

# Update on the Alpha-Gal Syndrome 2025

Is it wise to continue eating our close relatives & living close to tick infested wild animals.

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UNIVERSITY of VIRGINIA

## Learning Objectives in relation to the Alpha-Gal Syndrome (AGS)

At the conclusion of this Activity, learners should be able to:

- (i) Describe the clinical observations that led to the discovery of IgE ab to galactose alpha-1,3-galactose (alpha-gal)
- (ii) Identify the type of tick bites that are the primary cause of IgE responses to alpha-gal in the USA
- (iii) Specify the level of specific IgE antibody as a % of total IgE that is indicative of risk for having delayed reactions to meat or other products derived from non-primate mammals
- (iv) Describe the timing of reactions to alpha-gal
- (v) Recognize the variability in clinical manifestations and abdominal symptoms that can result from alpha-gal reactions

# Severe Cases of Alpha-gal Syndrome

Cases	Age	sIgE	Total IgE	Tick History	Reactions
2018 (JD)	56 M	10.8	164	On Mountain	Ate beef 3 ½ hours later collapsed, BP 40/0 Hospital; Tryptase of 90 ≠
Aug 2012 (IC)	73 F	28	111	Gardening	Ate pork 3 ½ hours later severe anaphylaxis Hospital; tryptase 30 ≠
April 2017 (JLS) A412	36 F	8.4	98	Hiking	Ate red meat 4 hours later severe abdominal pain collapsed confusion; Hospital 1 night †

\*Treated Warrenton    ≠Admitted to UVA.    †Admitted VCU

*The Immunology of Alpha-gal syndrome: History, Tick Bites, and Delayed Anaphylaxis to Red Meat. Platts-Mills T.A. Singh Gangwar R., Workman L., and Wilson J.M.*

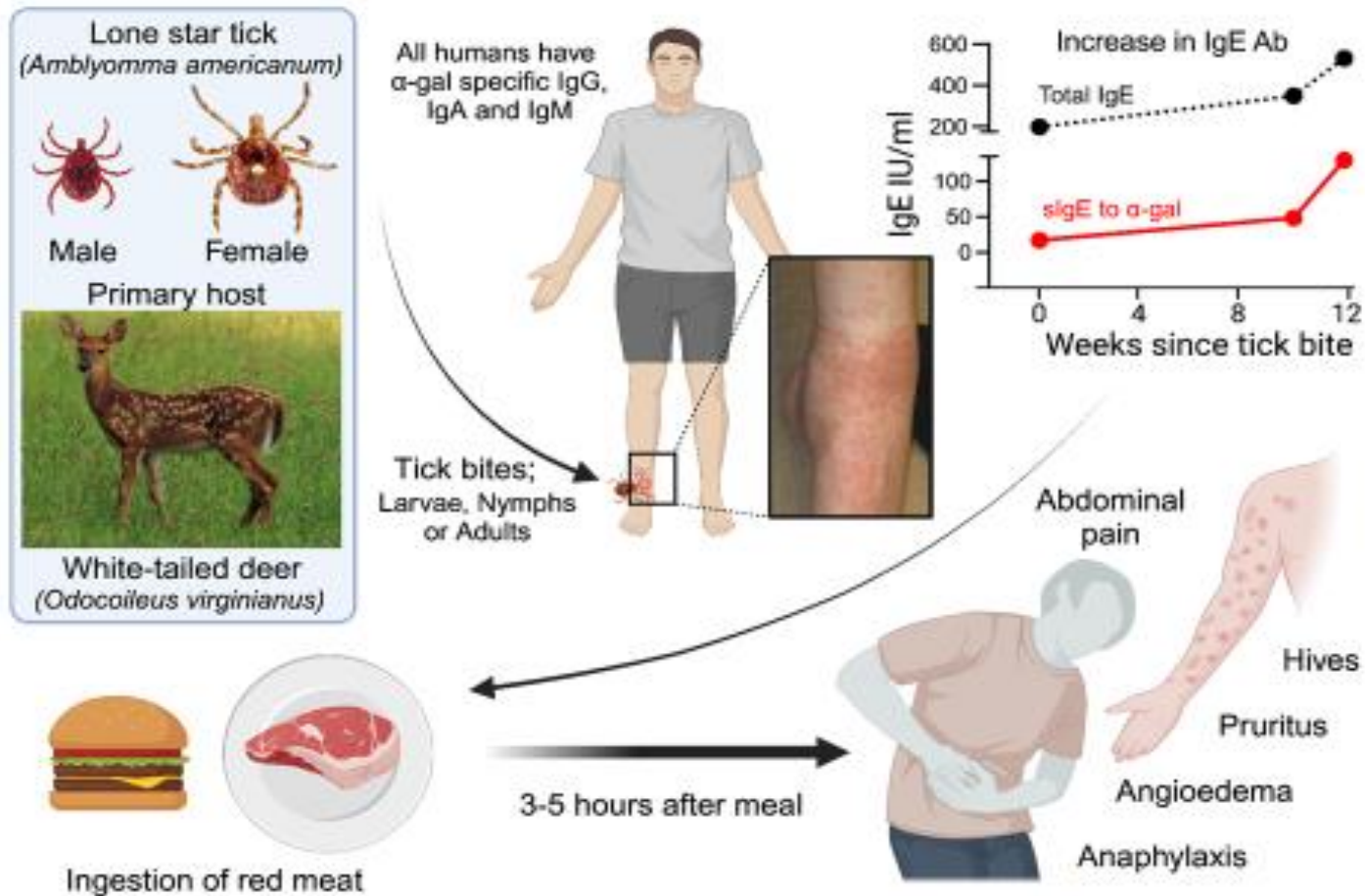
*Immunological Reviews on the Biology of IgE in press.*

## **Abdominal pain in Alpha-gal syndrome**

### **J.L.S. Female age 44**

- **June 2014** Initial tick bite caused persistent severe itching
- 
- **August 2014** Multiple G.I. issues with severe pain, no cause identified.
- 
- **Fall 2014** Repeated episodes including abdominal pain and hives.
- Emergency Department at Medical College of Virginia.
- 
- **July 2015** Walk in tall grass in Eastern MD, “chiggers”
- 
- **Sept 2015** Ate meat and four hours later developed abdominal pain.
- Lost consciousness in the bathroom while vomiting, and during that episode became combative and believes she had memory loss. Admitted to hospital.
- 
- **Oct 2015** Richmond Allergy: diagnosed, alpha-gal IgE 69.7 IU/ml.
- Advised to Avoid meat
- 
-

The primary drive for producing IgE to alpha-gal comes from tick bites, but all humans have a natural antibody response to this epitope. Production of IgE to alpha-gal continues for several weeks or months, after that time the subject can experience a reaction 3-5 hours after eating red meat.



