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Diagnosis of red meat allergy with antigen-specific IgE tests in serum



To the Editor:

Red meat allergy is a tick-associated hypersensitivity reaction characterized by anaphylaxis, angioedema, urticaria, and/or gastrointestinal symptoms occurring 3 to 6 hours after ingesting red meat including beef, pork, or lamb.¹ This disease is caused by IgE-mediated responses directed against galactose- α -1,3-galactose (α -gal), a carbohydrate produced by all mammals except humans and some nonhuman primates and that is also found in tick saliva.² The unusually long delay in symptom onset, nonspecific symptoms, and uncertain prevalence of red meat allergy can make this diagnosis challenging. However, it is critical to identify patients with red meat allergy to prevent potentially life-threatening reactions.

Although clinical presentation and history are essential for diagnosing red meat allergy, serum antigen-specific IgE tests and skin prick tests are often used.³ Previous work demonstrated strong associations between red meat allergy and elevated concentrations of antigen-specific IgE to beef, pork, and lamb; however, skin prick tests with commercial extracts of these meats have high false-negative rates.¹ Consequently, serum α -gal-, beef-, pork-, and/or lamb-specific IgE tests are primary diagnostic tools for red meat allergy.³ However, the diagnostic performance of these tests has not been reported. We therefore sought to determine the sensitivities, specificities, positive predictive values (PPVs), and negative predictive values (NPVs) for the α -gal-, beef-, pork-, and lamb-specific IgE tests.

We conducted a systematic literature search and identified 22 articles that reported individual patient data for these 4 tests from 135 patients with red meat allergy and 37 controls (see Fig E1 in this article's Online Repository at www.jacionline.org). These data were extracted and aggregated in a dataset representing patients from the United States ($n = 43$ [25.0%]), Sweden ($n = 22$ [12.8%]), Austria ($n = 33$ [19.2%]), other European countries ($n = 44$ [25.6%]), Australia ($n = 29$ [16.9%]), and China ($n = 1$ [0.6%]). Their clinical characteristics are presented in Table E1 in this article's Online Repository at www.jacionline.org. Of note, patients with red meat allergy had elevated concentrations of α -gal and beef IgE compared with controls, whereas pork, lamb, and total IgE did not differ between the groups.

We first determined the sensitivities and specificities for these antigen-specific IgE tests, including total IgE as a non-antigen-specific control. The α -gal IgE test was divided into 2 separate categories on the basis of whether α -gal IgE was measured with the heavily α -gal-decorated glycoprotein bovine thyroglobulin (α -gal-bTG) or with biotinylated α -gal antigen (α -gal-biotin). In both methods, IgE binding to antigen is α -gal-dependent.⁴ Strikingly, the sensitivity of serum α -gal-bTG IgE for diagnosis of red meat allergy was 100%, and the sensitivities for α -gal-biotin, beef, and pork IgE were all more than 89.0% (Table I). Each of these tests had significantly higher sensitivity than lamb or total

TABLE I. Sensitivities and specificities for IgE tests used to diagnose red meat allergy

Test	Sensitivity (95% CI)	Specificity (95% CI)
α -Gal IgE (bTG)	100.0 (95.9-100.0)*†‡	92.3 (74.9-99.1)*†§
α -Gal IgE (biotin)	89.1 (76.4-96.4)§	81.8 (48.2-97.7)¶
Beef IgE	92.7 (87.0-96.4)†¶	73.0 (55.9-86.2)‡
Pork IgE	89.0 (81.6-94.2) #	64.7 (46.5-80.3)¶
Lamb IgE	71.4 (55.4-84.3)	50.0 (6.8-93.2)
Total IgE	78.3 (68.4-86.2)	25.0 (5.5-57.2)

Sensitivities or specificities compared by 1-way ANOVA with Fisher least square difference *post hoc* test.

* $P < .05$ vs pork IgE.

† $P < .001$ vs lamb IgE.

‡ $P < .001$ vs total IgE.

§ $P < .05$ vs lamb IgE.

|| $P < .05$ vs total IgE.

¶ $P < .01$ vs total IgE.

$P < .01$ vs lamb IgE.

