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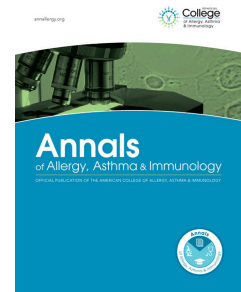
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Diagnosis of Peanut Allergy Using Continuous Likelihood Ratios

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Abbreviations:

AUC: Area Under the Curve

FN: False Negatives

FP: False Positives

LR: Likelihood Ratio

OFC: Oral Food Challenge

ROC: Receiver Operating Characteristics

sIgE: Specific IgE

SR: Systemic Reaction

TN: True Negatives

TP: True Positives

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Background:

Peanut allergy (PA) is associated with an economic and psychologic burden on patients and families. Its diagnosis includes tests for peanut specific IgE (sIgE), the values of which usually are categorized as positive or negative using a predefined cutoff (usually 0.35kU/L). With the use of Bayes theorem, this categorization can be replaced with a continuous interpretation if sIgE which accounts for the prevalence of PA and history of ingestion.

Objective:

We performed a pilot investigation with the results of oral food challenges (OFC) to evaluate a method for estimating the likelihood ratio (LR) for each value of sIgE. The LR could be used to estimate the probability of PA.

Methods:

OFC outcomes and serum IgE values from 117 children seen in an allergy clinic between January 2017 to November 2019 were obtained. Polynomial regression of the Receiver Operation Characteristics (ROC) curve was used to determine a LR for each value of sIgE. Linear regression was used to estimate a LR for each of value of sIgE.

Results:

sIgE ranged from <0.1kU/L to 35kU/L. Bayes' theorem and a ROC curve was used to estimate LRs for each value of peanut sIgE. The value of IgE associated with a LR of 1 was 0.22kU/L, which is comparable to other studies that used a value of 0.35kU/L to separate positive from negative results.

Conclusion:

When combined with estimates of pretest probability, this method should permit development of computerized decision-making algorithms to estimate the probability that a patient has peanut allergy.

Introduction

Peanut allergy is an important global public health issue, with a prevalence of between 0.22% and 1.7%, depending on geographic area of the world and the methodology used for assessment. (1) Among children with food allergy, peanut remains one of the most common offenders in the United States and is the most frequent food implicated in food induced anaphylaxis. (2) The prevalence of peanut allergy in the United States may have tripled from 0.4% to 1.4% in a recent 10-year period. (3) Peanut allergy is associated with substantial economic and psychologic burden on families. (4) There is no cure, though recently an approved treatment for peanut allergy has become available (5) and several others are under clinical development. (6) Therefore, peanut allergy is managed through peanut avoidance, and by carrying auto-injectable epinephrine to treat symptoms that may arise from unintended ingestion. (7) Given the burden of disease, it is important to limit the overdiagnosis of peanut allergy.

A definite diagnosis of food allergy cannot be made on the basis of laboratory tests alone. It requires gathering a detailed history prior to using diagnostic measures such as skin prick or laboratory tests. Diagnostic tests for peanut allergy are used to determine the likelihood of a systemic reaction (SR) if peanut is ingested. The gold standard or reference test for peanut allergy is an oral food challenge (OFC). Since an OFC is inconvenient, expensive and is associated with a risk of a SR, an index test such as measurement of peanut specific IgE (sIgE) is often used as a proxy for the reference test. Peanut-specific IgE is most commonly measured using the ImmunoCAP™ assay. (8)