*The Immunology of the Alpha-gal syndrome;  
Immunological Reviews. In Press 2025.*



# Discovery of Alpha-Gal-Containing Antigens in North American Tick Species Believed to Induce Red Meat Allergy

Gary Crispell<sup>1</sup>, Scott P. Commins<sup>2</sup>, Stephanie A. Archer-Hartman<sup>3</sup>, Shailesh Choudhary<sup>2</sup>, Guha Dharmarajan<sup>4</sup>, Parastoo Azadi<sup>3</sup> and Shahid Karim<sup>1\*</sup>

Data on alpha-gal in extracts from Lone Star Ticks: *Amblyomma americanum*

Lane 2,3,4; Unfed and fed mid-gut.

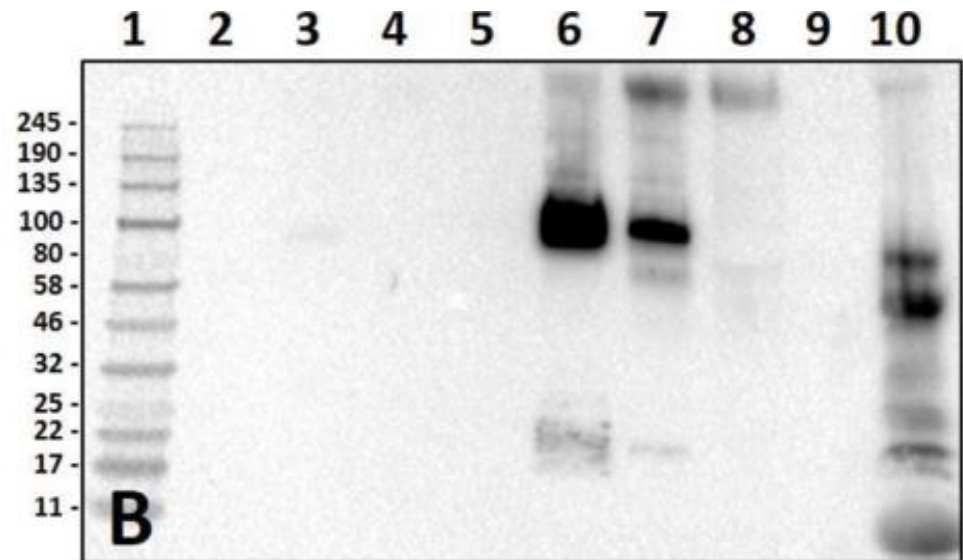
Lane 5; unfed salivary gland.

**Lane 6,7; 3&11day fed salivary gland.**

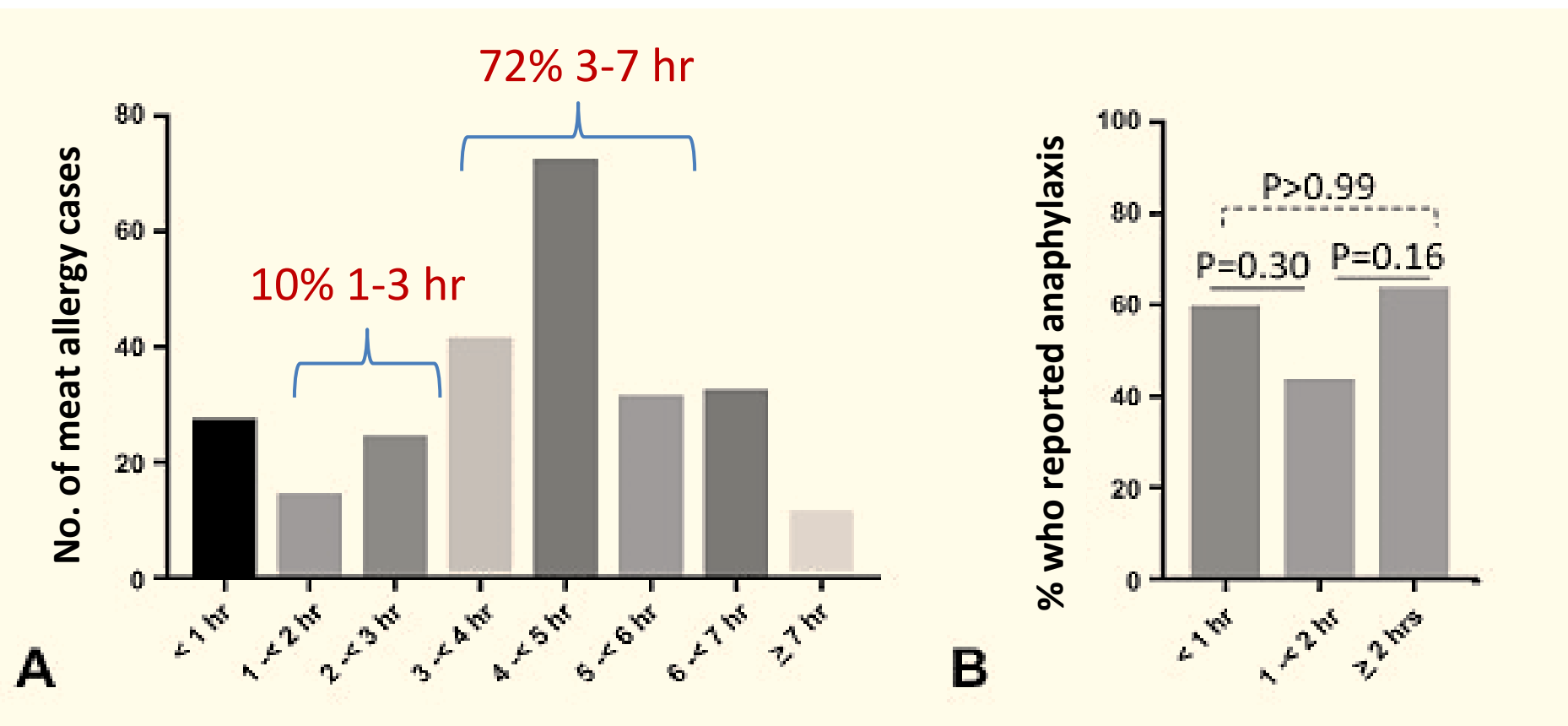
Lane 8; Pilocarpine induced saliva.

