lynchburg, Virginia, USA; ³Division of Allergy and Immunology, Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. **Correspondence:** Sarah K. McGill, MD, MSc. E-mail: mcgills@med.unc.edu.

Received January 18, 2022; accepted April 4, 2022



Figure 2. The lone star tick. Ticks are implicated in alpha-gal sensitization (courtesy of James Gathany, Centers for Disease Control).

Because the reaction is delayed, patients can awake with symptoms late at night and often do not relate their symptoms to meat ingestion.

DIAGNOSIS

The diagnosis of alpha-gal food allergy can be made with a positive test for alpha-gal IgE and improvement of symptoms on an appropriate avoidance diet, explained below. Alpha-gal IgE is an inexpensive serum-based test performed in the United States by Viracor-Eurofins and in Europe by Phadia ThermoFisher. Most commercial laboratories offer send-out tests to these reference laboratories.

The GI symptoms of alpha-gal allergy—abdominal pain, nausea, vomiting, and diarrhea—are not specific and overlap with those of other clinical entities, such as food poisoning and gut-brain disorders. We feel it is reasonable to test for alpha-gal in patients with unexplained GI distress and no red flag symptoms, particularly in those who live in or have traveled to geographic areas in the United States where the lone star tick is prevalent. Of

note, other species of ticks have been linked to alpha-gal allergy in numerous locations outside of the United States (see “Geographic Distribution”). Patients who have a history of allergic rhinitis, eczema, and other allergic conditions may be particularly at risk.

It is important to note that IgE antibodies are not a perfect diagnostic test. Patients with alpha-gal IgE elevations may not have clinical allergy symptoms, and patients with confirmed alpha-gal allergy on food challenge have tested negative for IgE antibodies.

MANAGEMENT: MEALS, MITES, AND MEDS

The cornerstones for managing alpha-gal allergy are meals (avoiding alpha-gal in the diet), mites (avoiding tick bites), and, for some patients, medications.

Meals

We recommend that patients with alpha-gal allergy avoid pork, beef, lamb, venison, other mammalian meats, organ meats, and derived fats, such as lard and tallow. Fish, other seafoods, chicken, and other fowl are fine to eat. We counsel that if symptoms persist, patients should exclude dairy in all its various forms (e.g., cow’s milk, cheese, butter, sour cream, and ice cream). Should symptoms still continue, we ask patients to avoid gelatin, food additives, and medications that contain a gelatin coating or are sourced from mammals (Figure 3).

Mites

We counsel patients on the importance of avoiding tick bites by wearing boots, light pants, and tick repellent in the woods because further bites can worsen the allergy, which otherwise may wane over time. Ticks typically access humans at their ankles, so wearing a tight mesh stocking as a legging covering from boot laces to above pants cuff is very effective at preventing this.

Meds and medical devices

In the case of dietary alpha-gal exposure, a long-acting antihistamine, such as fexofenadine, may be used to ameliorate symptoms. All patients with systemic symptoms of urticaria, hives, and/or angioedema are at significant risk for anaphylaxis and should be prescribed an epinephrine autoinjector. However, we do not routinely prescribe this in patients with GI-isolated symptoms. In our cohorts of patients with GI-isolated symptoms, anaphylaxis on follow-up was rare and only occurred in 1 patient with alpha-gal IgE level >100 kU/L.



Figure 3. Recommended order of alpha-gal elimination from the diet: (i) mammalian meat with or without dairy; (ii) dairy; and (iii) gelatin, gelatin capsules, and mammalian food additives.



Figure 4. Female ticks on a hiking boot. Ticks may be difficult to discern because of their small size (courtesy of James Gathany, Centers for Disease Control).

On the other hand, patients should be aware that some medications and medical devices contain alpha-gal, such as pancreatic enzymes, which are derived from pork, porcine patches, and cardiac valves. Alpha-gal allergic patients with porcine bioprostheses may experience early failure of their devices (9). Pigs that were engineered to not express alpha-gal have been approved by the Food and Drug Administration for human consumption and medical use.