IgE. The specificity of α -gal-bTG IgE for diagnosis of red meat allergy was 92.3%, significantly higher than that of pork (64.7%), lamb (50.0%), or total IgE (25%) (Table I). The specificities of α -gal-bTG, α -gal-biotin, and beef IgE did not differ significantly but were each higher than total IgE ($P < .01$; Table I). Receiver-operating characteristic curve analyses further revealed excellent performance of the α -gal-bTG, α -gal-biotin, and beef IgE tests with area under the curve of 0.97, 0.93, and 0.86, respectively, which did not differ significantly (see Fig E2 in this article's Online Repository at www.jacionline.org). Critically, the α -gal-bTG, α -gal-biotin, and beef IgE tests had significantly higher receiver-operating characteristic area under the curves than pork (0.72), lamb (0.68), and total IgE (0.42) (all $P < .05$).

Although sensitivity and specificity are useful indicators of a test's diagnostic performance, PPVs and NPVs are needed for clinical interpretation. PPVs and NPVs depend on disease prevalence (ie, pretest probability); however, the prevalence of red meat allergy is not known and may vary widely by geographic location or patient population. For example, in Denmark and Spain, approximately 2% of adults had elevated α -gal IgE concentrations,⁵ whereas at an allergy clinic in Virginia approximately 90% of patients with recurrent anaphylaxis, angioedema, and/or chronic urticaria were positive for α -gal IgE.⁴ Therefore, we calculated PPVs and NPVs across the entire range of pretest probabilities.

This analysis indicated that the α -gal-bTG IgE test had the highest PPV for all pretest probabilities, followed by α -gal-biotin, beef, and pork IgE (Fig 1, A). In contrast, lamb and total IgE had very poor PPV. If the pretest probability of red meat allergy is greater than 10% to 15%, an elevated α -gal or beef IgE concentration greatly increases the posttest probability of red meat allergy beyond 50%. Therefore, a positive α -gal or beef IgE result provides strong evidence in favor of red meat allergy. In contrast, NPV was similar for α -gal-bTG, α -gal-biotin, beef, and pork IgE for all pretest probabilities (Fig 1, B). Lamb and total IgE had very poor NPV. If the pretest probability of red meat allergy is less than approximately 90%, a negative test result for α -gal-bTG, α -gal-biotin, beef, or pork IgE decreases the posttest probability to less than 50%. Therefore, a negative result for any of these 4 tests strongly argues against a red meat allergy diagnosis.

