

ALPHA-GAL SYNDROME:

*How tick bites and IgE to a sugar are
changing the paradigm of food allergy*

DANISH DERMATOLOGICAL SOCIETY – 19 January 2023

Scott Commins, MD, PhD

Associate Professor of Medicine & Pediatrics



FEATURE

What the Mystery of the Tick-Borne Meat Allergy Could Reveal

Unraveling why tick bites are suddenly causing a strange reaction in some people who eat meat could help scientists better understand how all allergies work.



In mid-2000s, we became aware of two distinct forms of anaphylaxis

VOLUME 25 • NUMBER 24 • AUGUST 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Allergic reactions to
cetuximab (Erbix)



- 1) Immediate
- 2) Consistent
- 3) Regional

Allergic reactions to
beef, pork & lamb

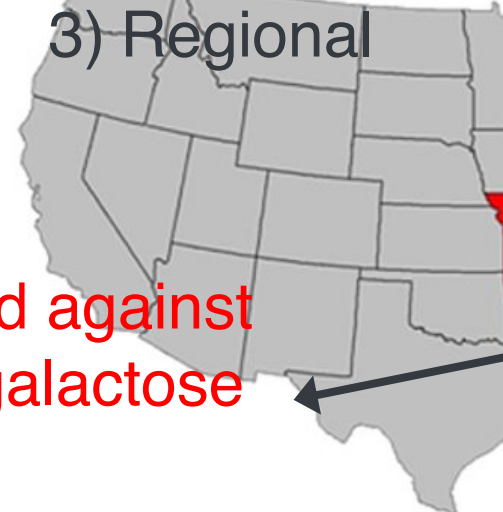
High Incidence of Cetuximab-Related Infusion Reactions in
Tennessee and North Carolina

Atopic History

Bert H. O'Neil, Robert Allen, David
and Richard M. Goldberg

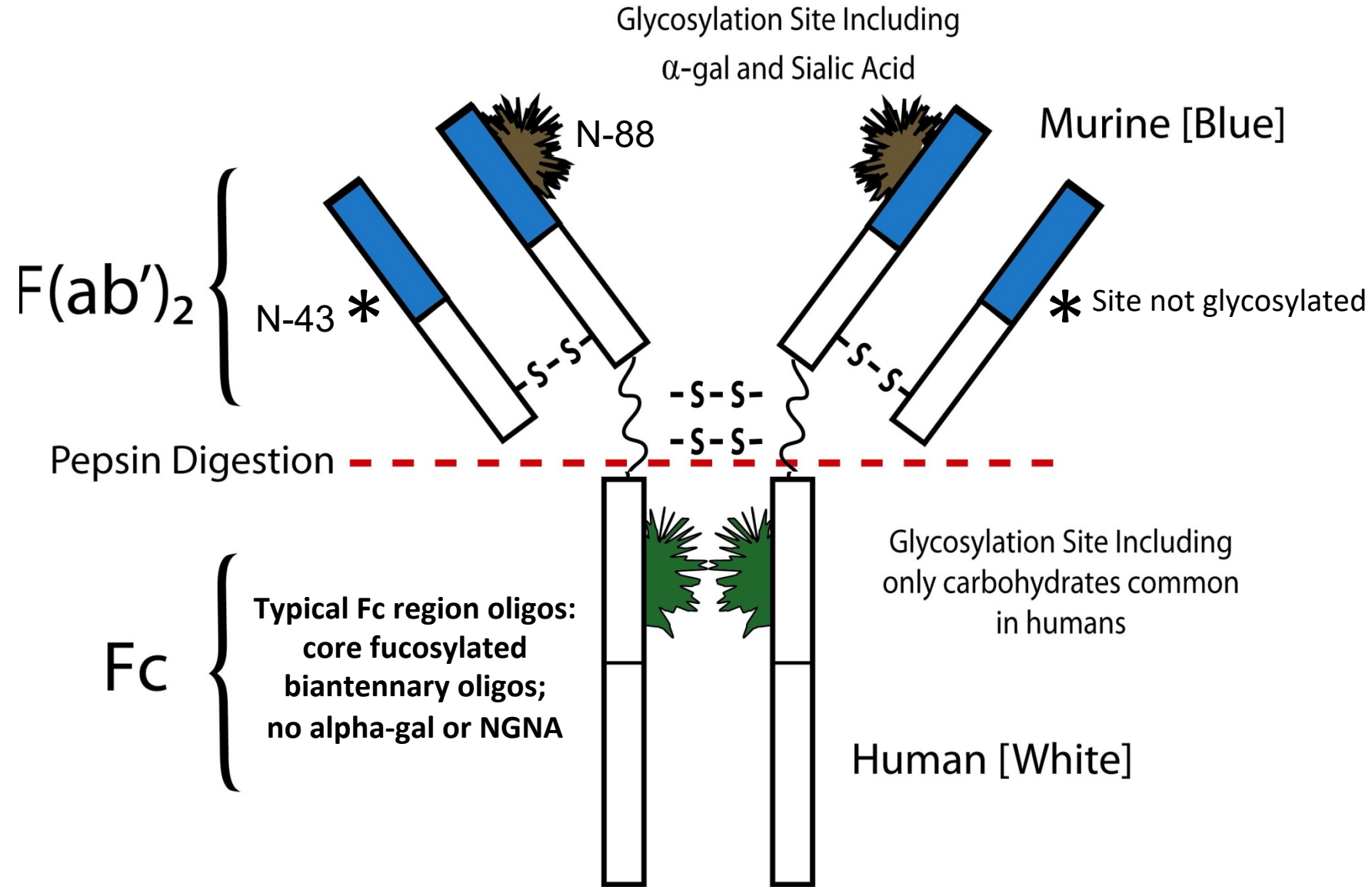
D. Berlin,

- 1) Delayed
- 2) Inconsistent
- 3) Regional



IgE antibodies directed against
galactose-alpha-1,3-galactose
("alpha-gal")

Imclone 'solved' the structure of cetuximab: revealed significant glycosylation with alpha-gal



ALPHA-GAL DETAILS

Blood group antigen A



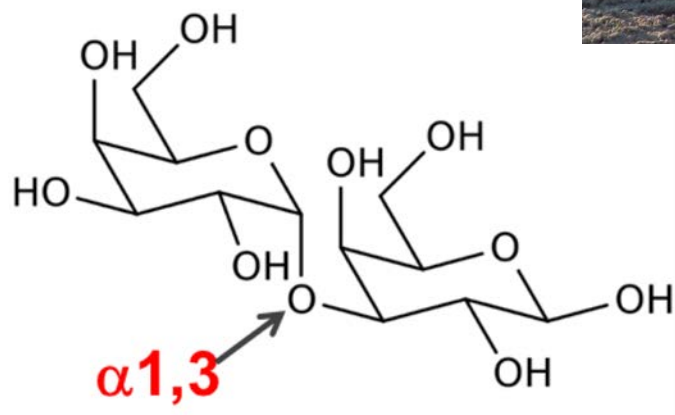
Blood group antigen B



Alpha-gal



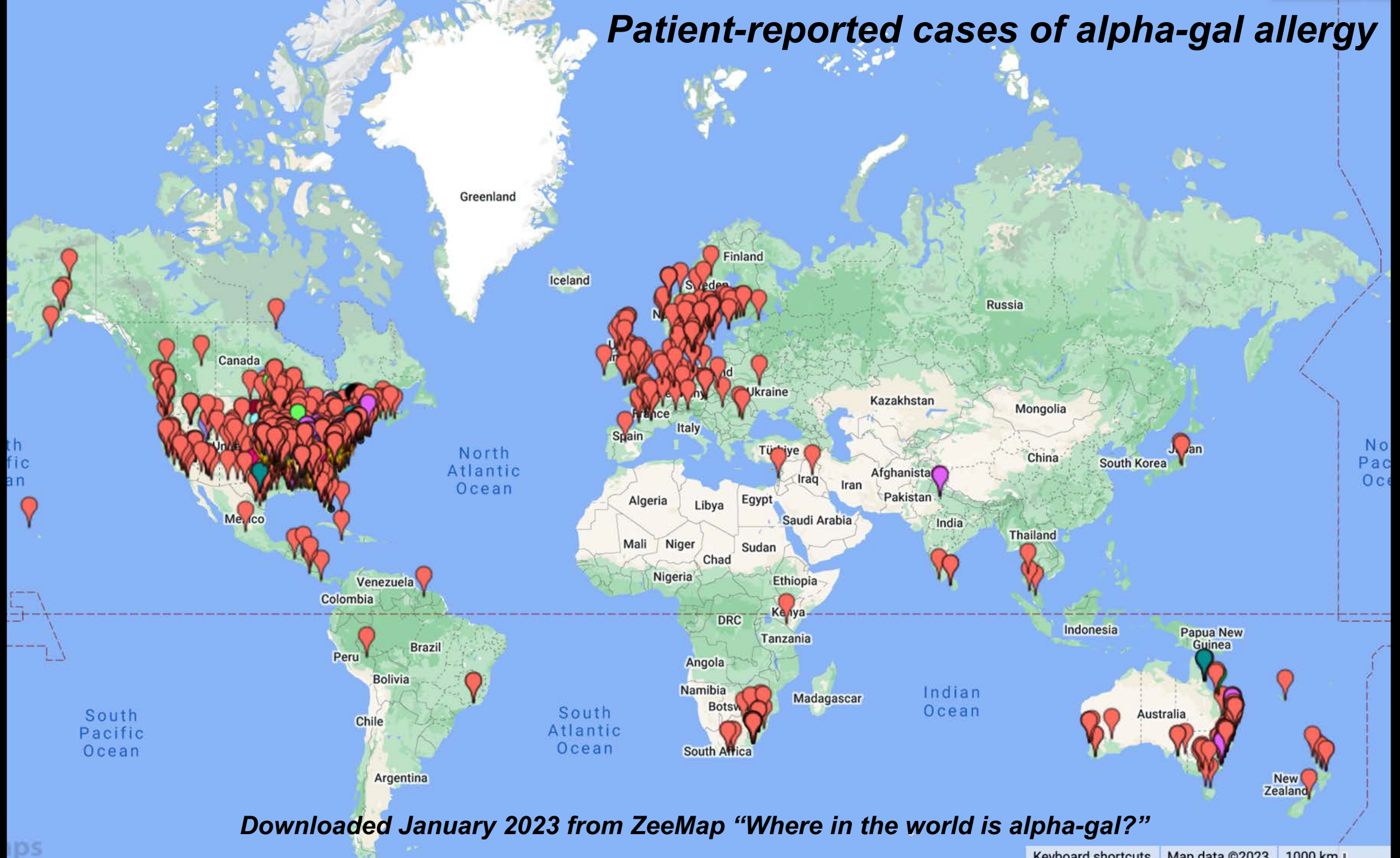
Glycan Structure Notation:



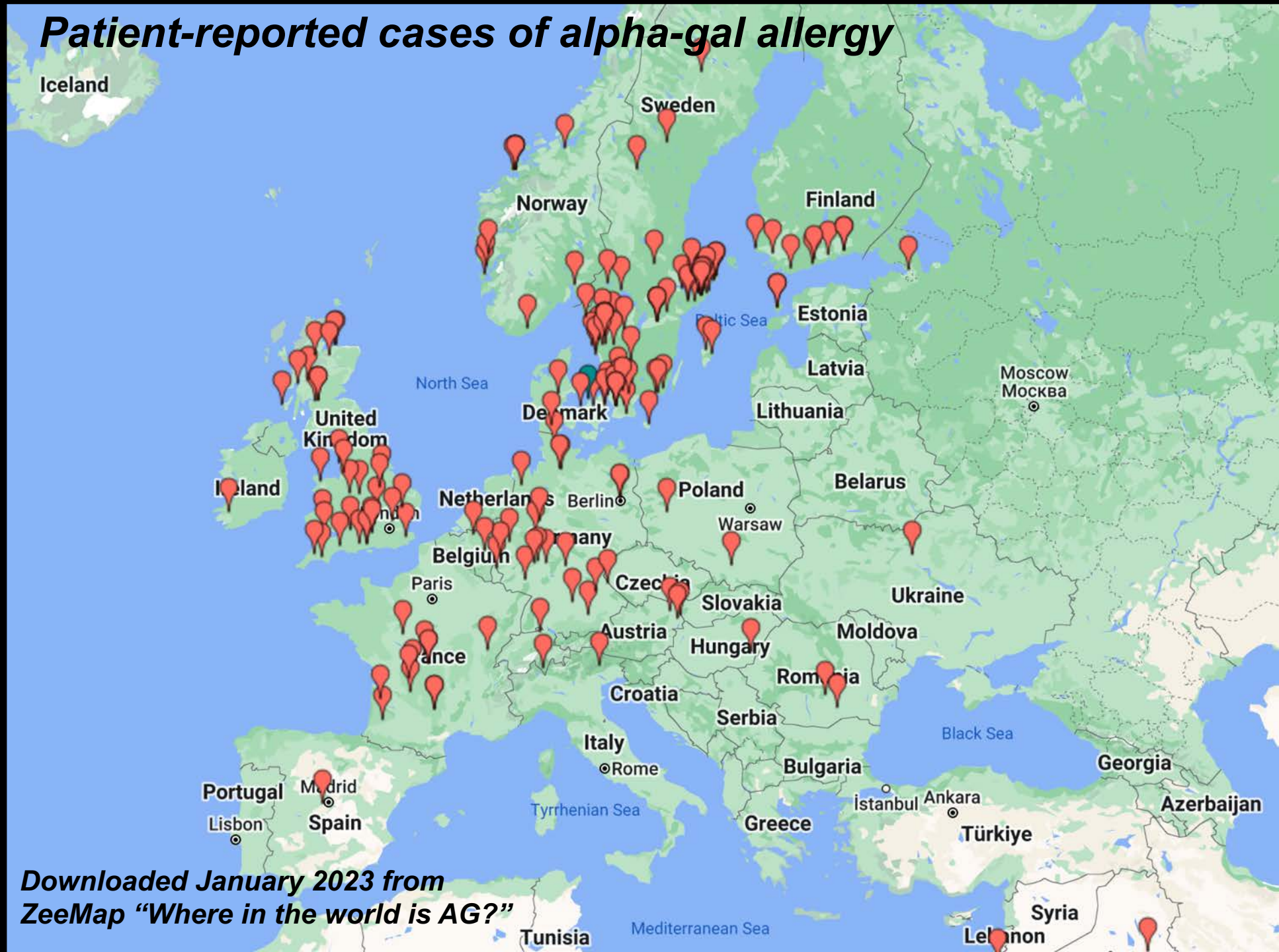
Alpha-gal



Patient-reported cases of alpha-gal allergy

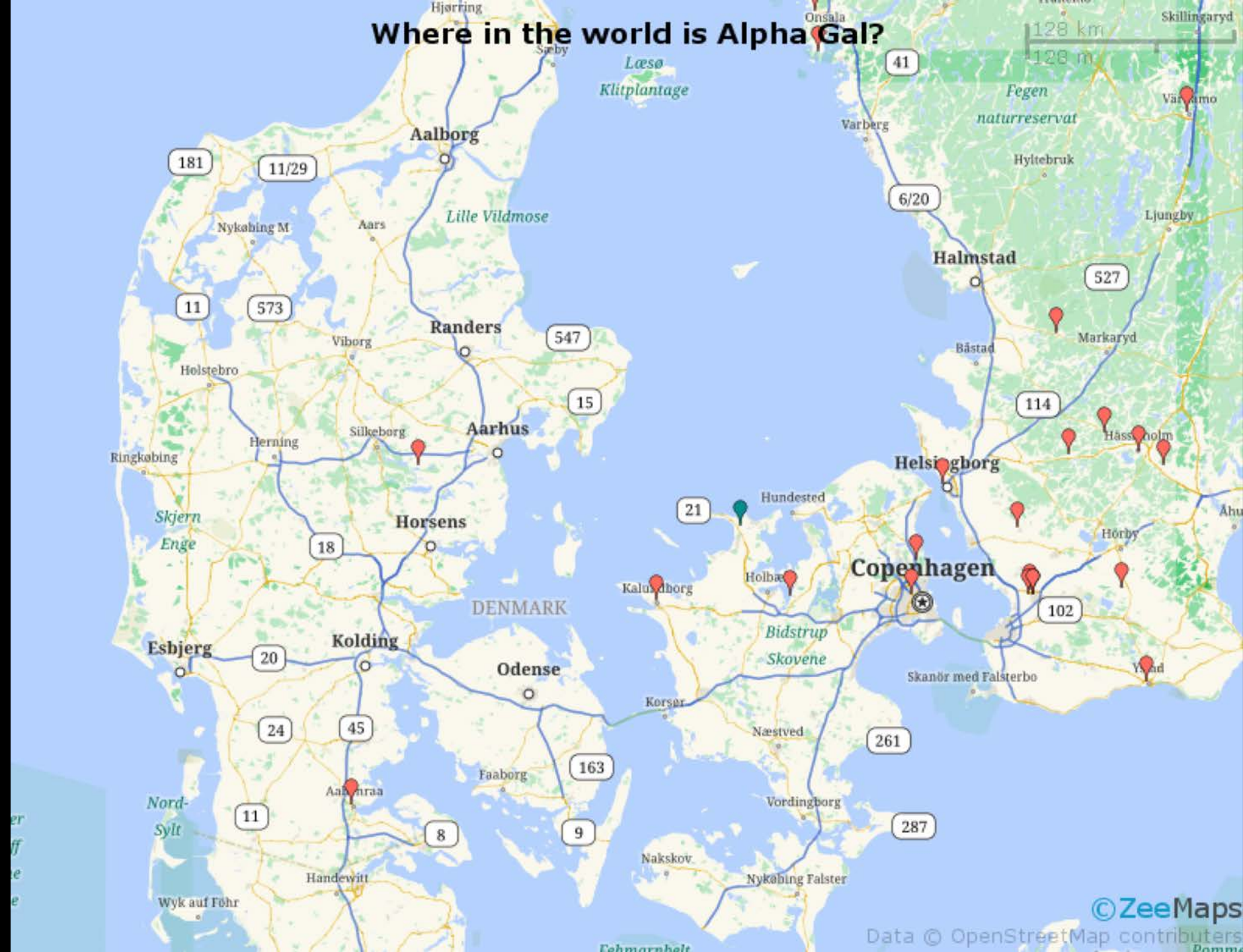


Patient-reported cases of alpha-gal allergy



***Downloaded January 2023 from
ZeeMap “Where in the world is AG?”***

Where in the world is Alpha Gal?



Where in the world is Alpha Gal?



In mid-2000s, we started to hear a similar history from a few adult patients:

“Hey Doc, I might be allergic to beef”

“but it’s weird...”

- The reactions do not happen right away
- The reactions do not happen every time
- Sometimes it’s really bad, other times just itching
- I might be bothered by pork now too...maybe lamb

Skin Testing Results: Often $<4\text{mm}$ SPT



PRICK TEST



INTRADERMAL

Prick test performed using lancette and intradermal testing with 25 gauge needle in the same patient on a single clinic visit.

Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose

Scott P. Commins, MD, PhD,^a Shama M. Satinover, MS,^a Jacob Hosen, BS,^a Jonathan Mozena, MD,^b Larry Borish, MD,^a Barrett D. Lewis, MD,^c Judith A. Woodfolk, MBChB, PhD,^a and Thomas A. E. Platts-Mills, MD, PhD^a *Charlottesville and Fredericksburg, Va, and Springfield, Mo*

JACI, February 2009

- 24 patients
- Virginia & Missouri
- Symptoms delayed 3-6 hours after eating mammalian meat
- Prick skin test often less than 4mm

Pork sausage challenge

Each patty ~25-30 grams with 10g fat/patty



Subject calls from car 30 minutes after being released to report progression of itching and “warmth to skin”



Initial picture upon arriving home (approximately 7.5 hours after eating pork sausage)

Approximately 8.25 hours after eating sausage





**-FC03 - sIgE to alpha-gal = 17.6
IU/mL; Total IgE = 184**

**-3:54 after consuming meat,
symptoms began as itching, flushing
and progressed: ultimately requiring
epinephrine**





AGS CLINICAL PRESENTATION

- 1) “Original” – signs/symptoms from red meat (fatty) ingestion;
tolerate dairy including pizza & ice cream
 - ❖ Itching, hives, swelling, N/V/D, hypotension, anaphylaxis

AGS CLINICAL PRESENTATION

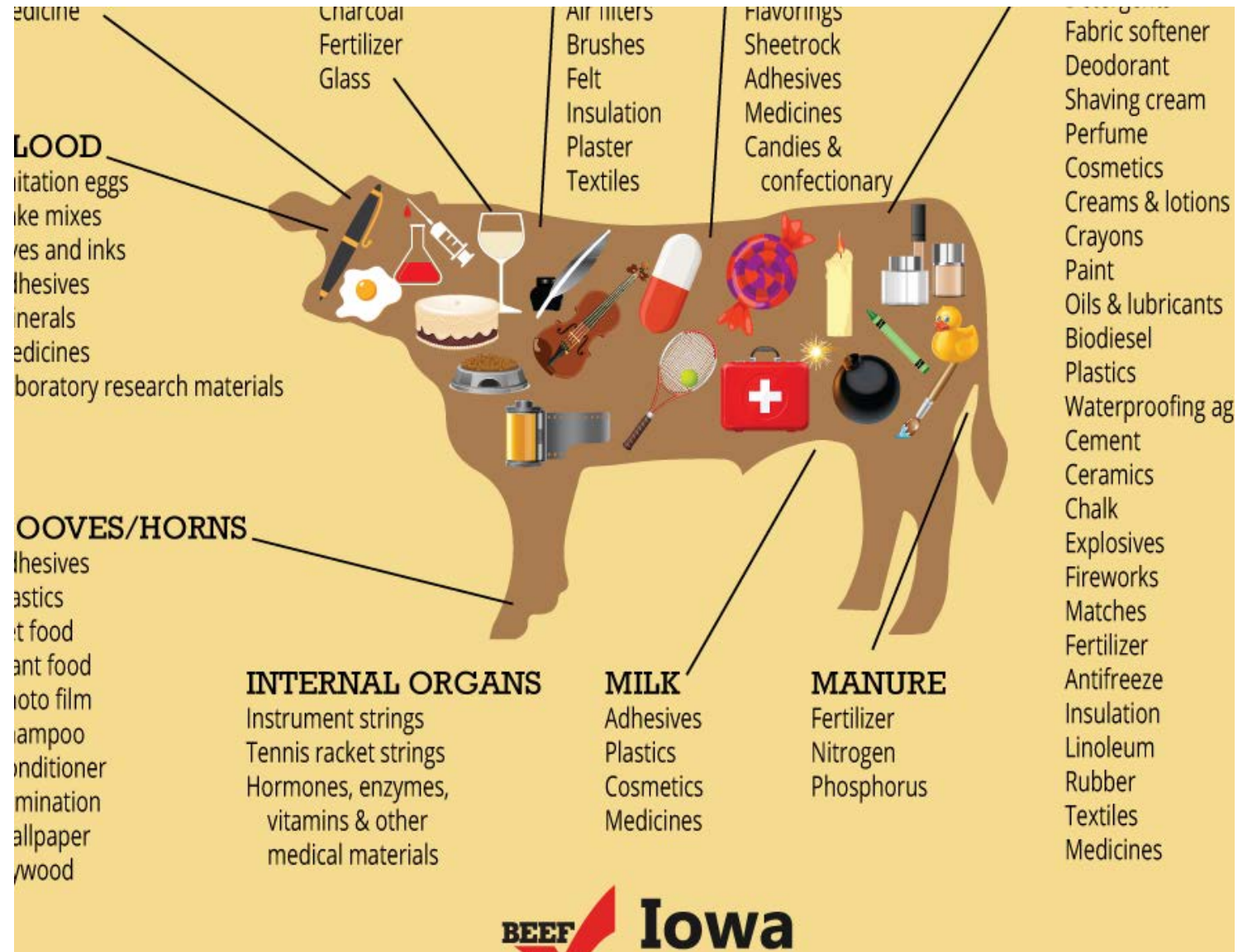
55 yo woman awoken from sleep at 1am due to itching of her palms. She noted her palms were “red and swollen” and when she turned on bedside lamp her torso was “covered in hives.” She reported feeling “intense” gastrointestinal cramping develop and collapsed on the way to the bathroom; the noise awakened her husband who called 911.

- She had leg of lamb at a restaurant for dinner earlier that evening
- And they enjoyed a “particularly good” bottle of wine with dinner

MANAGEMENT

- Avoidance diet:
 - *Mammalian meat, esp fatty cuts (ice cream)*
 - *Dairy and cheese often tolerated*
 - *Few issues with gelatin*
- Caution re: exercise, alcohol
- Monitor IgE to alpha-gal over time
 - *? Pork sausage (3) challenge when level declines significantly*

“Nearly all of the remaining weight is recovered as by-products”



EVERYTHING BUT THE Oink

No other animal provides society with a wider range of products than the hog.

By products from pigs play a vital, though less visible, role in maintaining and improving the quality of human life.





Phonograph records



Violin Strings



Bone China



Drumheads



Porcine Burn Dressings



Pigskin footballs



Cutting oils



Glycerin for explosives and antifreeze



Hides and skins for leather goods



Linoleum



Pet food



Stearin for making chewing gum and candies



Hair for artist brushes



Rennet for cheese making



Hearts for xenotransplantation



Gelatin for drug capsules



Insulin and ingredients for other medicines



Ingredients for surgical sutures



Fatty acids and glycerin used for matches



Gelatin for marshmallows and photographic film



Industrial lubricants

AGS PHENOTYPES & CLINICAL PRESENTATION

- 1) Original – signs/symptoms from red meat (fatty) ingestion;
tolerate dairy including pizza & ice cream
 - ❖ Itching, hives, swelling, N/V/D, hypotension, anaphylaxis
- 2) GI only – exclusive gastrointestinal symptoms from red meat /
dairy; occasionally symptoms are not as delayed

AGS CLINICAL PRESENTATION - "GI ONLY"

48 yo man from a rural area presented to the ED with "life-ending" abdominal pain. This was his 3rd acute care episode for abdominal pain in the past 6 months. An abdominal ultrasound was performed and several non-obstructing gallstones were noted. A cholecystectomy was performed.

- Two months later he returned to the ED with the same complaint
- He was referred to GI for further work-up; alpha-gal IgE =1.45
- Trial of red meat avoidance has resulted in no additional episodes over past 6 months

Isolated Gastrointestinal Alpha-gal Meat Allergy Is a Cause for Gastrointestinal Distress Without Anaphylaxis

Michael Croglia & Sarah McGill. *Gastroenterology*, In press

- Abdominal pain (87.5%), nausea (75%), and diarrhea (68.75%), mainly episodic (68.8%) vs chronic (31.25%), were the most common symptoms
- Nine patients (56.2%) met the criteria for diarrhea-predominant IBS
- Patients reported awakening at night with GI distress and did not report a response to every exposure
- No patient related GI symptoms to mammalian meat ingestion before diagnosis, and 75% recalled a tick bite
- The median time from symptom onset to diagnosis was 21 months

- Pancreatic enzymes Stone CA et al. *J Allergy Clin Immunol Pract.* 2020



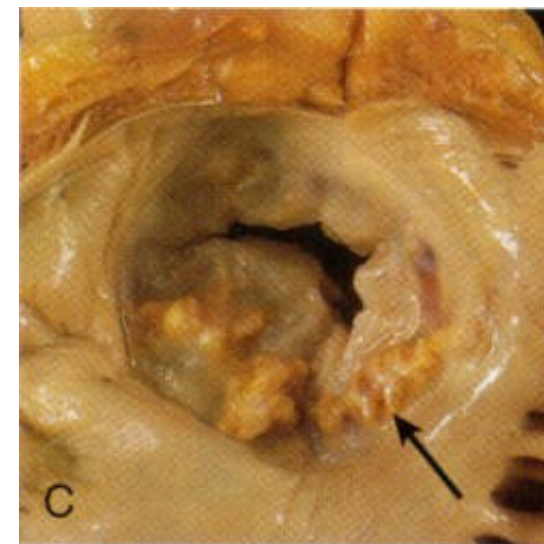
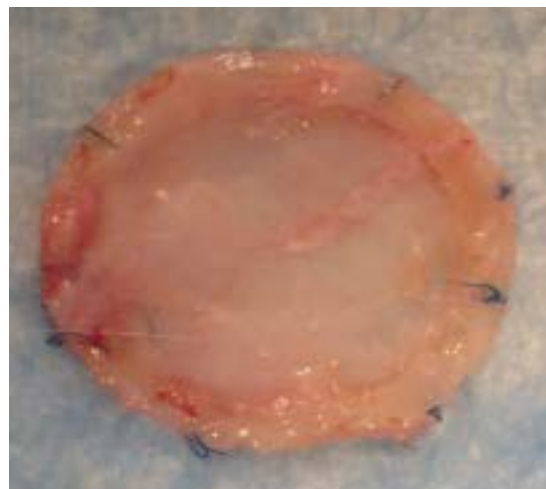
- IBS – how much of non-specific GI distress is AGS?
And does geography matter?

Then a patient with AGS had anaphylaxis following mitral valve replacement



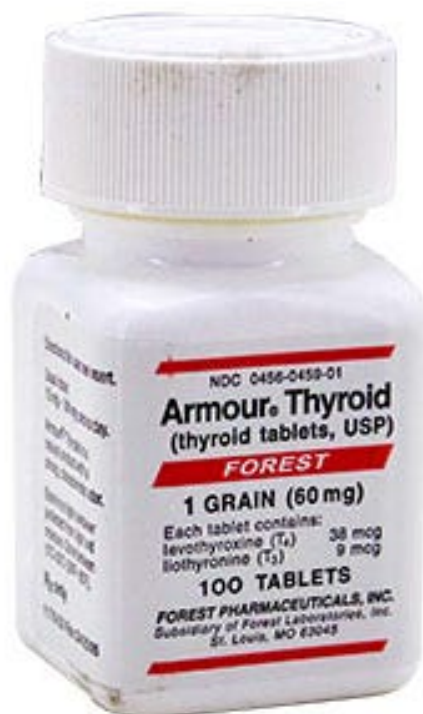
How deep are the implications?