Follow-up

Patients with GI-isolated alpha-gal may eventually be able to tolerate eating mammalian products again. We recommend following alpha-gal IgE levels until they normalize (this may take months to years), and then, patients may challenge themselves with small servings of dairy products. If that is tolerated, a small serving of lean meat is a reasonable next step. Patients who have systemic allergy symptoms have significant risk of anaphylaxis with mammalian product consumption, and this may be delayed several hours, so the challenge in this group should only be performed in a monitored clinical setting with the assistance of an allergist.

GI-ISOLATED ALPHA-GAL ALLERGY: PREVIOUS STUDIES

Food challenges are the most rigorous way to prove food allergy: Patients are exposed to the allergen and monitored for allergic symptoms. In a combined cohort of challenge-proven alpha-gal allergic patients in South Africa (4) and the United States (10), 40.7% of patients (37/91) had isolated GI symptoms. In addition to those studies published in the allergy literature, we (S.K.M. and R.D.R.) presented our experiences as gastroenterologists diagnosing alpha-gal allergy among patients who presented to our GI clinics with nonspecific GI concerns. We found elevated IgE antibodies to alpha-gal among 16 GI clinic patients in North Carolina and 122 patients in Virginia and followed up these patients after they were counseled to stop eating mammalian meat (2,3). The most common GI symptoms were abdominal pain, diarrhea, nausea, and vomiting, and only a small minority of patients exhibited rash or other systemic symptoms. A