The presence of food specific IgE is termed “sensitization”. A sensitized patient who can eat the food without having a reaction is termed food tolerant while a patient who has a systemic reaction following food ingestion is termed “food allergic”. Interpretation of peanut-sIgE usually involves identification of positive and negative cutoff values that are determined by comparing the probability of a reaction to sIgE values which generates a sigmoid curve. (9) The problem with this approach is that it does not account for the likelihood of a reaction that exists before the test is done (ie: pretest odds). For example, a peanut tolerant patient has a low likelihood of a SR after eating peanut even if they have a high peanut-sIgE. This is usually considered to be a “false positive” (FP) test. Similarly, a patient who has an objective SR following peanut ingestion is allergic to peanut even if they have a low peanut-sIgE. This is often referred to as a “false negative” (FN) test. Since the prior history is not accounted for when this approach is used, it can provide misleading estimates for the likelihood of a reaction. Clinical

history is necessary for determining the pre-test odds of peanut allergy. It is well documented that individuals can demonstrate sensitization even with peanut sIgE levels >15 kU/L but are also able to tolerate peanut ingestion (10)

Bayes' theorem can be used to combine the probability (ie: a number between 0 and 1) of a reaction before the test is done with the measurement of peanut-sIgE to determine an updated probability. (see Figure 1) A useful characteristic of a diagnostic test for estimating the post-test odds (the ratio of the probability of a peanut reaction to the probability of no reaction) is the likelihood ratio (LR). The likelihood ratio for peanut-sIgE is the probability of observing a given test result in a patient with peanut allergy divided by the probability of observing that same result in a patient without peanut allergy. The advantage of the LR as a measure of test performance is that it can be used mathematically to convert pretest odds into posttest odds of peanut-allergy since values are ratios. In addition, if there is more than one independent test (ie: history, skin test or in-vitro test for components), the posttest odds of one test can serve as the pretest odds for the next test (ie: $\text{Pretest odds} \times \text{LR1} \times \text{LR2} = \text{posttest odds}$). (See Figure 2) LRs are not dependent on the population prevalence of the disease and the history of ingestion because that is already accounted for in the pretest odds. Unlike other measures of test performance such as sensitivity, specificity and positive and negative predictive values, LRs can easily be used to estimate disease probability given the test results.

The performance characteristics and cut-off values for a diagnostic test can be determined by generating a Receiver Operating Characteristics (ROC) curve. (11) ROC curves are defined to be the relationship between the True Positive Rate (TPR) (ie: sensitivity) and the False Positive Rate (FPR) (ie: $1 - \text{specificity}$) for various cut-offs in a dichotomous (ie: positive or negative) test. The accuracy of the test is represented by the maximal area under the curve (AUC). An AUC of 0.7-0.8 is considered fair, 0.8-0.9 good, and >0.9 is excellent. (12)

Most LRs are expressed as either positive or negative when compared to a predetermined cutoff value for sIgE. (13) The problem with using a cutoff value is that test results that are near the negative or positive cutoff are treated the same as results that are much higher (or lower). Yet a peanut-sIgE < 0.35 kU/L is likely to be associated with a different risk of a reaction than a value of >14 kU/L. It would be better to estimate a LR for each value of peanut-sIgE.

The formula for LR is sensitivity/1-specificity which is the slope the ROC curve at each point. Analytically, the formula for a straight line is $y = mx + b$ where m is the slope and b is the y-intercept. To determine the slope at each point of an ROC curve which is not linear, it is necessary to determine the first derivative of the regression equation of the ROC curve. The 1-specificity values (which are the x-values) can then be converted back to specific IgE. This type of method was recently described by Fierz who used Bezier curves to estimate slopes of an ROC curve. (14)

For this retrospective analysis of patient data, we hypothesized that a LR can be determined for each value of peanut-sIgE in children with a history of peanut allergy. The use of continuous LRs may lead to more effective use of testing for the diagnosis of peanut allergy, given the current limitations in peanut allergy testing.

Methods

Data Source

De-identified clinical information related to patients who were seen in a pediatric allergy clinic and who underwent an oral food challenge (OFC) for peanut allergy was entered into a Redcap database. Since the procedures were performed for routine clinical service, the database was considered to be exempt from the need for IRB approval. The database was created by a board-certified Allergy/Immunology physician and all food challenges were conducted, evaluated, and documented by clinical staff under the supervision of an allergist or nurse practitioner. Data input was performed by a nurse practitioner.