- Pericardial patches
- Premature failure



Then a patient with AGS had anaphylaxis during cardiac catheterization





Rx only

Armour® Thyroid (thyroid tablets, USP)

Rev. August 2012

DESCRIPTION

Armour® Thyroid (thyroid tablets, USP)* for oral use is a natural preparation derived from porcine thyroid glands and has a strong, characteristic odor. (T3 liothyronine is approximately four times as potent as T4 levothyroxine on a microgram for microgram basis.) They provide 38 mcg levothyroxine (T4) and 9 mcg liothyronine (T3) per grain of thyroid. The inactive ingredients are calcium stearate, dextrose, microcrystalline cellulose, sodium starch glycolate and opadry white.

- Gelatin-based plasma expanders, such as Gelafundin, Gelofusine, Haemaccel
- Many vaccines, including those that contain gelatin or other mammalian byproducts. In the U.S., these include Zostavax, MMR, TDaP (Boostrix)
- Antivenom, such as crotalidae polyvalent immune Fab (CroFab)
- Other products that contain gelatin, such as:
 - Hemostatic agents, such as Surgiflo, Floseal hemostatic matrix and Surgifoam powder
 - Absorbable gelatin sponge, like Gelfoam
 - Gabapentin oral solution
 - Lidocaine patch
 - Gummy supplements
 - Vaginal capsules
 - Suppositories
 - Collagen-containing agents, including implants

TICKS. REALLY?

Adult female

Adult male

Nymph stage

Larval
stage



Bites from larval ticks and IgE to alpha-Gal



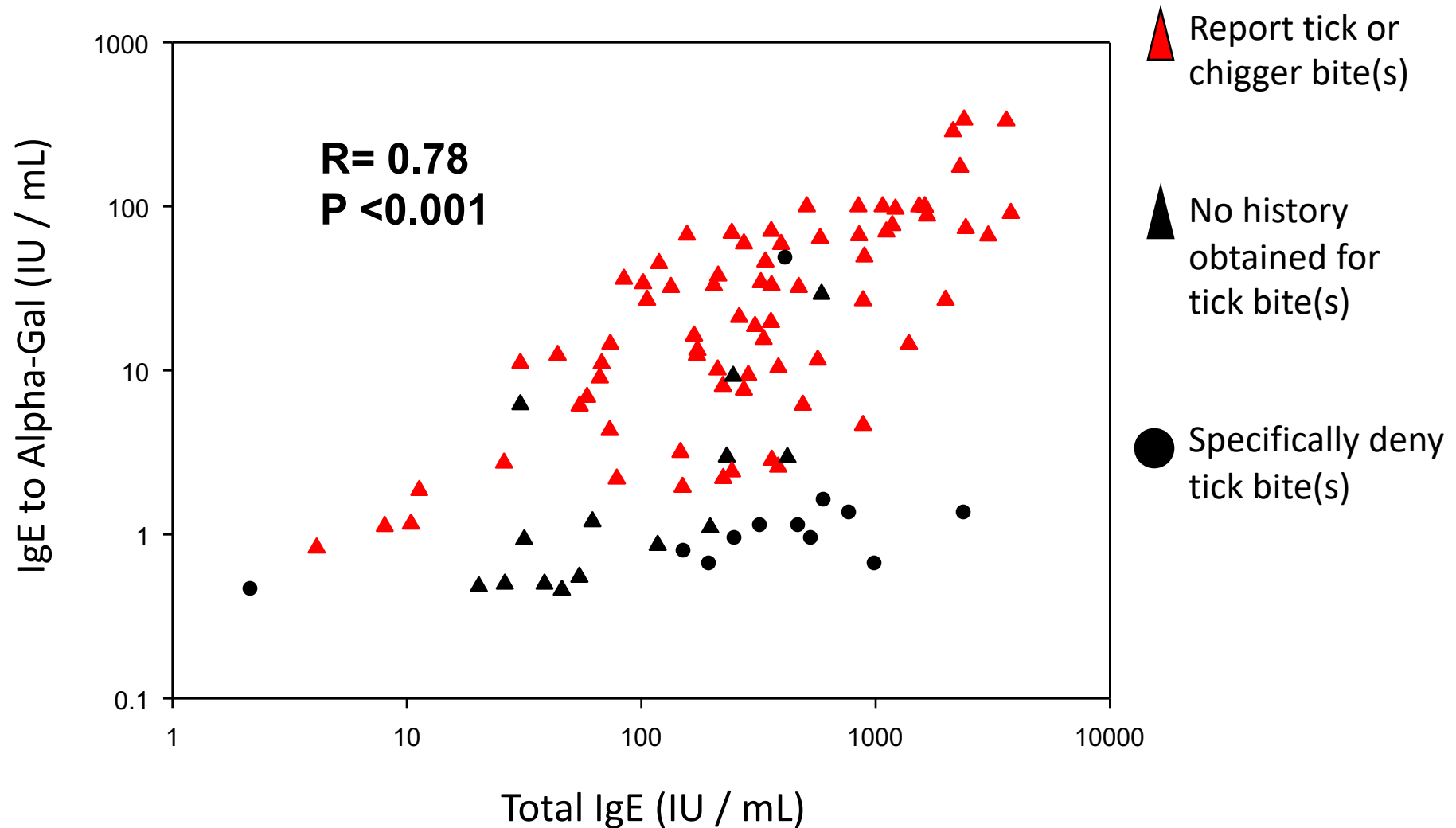
Photograph: August 23, 2009.

Test	5/21/09	10/9/09	11/6/09*
Alpha-Gal	negative	48.3	130
Total IgE	199	350	532

•Multiple bites by seed ticks are not uncommon in the Southeast.

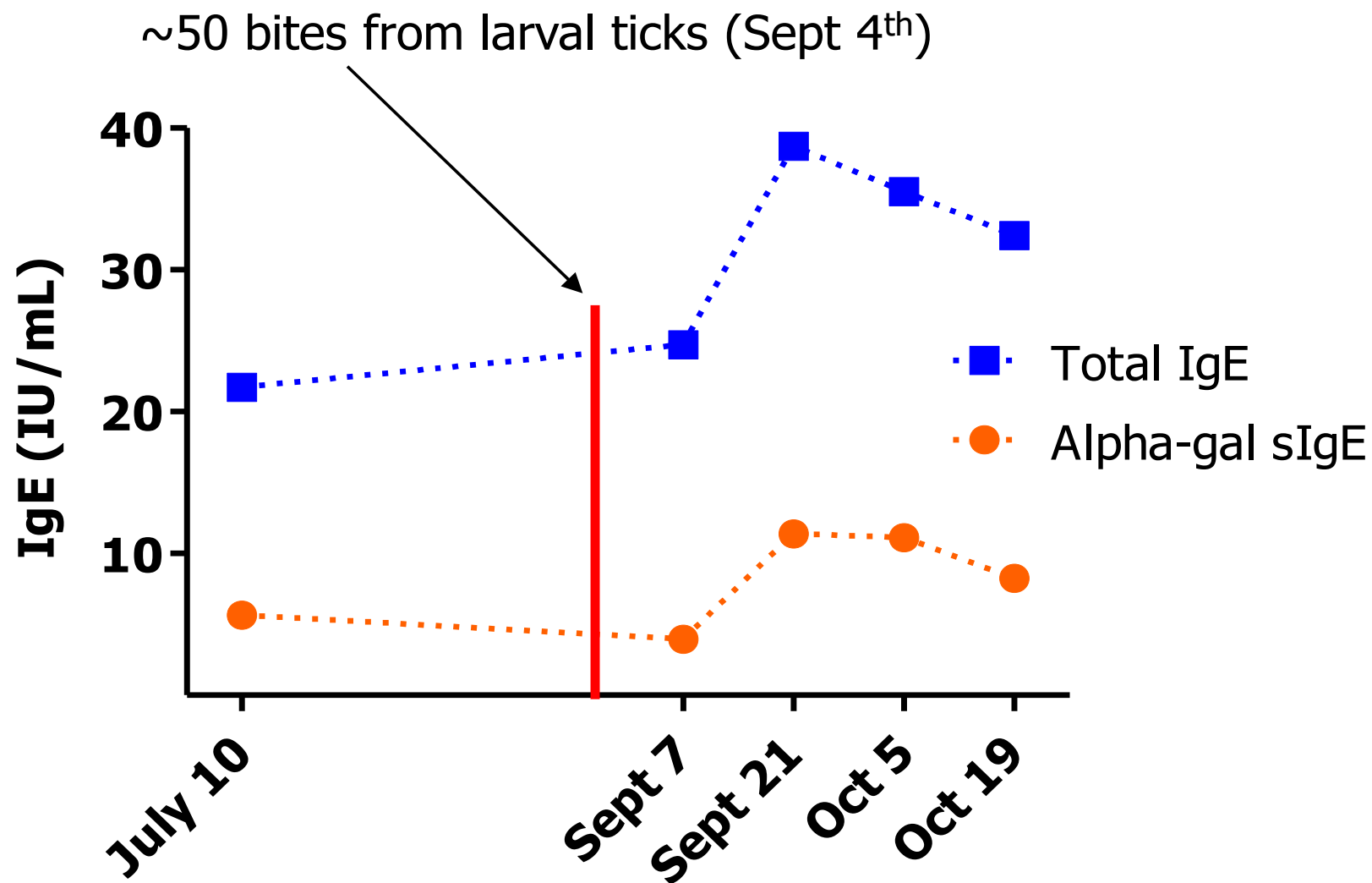
*Titers: Beef 19.2, Pork 10.1, Cat 17.5, Dog 19.8 IU/ml.
Chicken, Turkey, Roach, Dust Mite and Ragweed all <0.35 IU/ml
(undetectable).