Lane 9; BSA.

Lane 10; Sheep blood.

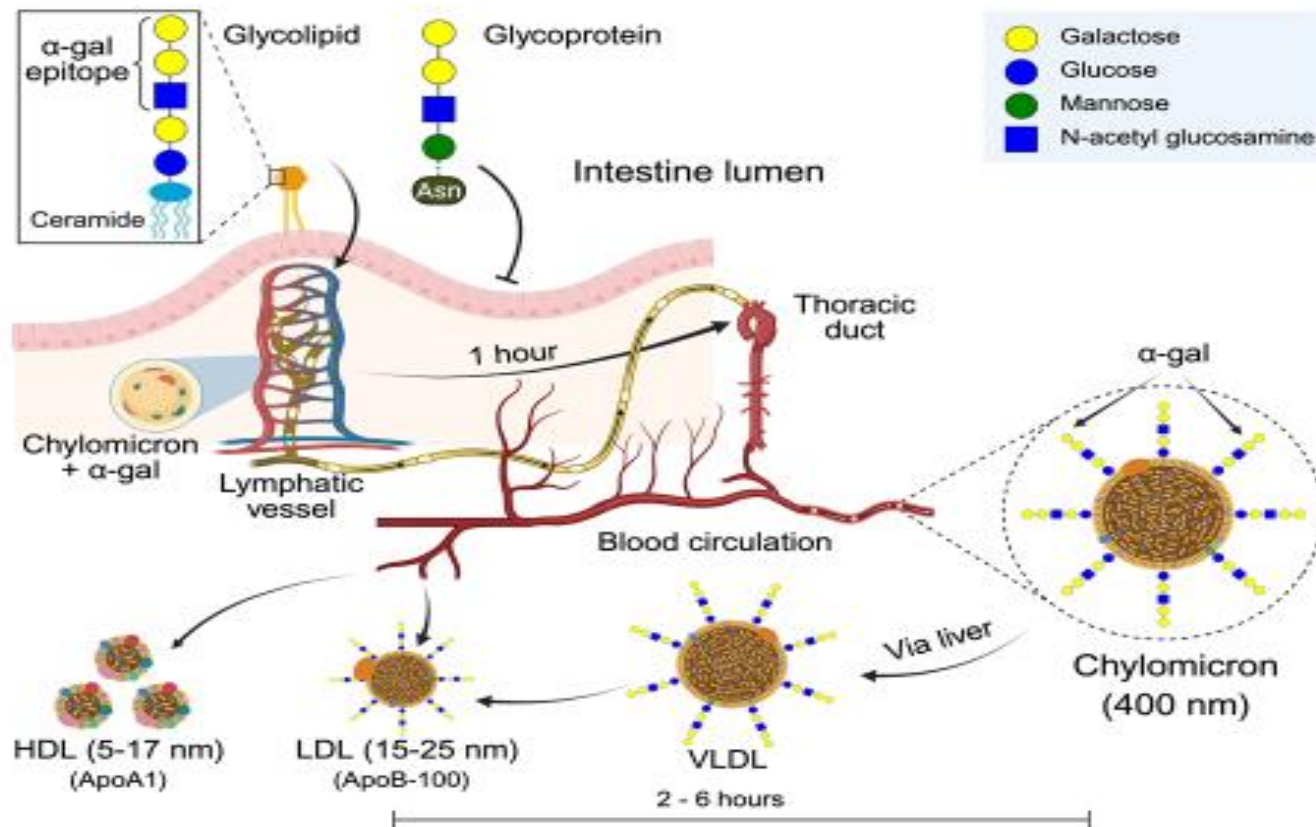


Reported time between eating meat and the onset of allergic reactions among 263 patients with IgE specific for galactose alpha-1,3-galactose (A), Severe reactions are not more common in patients with short delays (B).