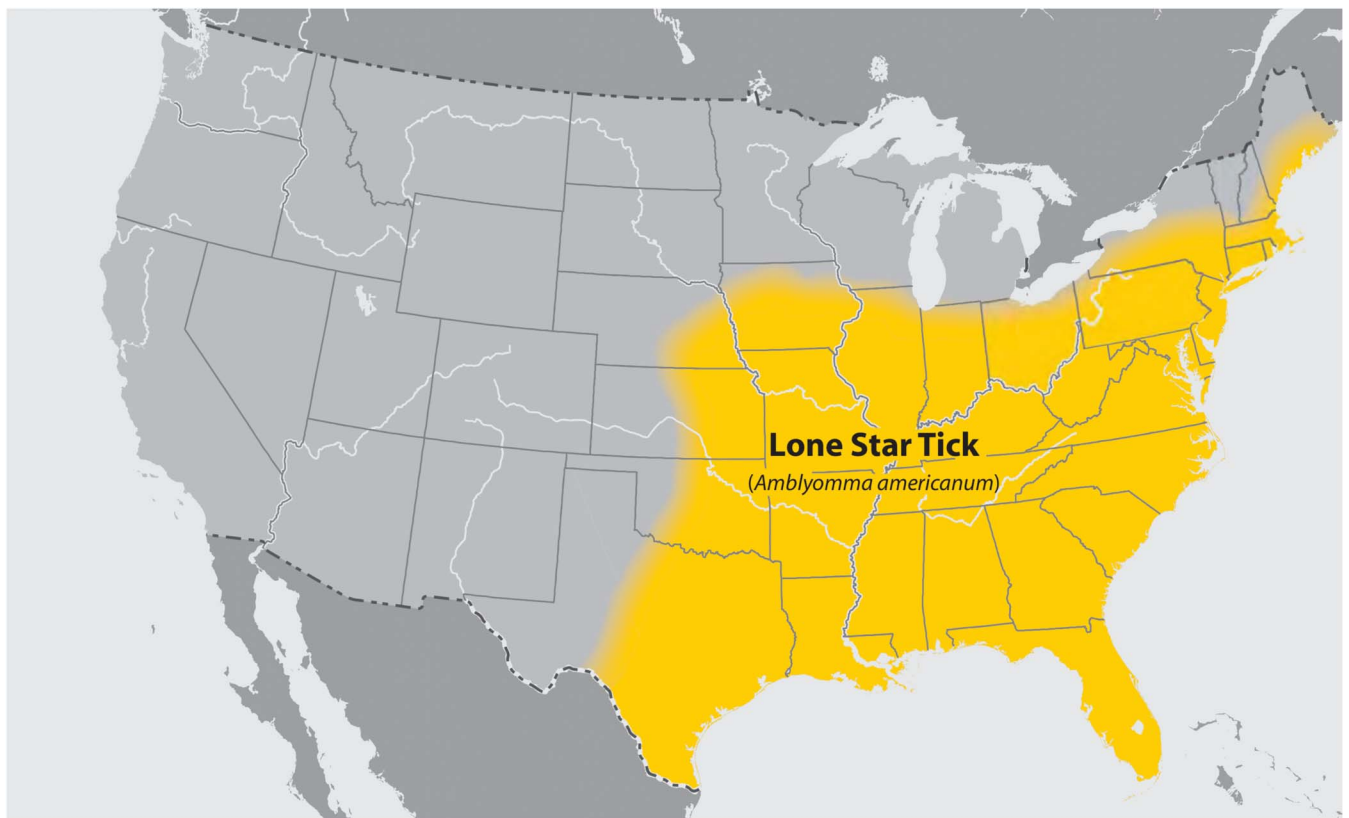


Figure 5. Range of the lone star tick, the primary tick implicated in alpha-gal sensitization in the United States (courtesy of the Centers for Disease Control).