Total IgE versus IgE to Alpha-Gal

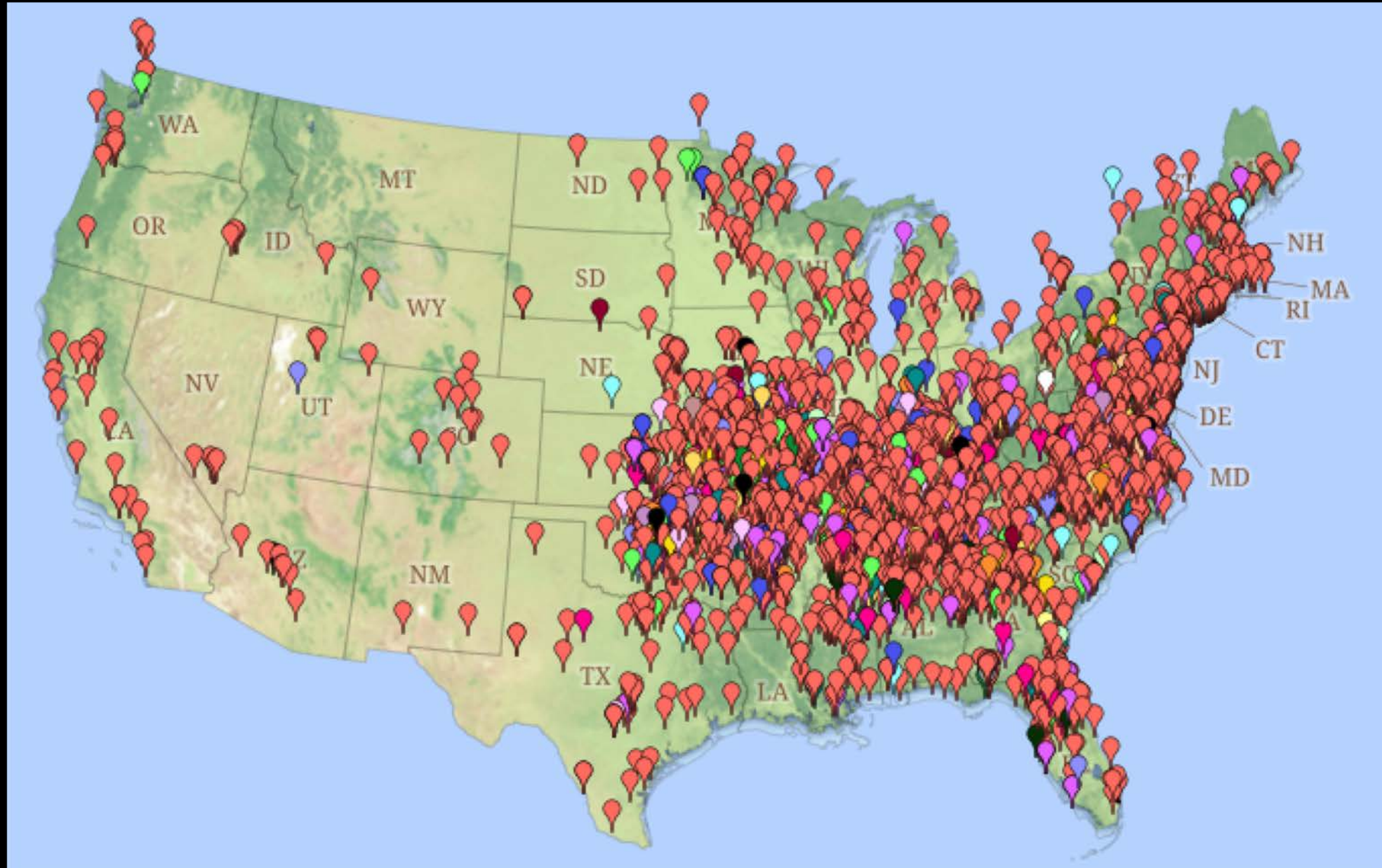




IgE to Alpha-gal and Total IgE Rise Following Tick Bites

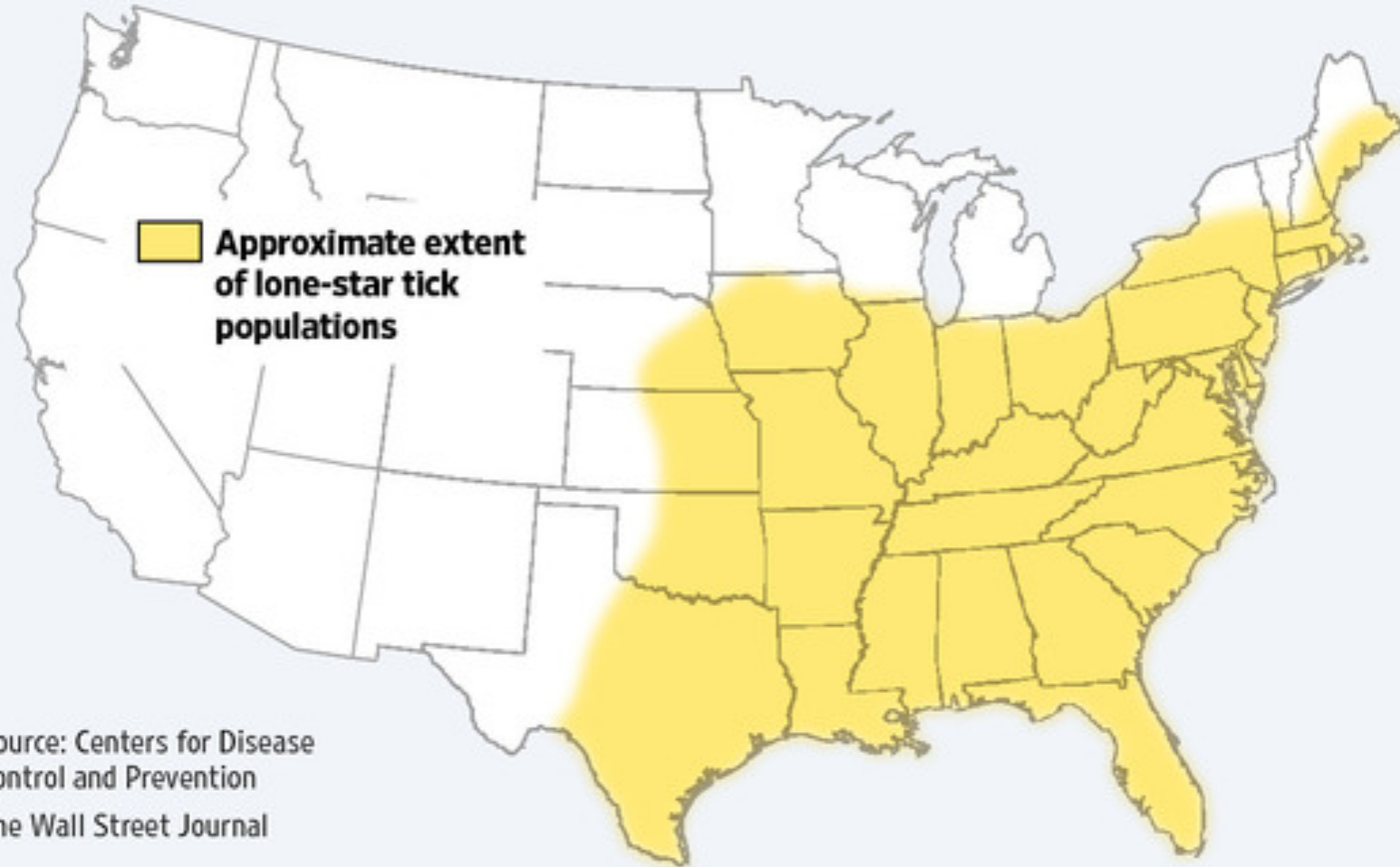


Patient-reported cases of alpha-gal allergy in the US



Tick Territory

The lone-star tick (not named for Texas) has spread significantly in recent years beyond the southeastern U.S.



Source: Centers for Disease
Control and Prevention
The Wall Street Journal

Different ticks, same allergy

> [Med J Aust.](#) 2009 May 4;190(9):510-1.

An association between tick bite reactions and red meat allergy in humans

[Sheryl A Van Nunen](#) ¹, [Kate S O'Connor](#), [Lesley R Clarke](#), [Richard X Boyle](#), [Suran L Fernando](#)

Affiliations + expand

PMID: 19413526

Abstract

Twenty-five patients living in a tick-endemic region of Sydney, New South Wales developed red meat allergy after experiencing large local reactions to tick bites. This represents a potentially novel cross-reaction between an arthropod and a food protein. (MJA 2009; 190: 510-511).

Implicated tick: *Ixodes holocyclus*

Different ticks, same allergy

Review > [Allergo J Int.](#) 2016;25(2):49-54. doi: 10.1007/s40629-016-0098-0.