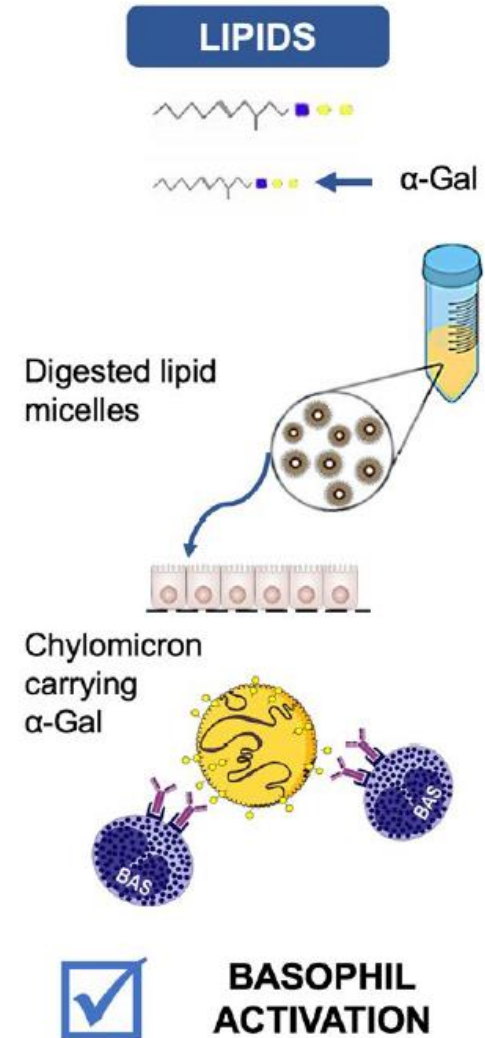
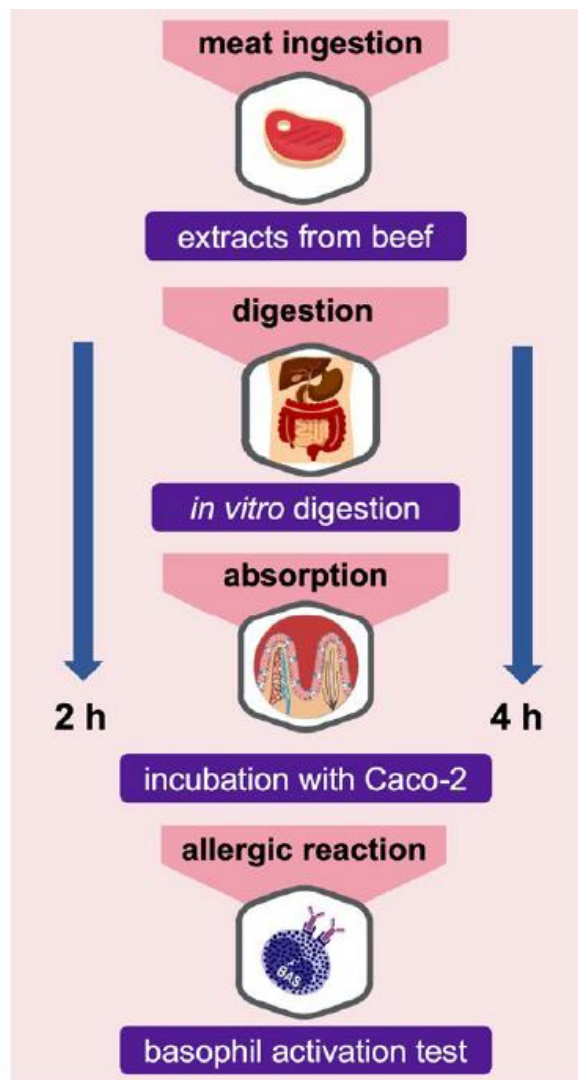
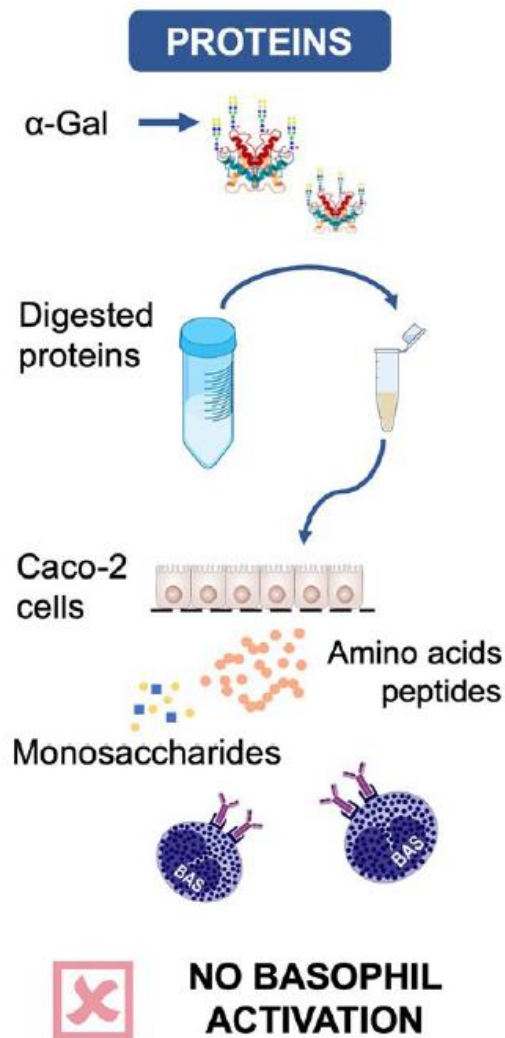
*Wilson J, Schuyler A, Commins S, et al JACI in practice; 2020*

Digestion of Beef allows Glycolipids to enter lacteals and form Chylomicrons. Once they enter the circulation it takes approximately three hours to become LDL which can pass out of the vessels into the extra vascular space.



*The Immunology of the Alpha-gal Syndrome: 2025*  
Platts-Mills TA, Sing Gangwar R., Workman L & Wilson JM  
*Immunological Reviews on the Biology of IgE (in press).*





Roman-Carrasco, Lieder,...Swoboda I. Only alpha-gal bound to lipids, but not to proteins, is transported across enterocytes as an IgE reactive molecule that can induce effector cell activation. Allergy 2019; 74: 1,956.

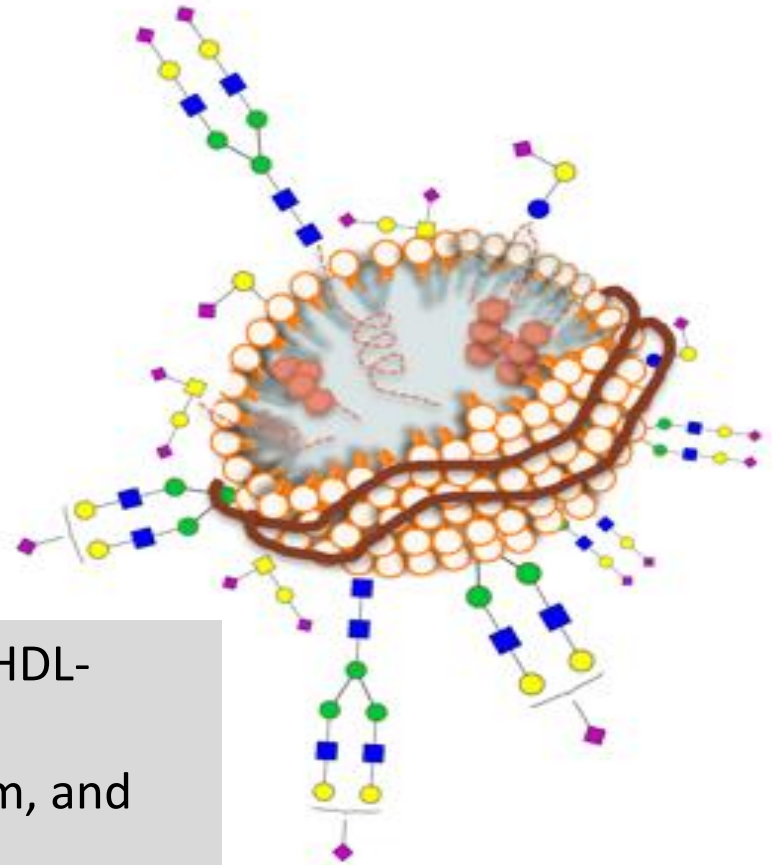
# LDL & HDL are Cholesterol laden particles with a surface layer of Apo-proteins and lipids including both Phospho- and Glyco-lipids

“The results demonstrate that the current depiction of HDL as “naked” particles is misleading and that in fact, HDL particles are covered with O-linked oligosaccharides”.