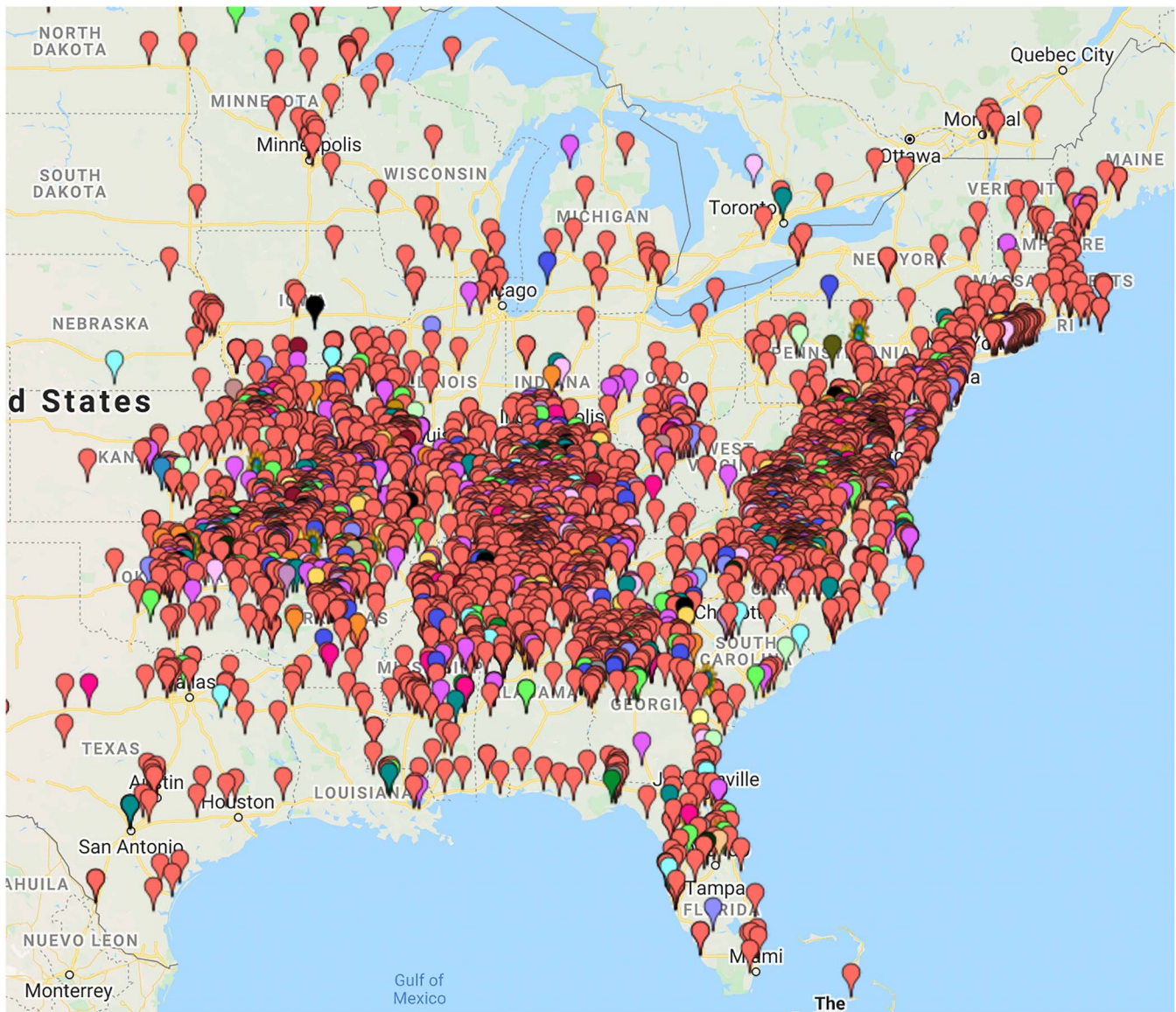


Figure 6. Patient-reported cases of alpha-gal allergy in a portion of the United States (available at Zeemaps.com).

majority of patients who were followed up after starting an alpha-gal avoidant diet endorsed improvement in symptoms on the diet.

PATHOPHYSIOLOGY

All mammals except Old World primates carry the alpha-gal carbohydrate antigen. Research supports that during a blood feeding, a tick injects alpha-gal and other haptens in its saliva into the human, provoking IgE antibody formation and thus sensitization to mammalian product ingestion (Figure 1) (11). The human GI tract is rich in mast cells, which act in the immune system to defend us from parasitic pathogens, among other roles. When a sensitized human eats mammalian meat, the alpha-gal is absorbed and presented to the alpha-gal-specific IgE present on mast cells, leading to mast cell degranulation. These mast cells release histamine and other products which act on cells to cause pain, vasodilation, inflammation, increased mucous secretion, and peristalsis.

ALPHA-GAL: THE STRANGEST FOOD ALLERGY

Alpha-gal allergy poses a diagnostic challenge because it does not fit the typical pattern of food allergy. IgE-mediated reactions are called immediate because they almost always occur quickly after exposure. By contrast, the reaction to alpha-gal is typically delayed by a few hours after eating. Most allergies cause reactions at each exposure. Not necessarily so with alpha-gal, both quantity and type of mammalian product consumed are important, and both alcohol and exercise seem to potentiate the reaction. Finally, most food allergies are due to proteins, develop as infants, and wane over time. Alpha-gal is a carbohydrate and has been described mostly in adults, although children also develop the allergy.

GEOGRAPHIC DISTRIBUTION AND CLIMATE CHANGE

Our understanding of the geographic distribution of alpha-gal allergy is based on case series (11). The Eastern United States is the region where alpha-gal has been most frequently reported,

although it extends from eastern Canada, to Texas, to Michigan. The syndrome has also been identified in Australia (12), Europe, Asia, and South Africa (4). In the United States, the lone star tick *Amblyomma americanum* (Figures 2 and 3) is strongly implicated in the development of alpha-gal allergy (13) and the geographic range of the tick (Figure 5) overlaps well with reported alpha-gal cases (Figure 6). Recently, the lone star tick has expanded its region into the Northeast United States, and climate change may lead to both further range expansion and longer active periods (14). Other hard ticks—*Ixodes ricinus* in Europe and *Ixodes australiensis* and *I. holocyclus* in Australia—have been implicated worldwide.