Patients

Between January 2017 and November 2019, 117 patients previously identified with a history of peanut allergy underwent an open oral food challenge (OFC) with peanut. Peanut-specific IgE (sIgE) was measured for each of these patients using ImmunoCAP fluorescence enzyme immunoassay. OFCs were performed based on clinical history and on the desire of patients and their parents to know whether they were peanut allergic. OFCs were standardized in methodology and escalated with a goal of 2000 mg of peanut protein. (15) Peanut sIgEs were measured within 1 year of the OFC.

Each OFC consisted of sequentially escalating doses of peanut protein ingested by the participant every 15 minutes as tolerated. Food protein was administered as peanut butter or as peanut flour mixed

in an appropriate vehicle such as applesauce or pudding depending on patient preference. Patients who tolerated 2000mg cumulative peanut dose during the challenge without having a reaction were considered to have a negative challenge.

Statistical Analysis

P-values for continuous variables were determined using paired T-test. Categories of initial reaction and peanut-sIgE were analyzed using chi-square. Sex and personal history were analyzed using the Z-score test for population proportions.

To determine the thresholds of sIgE that best discriminated challenge outcome, 2 columns consisting of sIgE and whether there was a reaction to OFC were sorted in an Excel spreadsheet in ascending order of sIgE. These values were used to construct a curve comparing peanut-sIgE and cumulative probability of having a SR during the challenge. In addition, for each value of sIgE, the TP (Sensitivity), FP, TN (Specificity) and FN were determined and a receiver operator characteristic (ROC) curve was constructed comparing sensitivity with 1-specificity. The same data was also analyzed in IBM SPSS to construct a ROC curve to estimate the area under the curve (AUC). A polynomial regression model was then used to fit to the ROC curve.

The definition of LR is Sensitivity/(1-Specificity) which is also the slope of the ROC curve at each value of 1-Specificity. To determine the slope of the ROC curve at each point, the regression formula for that curve was differentiated yielding the first derivative which is the equation for the slope of the curve at each point. Using this equation, a value for LR was determined for each value of 1-Specificity. The 1-Specificity values were then converted to their corresponding sIgE values. The curve of sIgE vs LR was then fitted to a log-linear regression curve so that LR could be estimated for any value of peanut-sIgE.

Data Management

Any value of sIgE <0.1 kU/L was set to 0.1 and >100 kU/L was truncated to 100. Also, when constructing the sIgE vs LR, values associated with a sensitivity of $>95\%$ and $<0.05\%$ were removed from the final linear regression curve since these were at the extremes of the ROC curve.

Results

Baseline Demographics

A total of 117 patients underwent OFC with peanut. Characteristics of these patients are shown in Table 1. Of these, 63% were male and 37% were female. A history of eczema was present in 50 (45%) of the patients. The mean age of the patients was 6.69 ± 4.12 years. A SR occurred during OFC in 54 patients. There was no significant difference between patients who reacted to OFC and those that did not in terms of sex or the presence of eczema. Mean peanut specific IgEs ranged from <0.1 kU/L to 35.7 kU/L and were slightly higher in the group that had a reaction during OFC, but this difference was not statistically significant. This range is limited at the higher end because patients with higher peanut-sIgEs were reluctant to undergo an oral challenge. The count of patients with peanut sIgE in whole unit categories by whether they reacted to an OFC is shown in Figure 3. Most of the patients with a negative OFC had a peanut sIgE <1 kU/L while patients who reacted had a peanut sIgE between 1-2 kU/L.

Table 1 also shows the number of patients in each of 5 categories of peanut-sIgE with and without a reaction. The difference in the distribution of such patients was statistically significant based on chi-square analysis indicating that patients with a lower sIgE were more likely to be in the no-reaction group. The distribution also illustrates the limited range of sIgE in this group with few patients having a sIgE greater than 10kU/L.

Results of OFCs

We next constructed a curve relating peanut-sIgE and the cumulative probability of a reaction to the OFC. (Figure 4) This generated a sigmoid curve which is commonly observed for this type of study. For our patients, a sIgE of 0.1 kU/L was associated with a probability of a reaction close to zero while values >10 kU/L were associated with probabilities close to 1 of a reaction in this sample.