Zivkovic: Gordon conference: 2018.

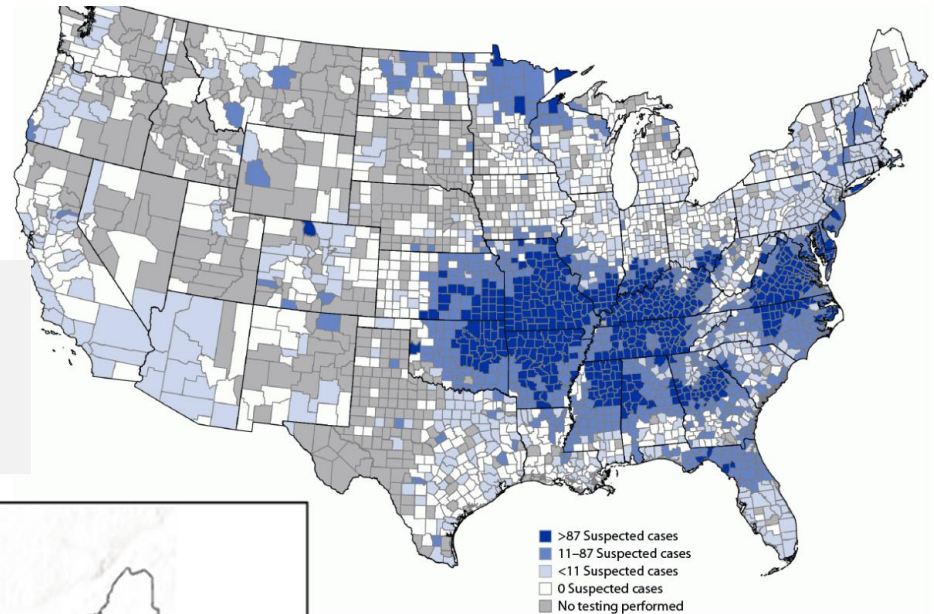
Roma EZ, and Zivkovic AM, Glycosylation of HDL-Associated Proteins and its Implications in Cardiovascular Disease Diagnosis , Metabolism, and Function. 2022.

Frontiers in Cardiovascular Medicine. 9-928566

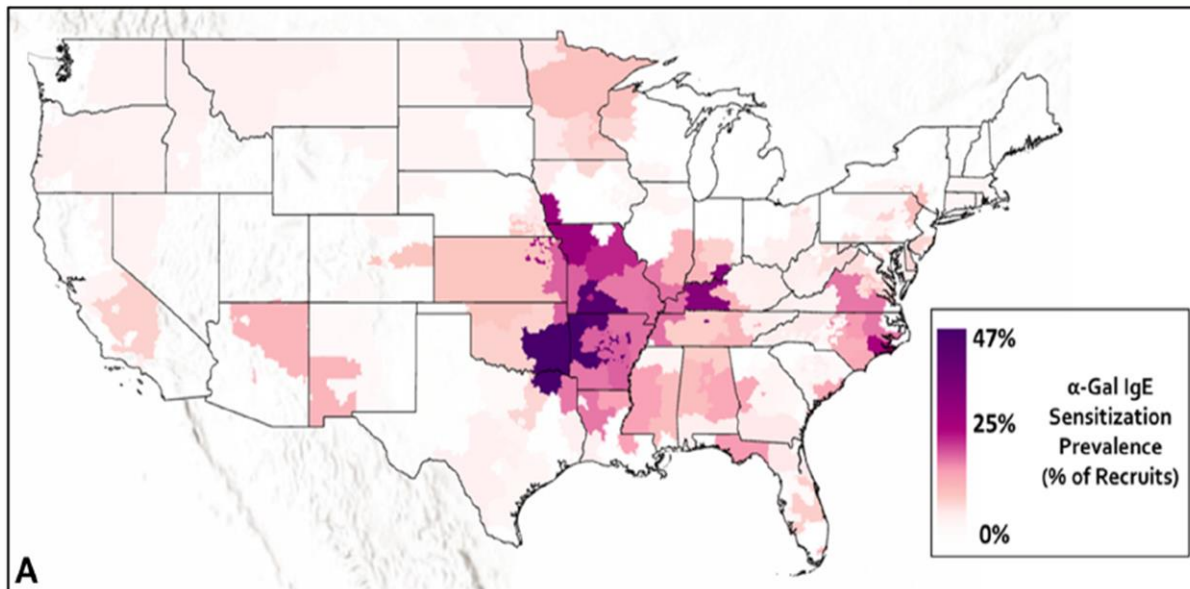


# Our map of Sensitization to Alpha-gal among army recruits vs recent CDC map of positive blood test results from the lab in Kansas City Mo.