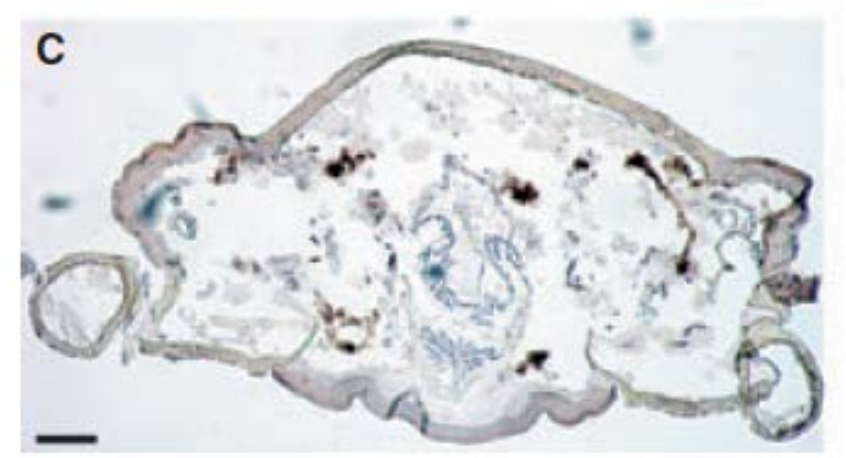
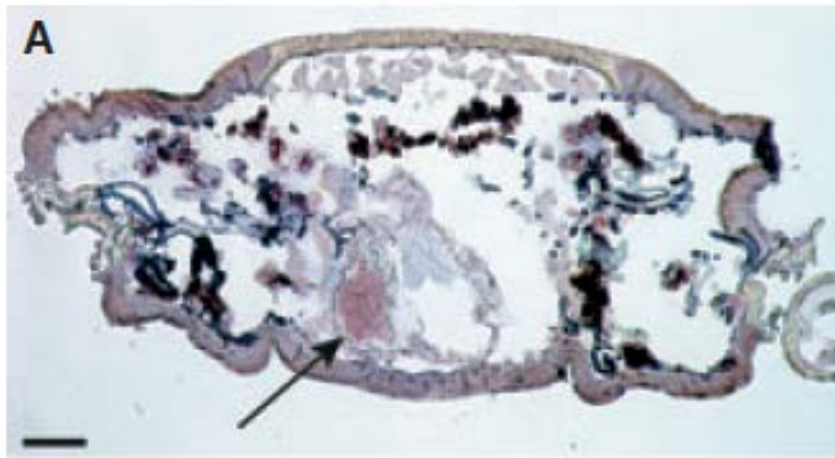
Epub 2016 Mar 23.

The red meat allergy syndrome in Sweden

Danijela Apostolovic ¹, Thi Anh Thu Tran ², Maria Starkhammar ³, Sara Sánchez-Vidaurre ⁴, Carl Hamsten ⁴, Marianne Van Hage ⁵

Affiliations + expand

PMID: 27656352 PMCID: [PMC5016537](#) DOI: [10.1007/s40629-016-0098-0](#)



Implicated tick: *Ixodes ricinus*

Different ticks, same allergy

short report | [Open Access](#) | Published: 13 May 2019

Alpha-gal allergy after a tick bite in Austria

[Veronika Pisazka](#), [Georg Duschler](#), [Adnan Hodžić](#), [Norbert Reider](#) & [Franz Allerberger MD](#) 

[Wiener klinische Wochenschrift](#) **131**, 385–388(2019) | [Cite this article](#)

> [J Invest Allergol Clin Immunol](#). 2018;28(2):106–112. doi: 10.18176/jiaci.0218. Epub 2017 Dec 13.

IgE to α -Gal in Foresters and Forest Workers From La Rioja, North of Spain

[M Venturini](#)¹, [T Lobera](#)¹, [A Sebastián](#)², [A Portillo](#)³, [J A Oteo](#)³

Affiliations + expand

PMID: 29235434 DOI: [10.18176/jiaci.0218](#)

Case Reports > [Ann Allergy Asthma Immunol](#). 2019 Dec;123(6):616–618.

doi: 10.1016/j.anai.2019.09.018. Epub 2019 Sep 28.

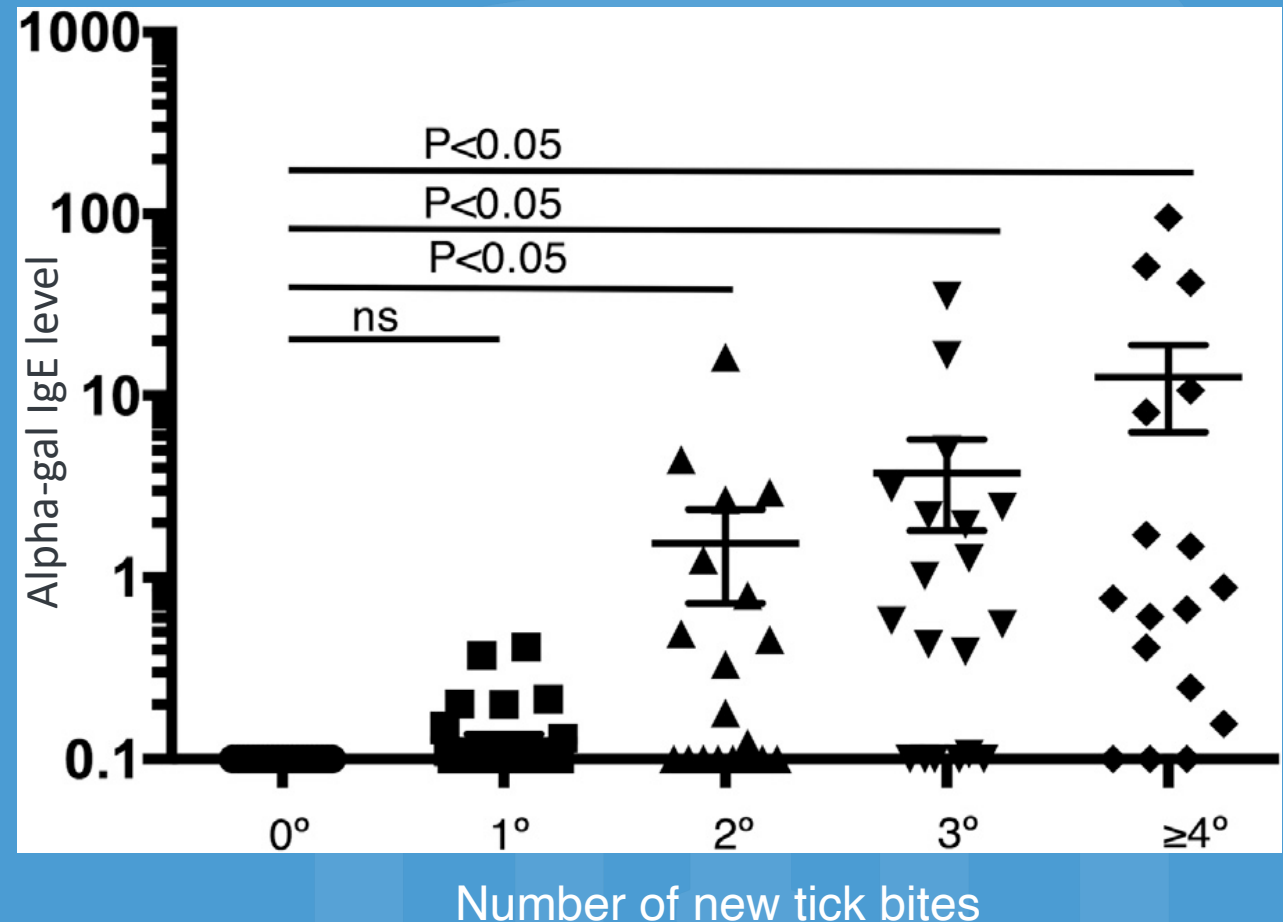
Allergy in frequent travelers: the alpha-gal story and the first UK case series

[Verah Harper](#)¹, [Annette Wagner](#)², [Pawel Sowa](#)³, [Krzysztof Rutkowski](#)⁴