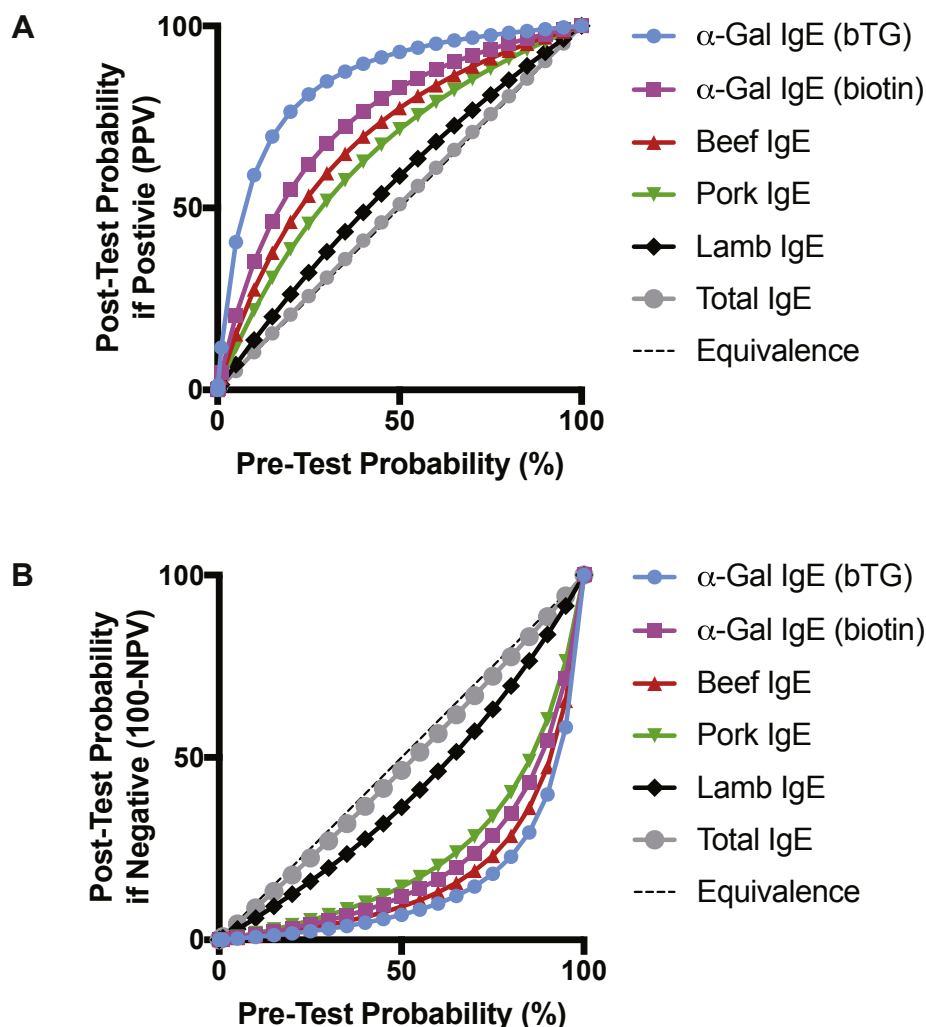


FIG 1. PPVs and NPVs of antigen-specific IgE tests for diagnosis of red meat allergy. PPVs (**A**) and NPVs (**B**) were calculated using sensitivities and specificities of the indicated tests for pretest probabilities (ie, prevalences) ranging from 0% to 100%. Posttest probabilities were defined as PPV (Fig 1, **A**) or 100 – NPV (Fig 1, **B**).

Taken together, these findings indicate that the α -gal-bTG IgE test is the most useful for establishing a diagnosis of red meat allergy, although α -gal-biotin, beef, and pork IgE are also effective. The diagnostic value of the beef and pork IgE tests may relate to the presence of α -gal in beef and pork extracts used for IgE capture.¹ Despite their favorable performance characteristics, these tests should be used and interpreted carefully. For example, none of these antigen-specific IgE tests can distinguish red meat allergy from tick allergy⁶ or cetuximab hypersensitivity,⁷ and pork IgE cannot discriminate between red meat allergy and pork-cat syndrome.⁸ In addition, 85% of helminth-infected patients have elevated α -gal IgE concentrations without evidence of red meat allergy.⁹ Therefore, the diagnostic value and interpretation of these tests depend on clinical context. We recommend measuring α -gal or beef IgE concentrations for diagnosis of red meat allergy only in patients who present with symptoms related to red meat exposure or who present with recurrent idiopathic anaphylaxis, angioedema, urticaria, or gastrointestinal symptoms. False positives should be considered in the above clinical scenarios or if the patient's symptoms do not improve after

avoiding meat ingestion and/or if challenging with offending meats fails to elicit symptoms.

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from the American Association for Clinical Chemistry and Abbott. A. M. Gronowski is a member of the scientific and medical advisory board of TheraNOS; serves as a consultant for Church and Dwight Co, Inc; and receives grant support from BioRad and Abbott Laboratories.

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Fatal anaphylaxis in France: Analysis of national anaphylaxis data, 1979-2011



To the Editor:

Anaphylaxis-related mortality (AMR) has been estimated at less than 1 per million population from the United States and the United Kingdom.¹⁻³ In these countries, the AMR remained stable during the last decade.¹⁻³ In contrast, the incidence of anaphylaxis fatalities increased in Australia from 1997 to 2013.⁴ The most common triggers of fatal anaphylaxis cases are drugs, insect venoms, and foods, with drugs accounting for most of the fatalities.¹⁻⁴ In France, comprehensive data from anaphylaxis-related deaths are collected by the National Mortality Center. The aim of our study was to determine the AMR in France and analyze time trends and specificities according to triggers, age groups, sex, and regional differences.