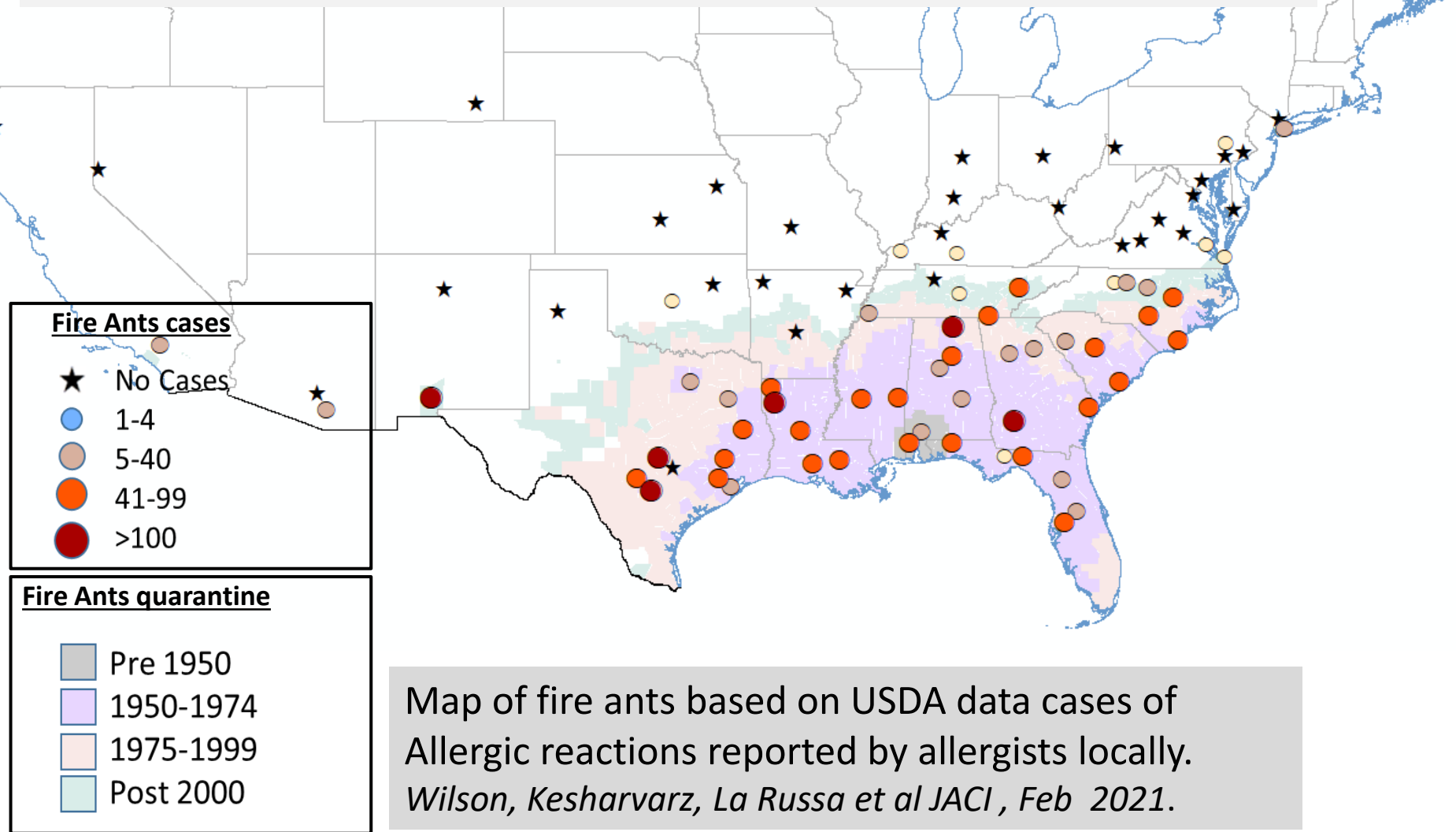
Positive IgE to alpha-gal in army recruits.  
Ailsworth S, Workman L, .....Nylund C, &  
Wilson J M, JACI in Practice 2023.



Geographic distribution of suspected alpha-gal syndrome per 1 million population per year -United States 2017-2022.



Cases of allergic reactions to fire ant stings & county based quarantine designed to restrict spread of the fire ant *Solenopsis invicta* following introduction in Mobile AL, in 1931



Map of fire ants based on USDA data cases of Allergic reactions reported by allergists locally.  
*Wilson, Kesharvarz, La Russa et al JACI , Feb 2021.*



## Ecological Havoc, the Rise of White-Tailed Deer, and the Emergence of *Amblyomma americanum*-Associated Zoonoses in the United States

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Bites of *Amblyomma americanum* can be Extremely Pruritic .  
Bites of adult or larval ticks have been associated with rapid rises in total IgE and specific IgE to galactose alpha-1,3-galactose.



Rash at 48 hours

# **SEVERE ABDOMINAL PAIN 4 HOURS AFTER EATING BEEF STEAK IN A 47-YEAR-OLD HEALTHY AIRLINE PILOT WITH NO PREVIOUS HISTORY OF FOOD ALLERGY.**

- ❖ In spring of 2024 he experienced a dozen “chigger” bites on his left ankle.
- ❖ In August 2024 he was camping with his family and, after a good day they and friends ate beef steak for supper and went to bed.
- ❖ At 2:00 AM he woke with abdominal pain and was writhing on the ground with vomiting and diarrhea which lasted 2-3 hours.
- ❖ In the morning he woke feeling well, walked for 5 miles, and ate a healthy breakfast. No one else in the group who ate steak had abdominal symptoms. However, he told his 16-year-old son “I thought I was going to die.”

## Questions

- (1) Are “chiggers” lone star larvae that can induce or boost specific IgE to galactose alpha-1,3 galactose?
- (2) Should the most severe abdominal pain you have ever experienced require medical evaluation?

# Death of the 47 year old Pilot

- On Labor Day 2024, he and his wife went to a BBQ at 3:00 PM and he ate a hamburger.
- After that he returned home and feeling well, he mowed the lawn from 5:00-600 PM. She left the house at 7:10 PM and at 7:20 PM their son phoned to say “Dad is sick again” implying that to him it seemed the same as the attack in August
- He got progressively worse, went to the toilet, and collapsed unconscious in the floor. His son initiated resuscitation and the EMTs continued for an hour before he was declared dead.
- History from Dr. Erin McFeely-pediatric physician in New Jersey,

## **POST-MORTEM:**

Extensive analysis of gross anatomy of cardiovascular system, lungs, airways and abdominal content all unremarkable.

**Conclusion:** No cause of death established

= Cardiac and other tissue analyses unremarkable

= Toxicology

Diphenhydramine	440 ng/mL
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Ethanol	49mg /dL
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Blood Alcohol Concentration	0.049 mg/dL
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**April 25:** Oxalated blood provided by Dr. Alison Matone who conducted the post-mortem and offered an opinion that she was not convinced death was due to anaphylaxis.

**Question:** Should unexplained death of an otherwise healthy 47-year-old require serum analysis for total IgE, tryptase, alpha gal, and other allergens?