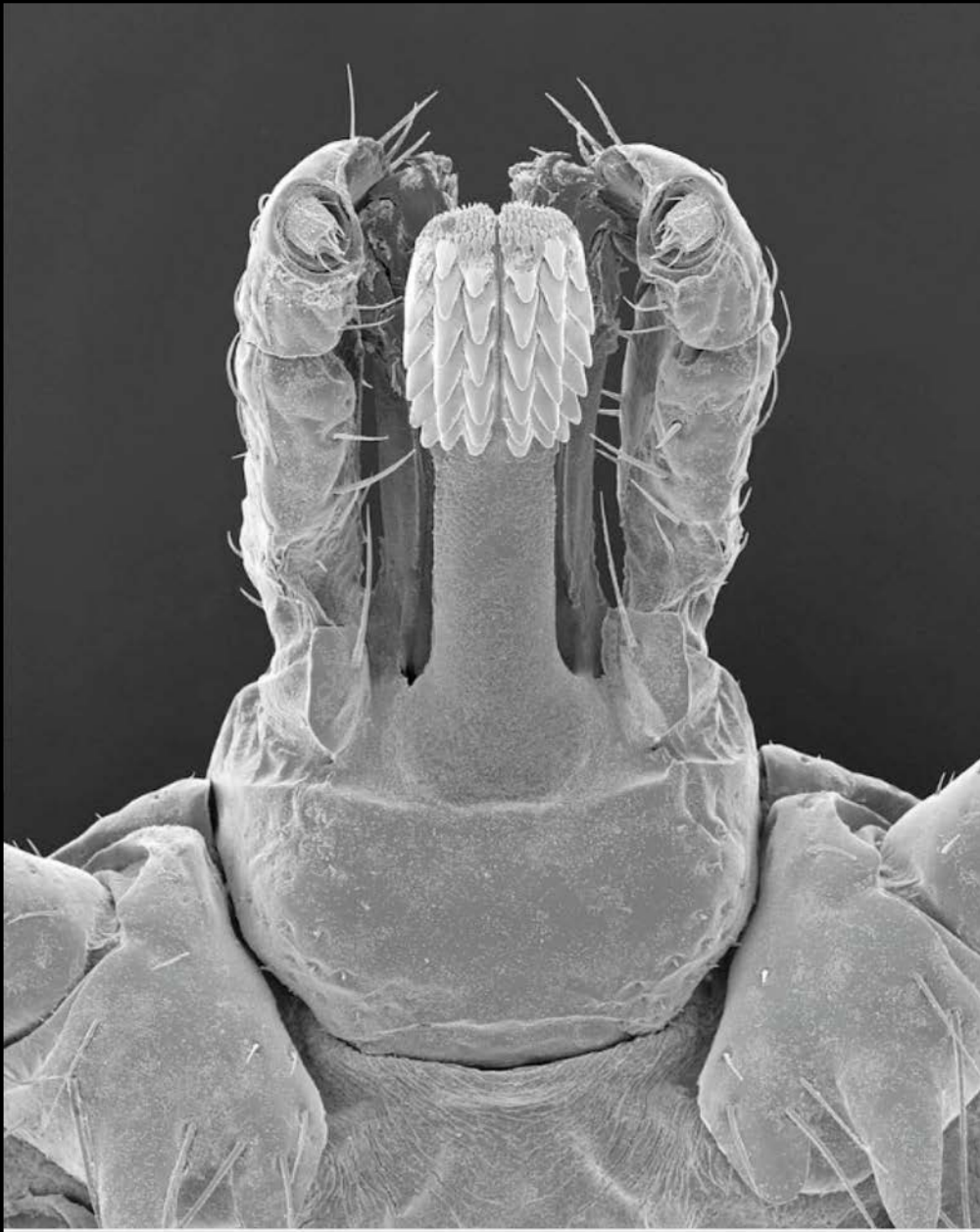
Implicated tick: *Ixodes ricinus*

Alpha-gal IgE response to tick bites

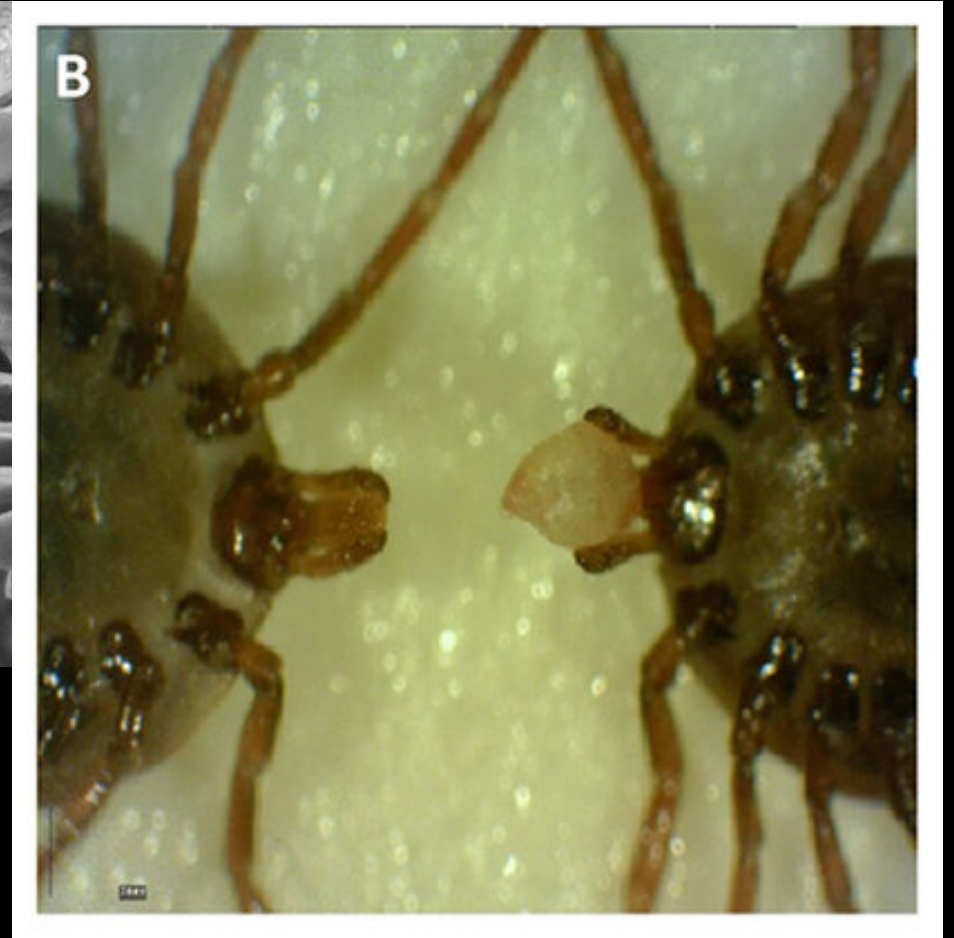
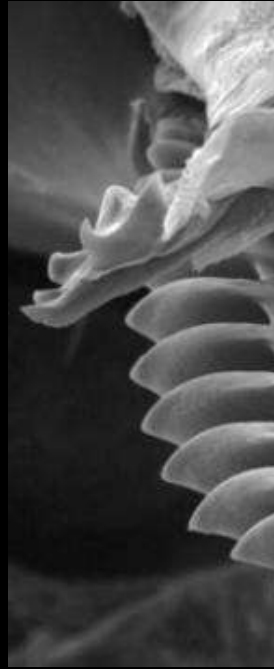
- IgE to alpha-gal increased with time following one or more tick bites
- IgE to alpha-gal (kU/L) increased in patients with increasing numbers of tick bites



Hashizume H, et al. Repeated *Amblyomma testudinarium* tick bites are associated with increased galactose- α -1,3-galactose carbohydrate IgE antibody levels: A retrospective cohort study in a single institution. *J Am Acad Dermatol*. 2018

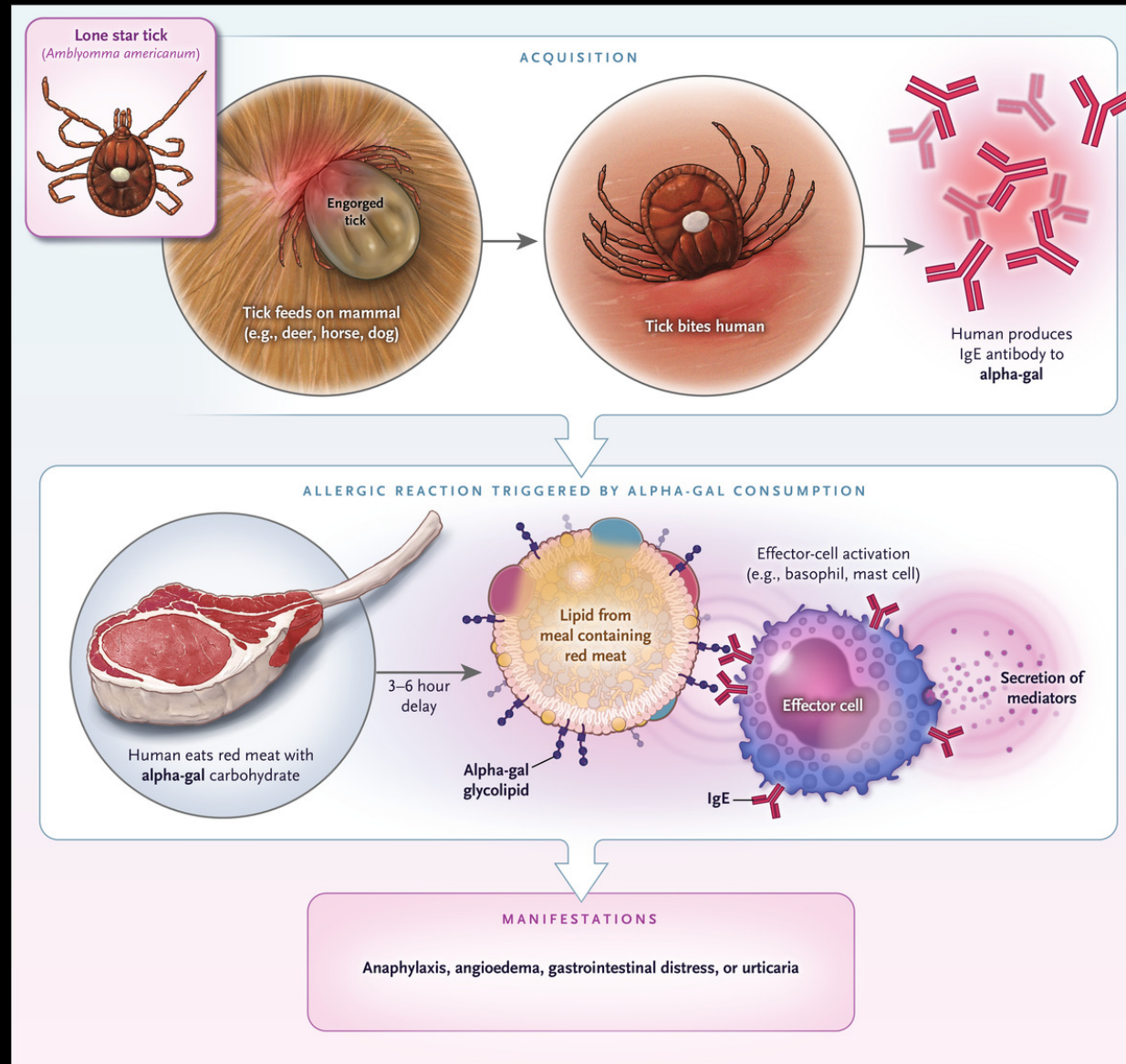


Lone Star Tick Head (Amblyomma americanum) by Dennis Kunkel



Bullard, R ... Karim, S. (2016). Structural Characterization of Tick Cement Cones collected from in vivo and artificial membrane blood-fed Lone Star ticks (*Amblyomma americanum*). *Ticks and Tick-borne Diseases*.

Sensitization and Mechanism Leading to Clinical Appearance of Alpha-gal Syndrome



Antal valgte ydelser 1 / 90

Analysenavn	Svarhastighed
Galactosyl-(1-3)galact.(o215)-IgE;P	Rutine

ImmunoCAP

Component nGal- alpha-1,3-Gal (alpha-Gal)



Details

This test contains allergen nGal-alpha-1,3-Gal (alpha-Gal) from bovine thyroglobulin

Code: o215

LOINC: 73837-7

Results Reported: Quantitative

Shailesh Choudhary
Onyinye Iweala
Claire Addison
Shivangi Choudhary

Sarah McGill
Evan Dellon
Kristy Ainslie
Eric Bachelder

Univ Southern MS
Shahid Karim
Gary Crispell

Alpha-gal Study Subjects

<u>CDC</u>		
Paige Armstrong	C. Ben Beard	Brad Biggerstaff
Alison Binder	Dena Cherry-Brown	Cecilia Kato
Gil Kersh	Lyle Petersen	Amy Peterson
William Nicholson		



Centers for Disease
Control and Prevention
National Center for Emerging and
Zoonotic Infectious Diseases



National Institute of
Allergy and
Infectious Diseases

Scott Smith
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Anubha Tripathi

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Erin McGintee
Shawna Pochan
Walter Oliveira
Hayley James
Whitney Stevens

Paul Bellamy
Johanna Smeekins
Fred Finkelman
Ron Falk
Barrett Lewis
Michael Land
Scott Boyd
Kelly Cox



“It is better to know some of the questions
than all of the answers.”