All deaths in France are recorded by a physician and death certificates are collected and analyzed by the CEPIDC Unit of the National Institute of Health and Medical Research. We included all reported deaths recorded under International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision codes related to anaphylaxis, from 1979 to 2011. As previously described, triggers of fatal anaphylaxis were placed in 4 groups, foods, iatrogenic (drugs and contrast media), venoms, and unspecified.¹⁻³ Data about the characteristics of the French population were collected from the databases of the French National Institute for Economical and

Statistical Studies. The geographical regions North and South were defined using the official French mapping. The AMR was calculated by standardizing to the age distribution (by 5-year periods) of the overall census population of 2011 as a standard population. AMR is expressed as per million population per year. We used a log-linear Poisson regression model to assess the impact of time period, age, sex, and geographic region on anaphylactic deaths. All regression analyses were adjusted for age effect and a multivariable log-linear Poisson regression model was further used. Statistical testing was done at the 2-tailed alpha level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC). The study was approved by the National Research Ethics Committee of the French Pediatric Society.

From 1979 to 2011, 1603 fatal anaphylaxis cases were identified: 1564 (97.6%) occurred in adults and 39 (2.4%) in children. The AMR was higher in the adult population (0.84; 95% CI, 0.79-0.88) than in the pediatric population (0.08; 95% CI, 0.05-0.10) ($P < 10^{-4}$). From 2005 to 2011, the overall AMR was 0.60 (95% CI, 0.52-0.68). The highest AMR was observed in the 70 year or more age group (3.50; 95% CI, 3.25-3.76). The AMR was higher in men (1.08; 95% CI, 1.00-1.16) than in women (0.86; 95% CI, 0.80-0.92) ($P < 10^{-4}$) and it was similar comparing the southern and the northern regions for all causes ($P = .15$) (see Fig E1 in this article's Online Repository at www.jacionline.org). In the whole population, annual percentage change for case fatality rate was -2.1% (95% CI, -2.6 to -1.6), indicating a significant decrease during the study period ($P < 10^{-4}$) (Fig 1).

Triggers of anaphylaxis were iatrogenic ($n = 1011$ [63%]), unspecified ($n = 364$ [23%]), venoms ($n = 220$ [14%]), and food ($n = 8$ [0.6%]) (see Table E1 in this article's Online Repository at www.jacionline.org). The overall iatrogenic-related AMR was 0.53 (95% CI, 0.50-0.56) and this rate decreased over the study period ($P < 10^{-4}$) (Fig 1). Among the iatrogenic causes, drugs ($n = 930$ [92%]) were primarily implicated, with antibiotics ($n = 725$ [78%]) mainly involved. Venom-induced AMR was stable during the time period at 0.12 (95% CI, 0.10-0.13) (Fig 1). Most of these cases were recorded in adults 40 years or older, especially in the 70 years or older group (55 cases). It was higher in men than in women ($P < 10^{-4}$), in the South than in the North ($P = .003$). Food-induced anaphylaxis was the least common cause of fatal anaphylaxis and food-induced AMR was under 0.01. Most of unspecified-related anaphylaxis fatalities ($n = 160$ [44%]) occurred in persons 70 years or older (Fig 2) with a stable AMR of 0.19 (95% CI, 0.17-0.21) in the whole population (Fig 1). The highest unspecified-related AMR was observed in persons 70 years or older (0.77; 95% CI, 0.65-0.89) and in men as compared with women ($P = .02$).

In the multivariate analysis, older age and male sex were associated with an increased risk for anaphylaxis death of any cause of 32% (95% CI, 30-33) for each 5 years from birth and a 29% (95% CI, 17-42) increased risk for male sex.

The AMR (expressed as per million population per year) that we observed during the time period is quite similar as those observed in the United States (1999-2009; 0.69), and Australia (2013; 0.99), Finland (1996-2013; 0.59) and higher than that reported in the United Kingdom (1992-2012; 0.47).¹⁻⁵ Although the AMR remains stable in the United States and the United Kingdom, an increase in anaphylaxis fatalities of 6%/year is reported in Australia (1997-2013).^{1,2,4} In contrast, our data