# BLOOD TESTS ON HEMOLYZED BLOOD IN APRIL 2025

## UNIVERSITY OF VIRGINIA

TEST NAME	Result IU/ml	RVs*
Total Serum IgE	15.2	
Serum IgE to alpha-gal	0.38 (2.5% total)	174
Beef	0.17	89
BSA	<0.1	10
Pork	0.8	52
Horse	<0.1	29
Gelatin	<0.1	15
Chicken	<0.1	14
Egg White	<0.1	15
Peanut	<0.1	22
Ragweed	0.36	169
Grass pollen	0.68	308
Silver birch	0.14	76
Alternaria	< 0.1	22

\*Response Value

## MAYO CLINIC

Tryptase	
IgG>2000 ng/ml	

## **FOUR QUESTIONS**

- Should public know that “chiggers” are in most cases larval lone star ticks and can cause sensitization to alpha-gal, i.e., red meat?
- Should an unexpected severe episode of abdominal pain be investigated, including possible anaphylaxis?
- Should unexplained death of a healthy 47-year-old person be investigated for possible allergic causes?
- Is there a differential diagnosis for the episodes of severe abdominal pain with vomiting and diarrhea each of which occurred 3-4 hours after eating beef?

# Colleagues: 2006-2025

## University of Virginia

**Jeff Wilson**

Alexander Schuyler

**Benham Keshavarz.**

**Peter Heymann**

Jake Hosen

**Angela Taylor**

**Coleen McNamara**

**Lisa Workman**

Scott Commins

**Nathan Richards**

**Bill Richards.**

## Africa and S.America

Phil Cooper London & Ecuador

Manuel Soto-Quiros, Costa-Rica.

Dr Addo Yobbo Ghana.

**Lucy N’Ganga, Kenya**

Joseph Odiambo, Kenya

## Alpha-Gal Research 2006-18

**Christine Chung, Nashville**

**Beloo Mirakhur, BMS**

Marianne Van Hage.

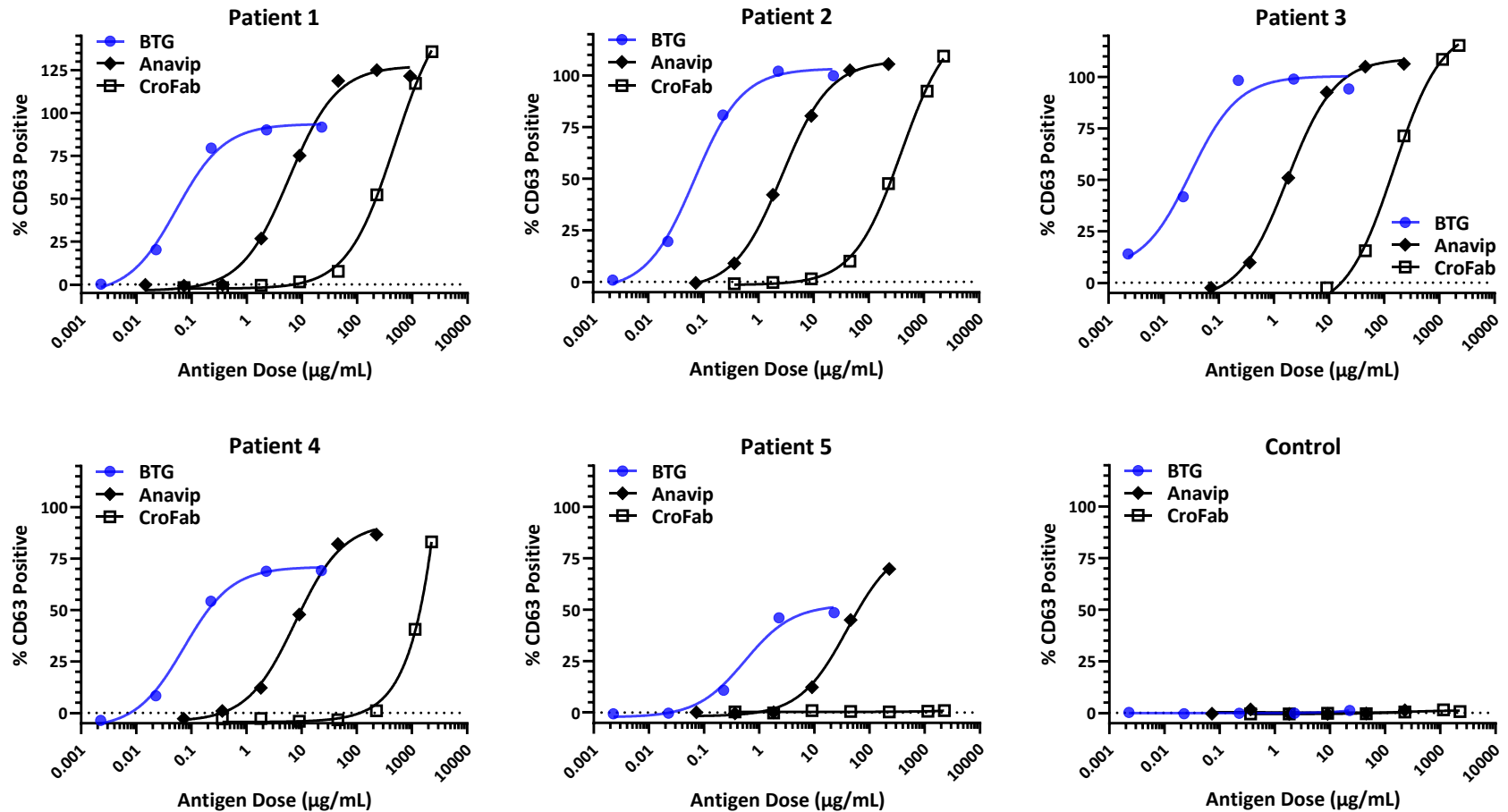
**Qinwei Zhou; ImClone**

**Tina Hatley, Bentonville.**

Tilo Biederman Munich.