- James Thurber

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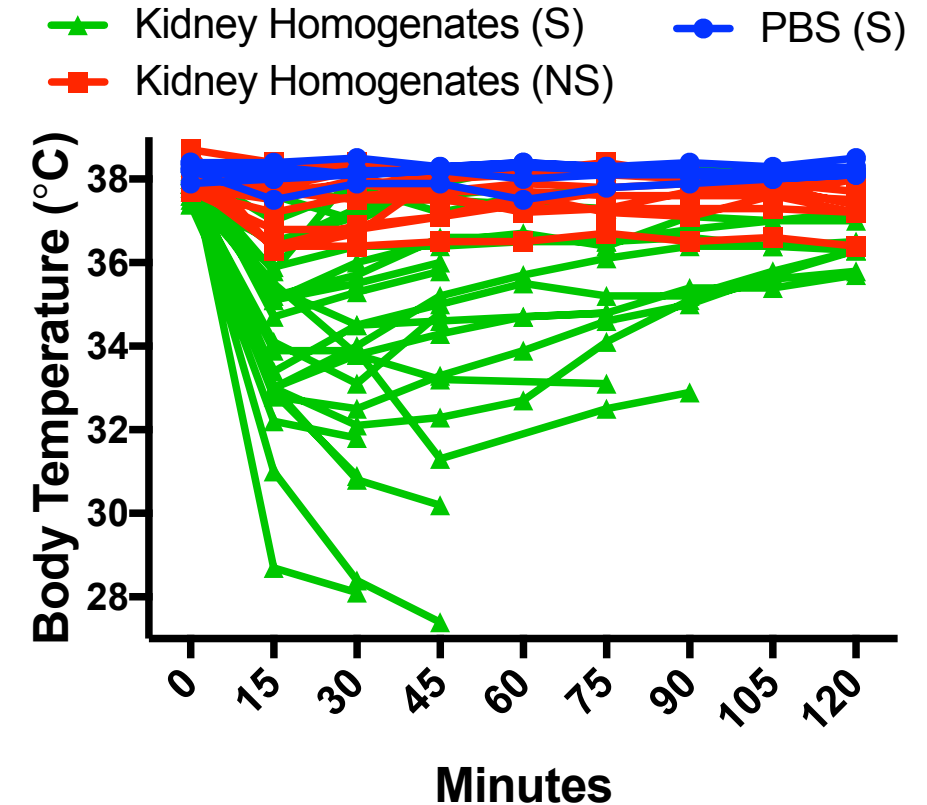
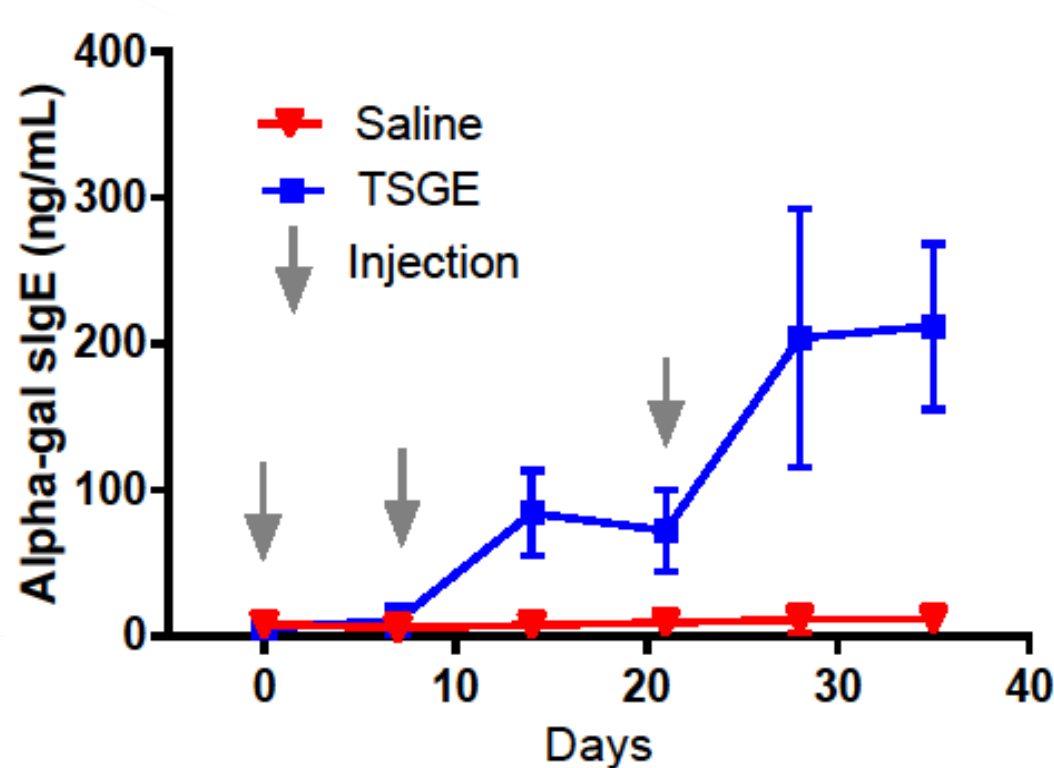
Twitter: @scott_commins



UNC | COMMINS LAB

Research makes us tick.

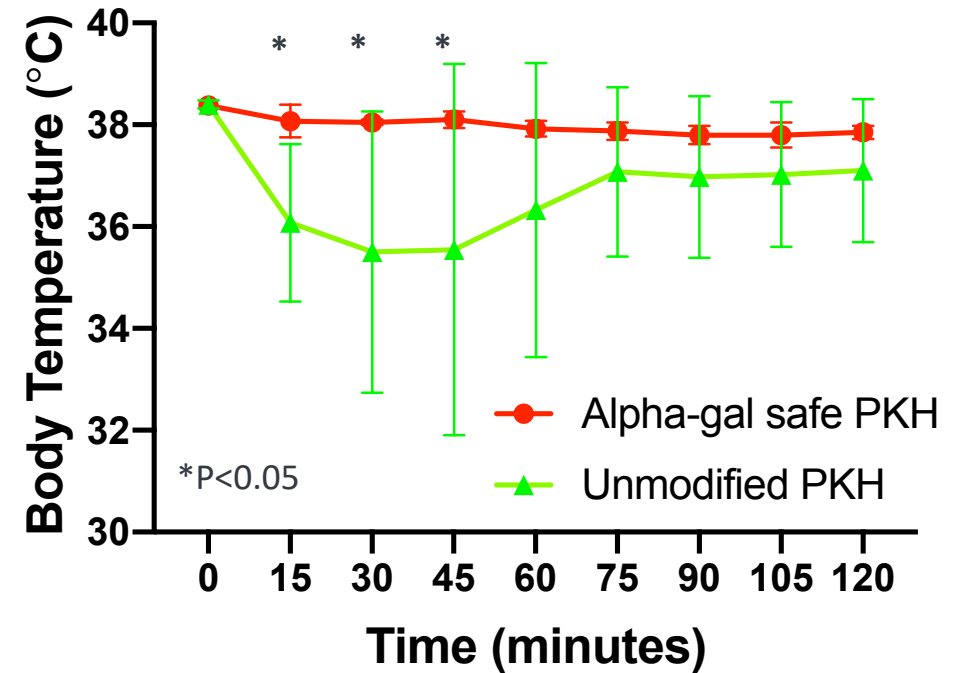
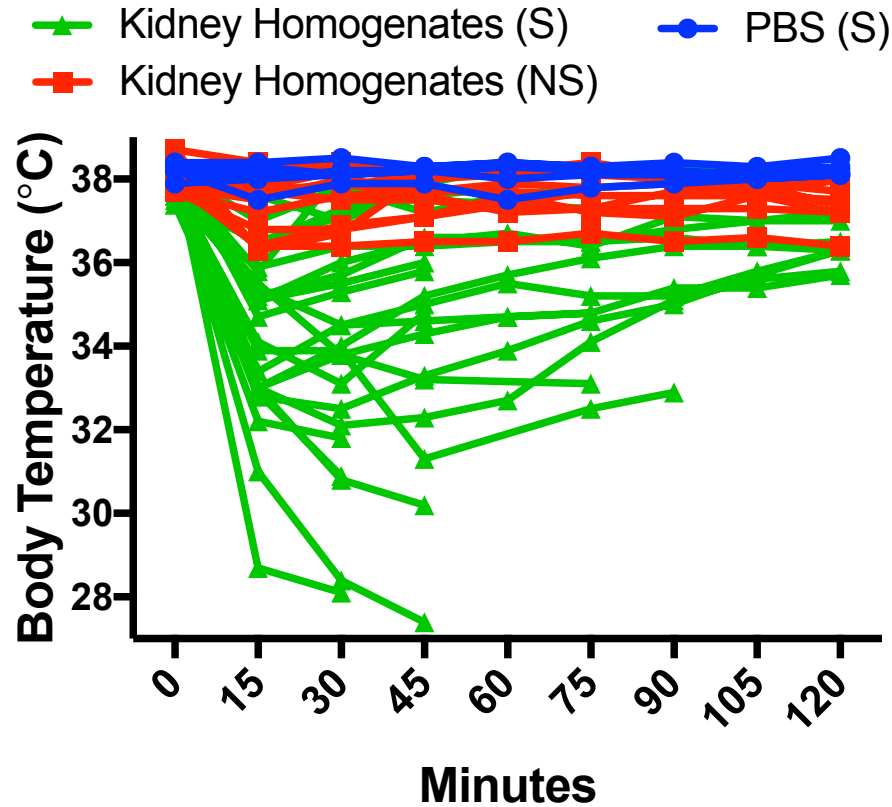
Current research and future directions



Alpha-gal specific IgE levels rise in AG KO mice after intradermal injection with *A. americanum* tick salivary gland extract (TSGE) and mice react to oral challenge with pork kidney homogenate

Choudhary SK et al., Immunity Inflamm & Dis.

Current research and future directions



Shailesh Choudhary, PhD