METHODS

Systematic search

A comprehensive systematic review of the literature was carried out to identify peer-reviewed articles reporting individual patient data on red meat allergy. PubMed and Scopus were searched using the Boolean search terms: (alpha gal or alpha-gal or Galactose-alpha-1,3-galactose) and (IgE or immunoglobulin E or antibody or allergen). This search yielded 1465 articles in PubMed and 168 articles in Scopus (Fig E1). Manual review of titles identified 181 unique articles with potential for inclusion, and abstracts for each were carefully read to exclude reviews and identify articles ($n = 52$) for which full-text copies were obtained. These 52 articles were assessed for inclusion in the study and were required to meet the following *a priori* inclusion criteria: the article must be an original research article related to meat allergy in a peer-reviewed journal and report patient-level data on α -Gal-specific IgE as well as beef-, pork-, or lamb-specific IgE quantified for at least 1 human subject. Of these, 29 full-text articles were excluded for the following reasons: the study did not report patient-level data ($n = 14$); the study did not report data on α -Gal-specific IgE ($n = 1$); the study did not report data for beef, pork, or lamb IgE ($n = 9$); or the study was unrelated to meat allergy ($n = 3$). An additional 3 studies were excluded because α -Gal-specific IgE concentrations were used to select patients or controls (ie, nonindependence). In one study,^{E1} the subjects identified by screening for α -Gal-specific IgE concentrations were excluded because of nonindependence; however, 5 patients from Missouri were initially identified on the basis of clinical presentation only and were included in our analysis. A total of 22 studies met the inclusion criteria and represented a combined 172 patients ($n = 135$ patients with red meat allergy, $n = 37$ controls without red meat allergy) who were seen at allergy clinics for other problems or nonallergic adults).^{E1-E22} Individuals were excluded if they were known to have a local or systemic allergy to ticks. These individual patient data were extracted and aggregated for analysis. One article^{E12} was in Dutch and was translated with Google Translator.

Test performance

The α -gal IgE test was categorized on the basis of method of antigen-specific IgE capture. In one method, the heavily α -gal-decorated glycoprotein bTG is used to capture IgE, whereas in the other method biotinylated α -gal substrate is used for IgE capture.^{E23} For both methods, IgE binds the target antigen in an α -gal-dependent manner.^{E23} Test results for serum α -gal IgE (bTG), serum α -gal IgE (biotin), serum beef IgE, serum pork IgE, and serum lamb IgE were considered to be positive if more than 0.35 IU/mL or negative if 0.35 IU/mL or less. Total IgE was considered to be positive if more than 100 IU/mL or negative if 100 IU/mL or less. If a test result was reported as "less than 0.1 IU/mL," "less than 0.35 IU/mL," or "more than 100 IU/mL," the value was recorded as 0.1, 0.35, or 100, respectively. Two-by-two tables were constructed to determine the sensitivities and specificities for each test. Receiver-operating characteristic (ROC) curves were generated for each test, and areas under the ROC curve with 95% CIs were calculated. Because PPVs and NPVs are dependent on disease prevalence (ie, the pretest probability for a given patient subpopulation), these values were calculated using the following equations:

$$PPV = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

$$NPV = \frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}$$

The prevalence (ie, pretest probability) was varied from 0% to 100% to model the PPV and NPV for any possible pretest probability of disease.

Statistics

Age, total IgE concentration, and antigen-specific IgE concentrations in subjects with red meat allergy and control subjects were compared using Student *t* test. The percentages of patients who were female and the percentage of patients with a reported history of tick bites were compared by Pearson chi-square tests. Sensitivities, specificities, and ROC area under the curve were

compared using 1-way ANOVA with Fisher least square difference *post hoc* test. Significance was defined as a *P* value of less than .05. Sensitivities, specificities, and their 95% CIs were calculated using GraphPad MedCalc (GraphPad Software, La Jolla, Calif). All other analyses were performed using GraphPad Prism 7 (GraphPad Software) or IBM SPSS Statistics version 24 for Mac (IBM Corporation, Armonk, NY).

Ethics

This study involved deidentified patient data previously reported in the literature and therefore did not require institutional review board approval. No patient charts were accessed for this study. Except for case reports of 3 or fewer patients that do not require approval by an institutional review board or its equivalent, all studies that contributed data to the present analyses (see below) provided an explicit statement that the study protocol involved informed consent and approval by an ethics board or committee.