THE ALPHA-GAL ALLERGY DISCOVERY STORY

The alpha-gal sugar was known by earlier researchers to be problematic because it is the major barrier to xenotransplantation. All humans carry IgM, IgG, and IgA to alpha-gal. A pork kidney transplanted into a human, for example, would almost immediately be rejected by an immunologic attack mediated by these non-IgE alpha-gal antibodies (15). In 2008, oncologists in North Carolina, Missouri, and Tennessee noted that 1 in 5 patients receiving infusions of the chemotherapy agent cetuximab was developing anaphylaxis, although anaphylaxis had been rare in clinical trials. Researchers discovered that the patients who anaphylaxed had alpha-gal IgE, and cetuximab is a chimeric antibody heavily glycosylated with murine alpha-gal (16). Around the same time, researchers in Virginia and Australia were noting patients with delayed anaphylaxis to mammalian meat and a history of tick bites (6,12). Both observations were due to alpha-gal allergy.

CONCLUSION

Alpha-gal allergy is an emerging clinical syndrome, and gastroenterologists, particularly those practicing in the Southeast, Midwest, and mid-Atlantic regions, along with those in Europe, Asia, and Africa, may see patients who have GI symptoms from this allergy to mammalian products. We need more research to better understand the epidemiology, pathophysiology, and outcomes of patients with GI-isolated alpha-gal allergy.

CONFLICTS OF INTEREST

Guarantor of the article: Sarah K. McGill, MD, MSc.

Specific author contributions: S.K.M. wrote the article with critical revisions from R.D.R. and S.P.C.

Financial support: None to report.

Potential competing interests: S.K.M. and R.D.R. disclose no competing interests. S.P.C. discloses: Genentech-speaker's bureau; Uptodate-author's royalties; NIH, CDC-research grants.

REFERENCES

1. Commins SP, Platts-Mills TA. Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). *Curr Allergy Asthma Rep* 2013;13:72–7.
2. Croglia MP, Commins SP, McGill SK. Isolated gastrointestinal alpha-gal meat allergy is a cause for gastrointestinal distress without anaphylaxis. *Gastroenterology* 2021;160:2178–80.e1.
3. Richards NE, Richards RD Jr. Alpha-gal allergy as a cause of intestinal symptoms in a gastroenterology community practice. *South Med J* 2021;114:169–73.
4. Mabelane T, Basera W, Botha M, et al. Predictive values of alpha-gal IgE levels and alpha-gal IgE: Total IgE ratio and oral food challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. *Pediatr Allergy Immunol* 2018;29:841–9.
5. Houchens N, Hartley S, Commins SP, et al. Hunting for a diagnosis. *N Engl J Med* 2021;384:462–7.
6. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 2009;123:426–33.
7. Kinoshita M, Newton S. Alpha-gal allergy in a 6-year-old male: A case report. *JNMA J Nepal Med Assoc* 2019;57:379–81.
8. Richards NE, Makin T, Smith A, et al. IgE to the mammalian allergen galactose-alpha-1,3-galactose as a cause of isolated gastrointestinal distress. *Am J Gastroenterol* 2021;116:S537.
9. Kuravi KV, Sorrells LT, Nellis JR, et al. Allergic response to medical products in patients with alpha-gal syndrome. *J Thorac Cardiovasc Surg*. Published online April 9, 2021 (doi: 10.1016/j.jtcvs.2021.03.100).
10. Commins SP, James HR, Stevens W, et al. Delayed clinical and ex vivo response to mammalian meat in patients with IgE to galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 2014;134:108–15.
11. Platts-Mills TAE, Commins SP, Biedermann T, et al. On the cause and consequences of IgE to galactose-alpha-1,3-galactose: A report from the national institute of allergy and infectious diseases workshop on understanding IgE-mediated mammalian meat allergy. *J Allergy Clin Immunol* 2020;145:1061–71.
12. van Nunen S. The association between *Ixodes holocyclus* tick bite reactions and red meat allergy. *Intern Med J* 2007;37(suppl 5):A128–A135.
13. Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 2011;127:1286–93.e6.
14. Molaei G, Little EAH, Williams SC, et al. Bracing for the worst—range expansion of the lone star tick in the northeastern United States. *N Engl J Med* 2019;381:2189–92.
15. Galili U. The alpha-gal epitope and the anti-Gal antibody in xenotransplantation and in cancer immunotherapy. *Immunol Cell Biol* 2005;83:674–86.
16. Chung CH, Mirakhor B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 2008;358:1109–17.