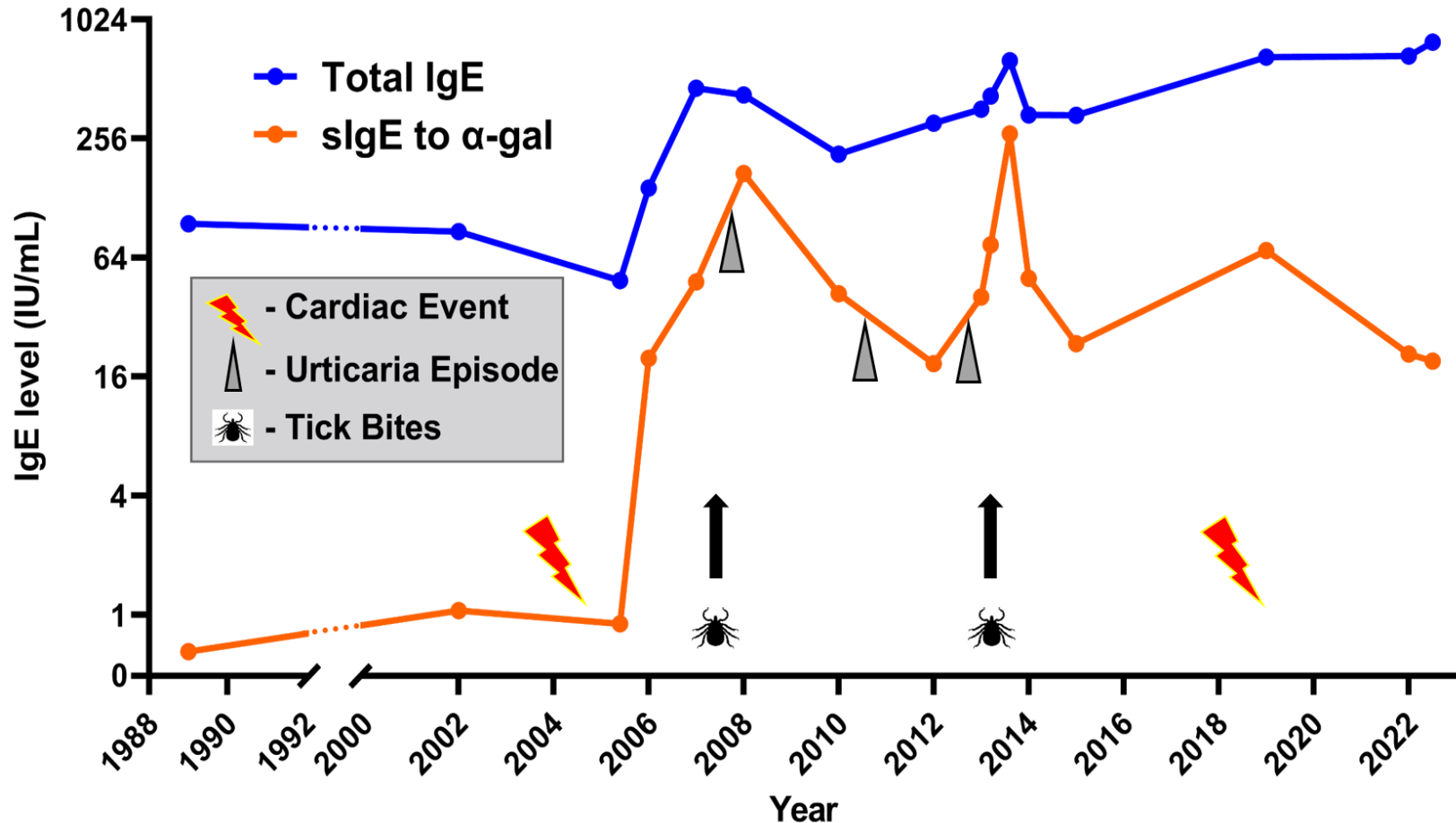
And the many other colleagues who have enrolled or referred adult and pediatric cases with the alpha-gal syndrome; and all those who helped in mapping the cases.

# Basophil activation in blood from nine patients with AGS and one control as judged by CD63 % positive cells: Stimulation compared between Bovine Thyroglobulin (BTG); Anavip; & CroFab.



*Results are presented as values of % CD63 positive, normalized based on the Anti Fcepsilon positive control and baseline negative control( stimulation buffer; 0%.*

A thirty four year case report with tick bites, two cardiac events, delayed episodes of Urticaria, and major rises in both total and specific IgE.



*Occasional tick bites have occurred in most years since 2010 with variable persistence of pruritis.*

# Longitudinal ImmunoCAP Results for Total IgE vs specific IgE, panIgG, IgG4 and IgG3 to galactose alpha-1,3-galactose

-----alpha-gal Specific Results\* -----

sample ID/event	date of draw	total IgE kU/L	IgE kUA/L	pan IgG ug/ml	IgG4 ug/ml	IgG3 ng/ml
TPM 1989	1989	94.9	0.04	1.29	nd	287
TPM 2002	4/20/2002	49	0.51	0.71	nd	<100
<b>1st cardiac event, 3/1/05</b>						
<b>Sugar Hollow tick bomb, 8/7/07</b>						
E036a	5/21/2007	144	19.80	3.05	nd	210
E036o	4/2/2012	286	27.70	1.58	0.09	<100
<b>Pasture Fence tick bomb, 8/25/13</b>						
E036u	8/29/2013	334	40.50	nd	nd	nd
E036w	9/20/2013	633	89.30	7.59	0.09	243
<b>2nd cardiac event, 8/19/18</b>						
E036au	2/10/2021	575	26.40	6.03	nd	1303
E036bm	5/31/2023	781	14.50	5.88	0.33	1196
E036bp	9/21/2023	1350	116.00	19.6	4.76	9160
E036bs	3/20/2024	1171	60.50	6.11	nd	2322

nd = not determined  
 IgG4 LoD = <100ng/ml  
 \*assayed using o215 CAP

## Conclusions in relation to the Alpha-Gal Syndrome (AGS)

- (i) IgE ab to galactose alpha-1,3-galactose (alpha-gal) were discovered in sera from patients who had immediate reactions to the first infusion of Cetuximab.
- (ii) In the USA IgE responses to alpha-gal are primarily caused by bites from adult, nymphal or larval Lone Star Ticks.
- (iii) Subjects with levels of IgE ab > 2% of their total IgE are at risk of having delayed reactions to meat or other products Non Primate Mammals.
- (iv) Despite delays as long as 4 hours after eating meat can become severe within as little as 15 min.
- (v) Abdominal symptoms can be a minor or major feature of reactions without other features to suggest that the reactions are allergic.