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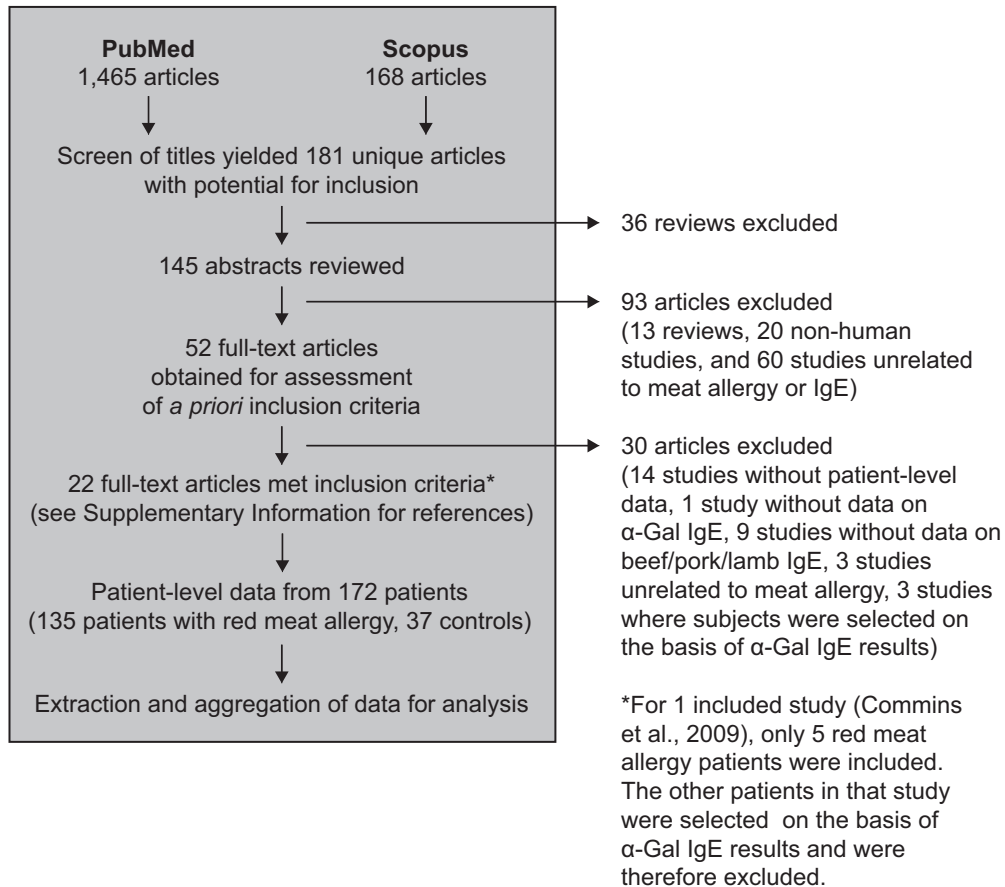


FIG E1. Systematic search and meta-dataset generation. PubMed and Scopus were searched as described in the [Methods](#) section. Screening titles and reviewing relevant abstracts identified 52 articles that were reviewed for exclusion/inclusion, of which 22 were included. These articles contained deidentified patient data for 135 patients with red meat allergy and 37 controls that were extracted and aggregated for analysis.

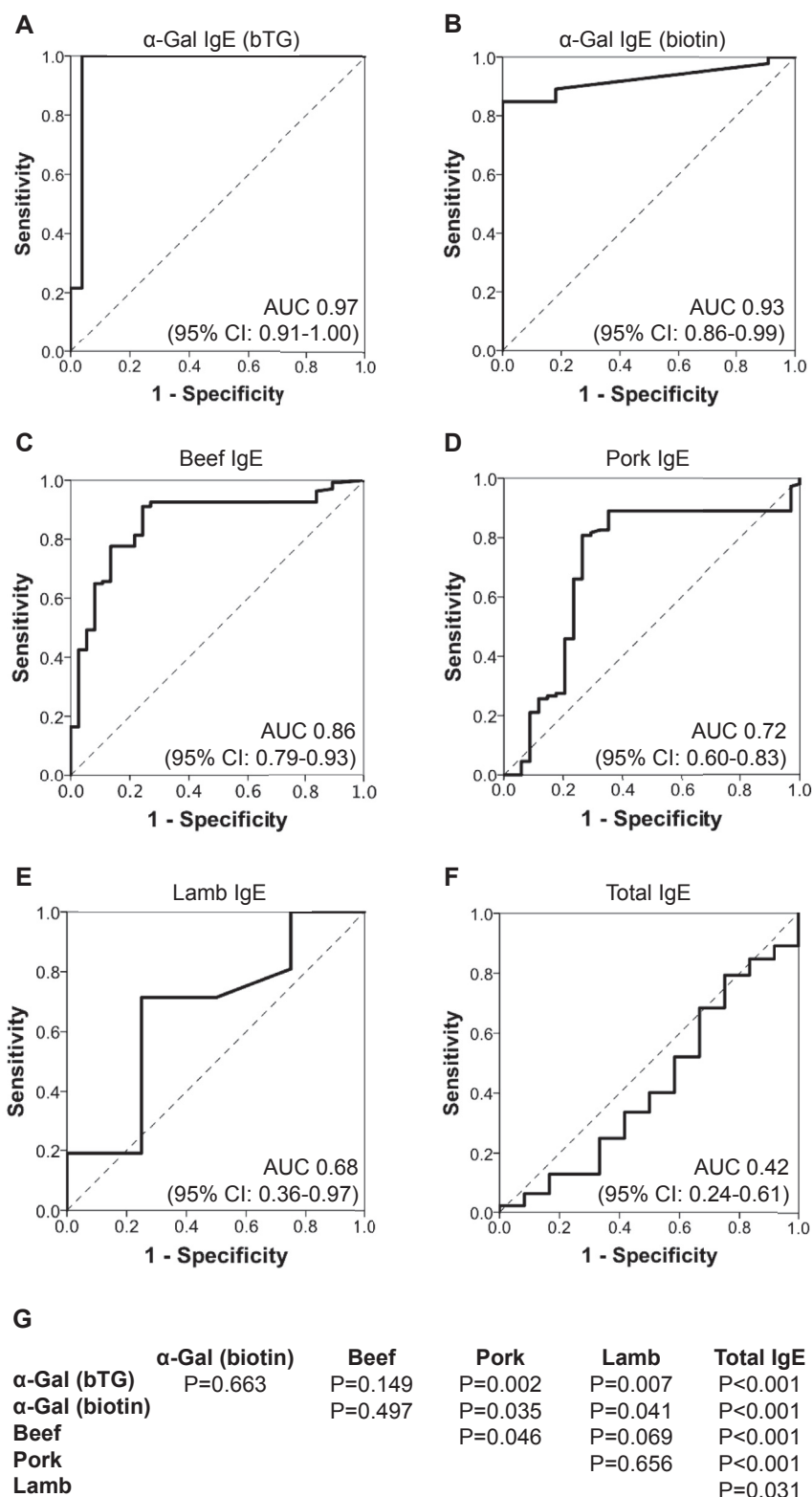


FIG E2. ROC curve analyses for serum IgE tests for diagnosis of red meat allergy. Area under the curve (AUC) with 95% CI was calculated for **(A)** α -gal-bTG IgE, $n = 115$, **(B)** α -gal-biotin IgE, $n = 57$, **(C)** beef IgE, $n = 172$, **(D)** pork IgE, $n = 143$, **(E)** lamb IgE, $n = 46$, and **(F)** total IgE, $n = 104$. **G**, P values for ROC AUC comparisons by 1-way ANOVA with Fisher least square difference *post hoc* test.

TABLE E1. Subjects' characteristics

Characteristic	Control	Red meat allergy	<i>P</i> value
N	37	135	
Age (y)	36.7 (5.2)	53.8 (1.3)	.006
Sex (% male)	26.7	55.6	<.001
Known tick bites (%)	3.6	19.4	.013
Total IgE (IU/mL)	653 (231)	463 (69)	.446
α-Gal IgE, serum (IU/mL)	2.5 (2.1)	42.8 (4.9)	<.001
Beef IgE, serum (IU/mL)	1.4 (0.6)	11.1 (1.4)	<.001
Pork IgE, serum (IU/mL)	4.7 (1.9)	6.3 (0.7)	.419
Lamb IgE, serum (IU/mL)	1.7 (1.4)	3.5 (0.7)	.297

All data reported as mean (SEM), except sex and tick bites, which are reported as percentage. Comparisons by 2-tailed Student *t* test assuming unequal variances, except sex and known history of tick bites, which were compared by Pearson chi-square tests.