Construction of the ROC curve

The ROC curve for our patients is shown in Figure 5. The area under this ROC curve was 0.716 (CI 0.623-0.809) which is considered to be fair. Polynomial regression of the points on the ROC curve yielded an equation of $y = -1.3808x^2 + 2.253x + 0.0196$ where y is sensitivity and x is 1-specificity. The curve had a R^2 value of 0.99 indicating a high correlation between the measured data and the regression curve.

Determination of LRs for sIgE

The first derivative was determined for the polynomial regression equation of the ROC curve. This was calculated to be $y = -2.7616x + 2.3253$. Since the slope of the ROC curve is also the LR, this also is the equation for LR. We next used this equation to estimate a LR for each value of 1-specificity. Each of these values was then converted to its corresponding peanut-sIgE. (Figure 5) Log-linear regression of this curve yielded an equation of $y = \log(0.9491x + 1.6206)$ where y is the LR and x is the sIgE. This curve had a R^2 value of 0.98.

Cutoff Value for LR

To estimate a LR cutoff value for sIgE (ie: a value that separates LR values <1 from those >1), we set the LR to 1.0 and solved for sIgE as $x = 10^{(1-1.6206)/0.9491}$. This gave a value of 0.22kU/L for the LR cutoff of sIgE. This means that values of sIgE less than 0.22kU/L are associated with a LR less than 1, which are associated with a decreased likelihood of a SR if peanut is eaten. Values of sIgE greater than 0.22kU/L are associated with a LR greater than 1, which are associated with an increased likelihood of a SR if peanut is eaten. A LR of 1.0, which corresponds to the 0.22 kU/L LR cutoff value for sIgE, does not alter the pre-test probability and is therefore associated with no change in the likelihood of a SR.

Range of LRs

The LRs in our analysis ranged from 0.67 to 2.57 which corresponded to sIgEs of 0.1kU/L and 10kU/L respectively. We compared this range to ranges from other studies that used 0.35kU/L as a positive or negative cutoff for sIgE. (Table 2). LRs for sIgE > 0.35 kU/L in those studies ranged from 2.3 to 11.6 while LRs for sIgE < 0.35 kU/L ranged from 0.06 to 0.47. The LR for sIgE > 0.35 kU/L in our study of 3 was in the range found by the other studies, however, the LR for sIgE < 0.35 kU/L of 0.47 in our study was at the high end of the range found in the other studies. In other words, using our results, an elevated sIgE is as sensitive for identifying peanut allergy as other studies, however, it is not as good for ruling out peanut allergy when sIgE is low.

Use of LRs to Determine Posttest Probability

Table 3 provides examples of how to use LRs from our analysis to convert from pretest probability to posttest probability for various values of pretest probability. The pretest probabilities are estimates of the probability of a reaction assuming that a patient tolerates peanut (arbitrarily set at 0.1%), has no

history of ingestion in an unselected population (1.5%) (1), is between the ages of 5-11 months and has eczema and/or egg allergy (17%) (16) or if there is a clear history of peanut allergy (arbitrarily set at 99%). The likelihood ratios correspond to sIgE values of 0.1 kU/L (0.67) and 10 kU/L (2.57). The use of these values is shown graphically in the Fagan nomogram shown in figure 6.

Discussion

The most useful characteristic of a diagnostic test is the Likelihood Ratio (LR) which is defined as the probability of having the disease given the test results divided by the probability of not having the disease given those same test results. When used for medical decision making, likelihood ratios are usually dichotomous in that there is a LR for a positive test and a LR for a negative test. This is done for convenience since a test can be described as “positive” or “negative” without having to do mathematical calculations. It is possible to create LRs with 3 or more levels or even continuous levels with a LR for each value of the test. These may provide more mathematical precision which would be useful for computerized decision-making algorithms. The problem with a single positive or negative cutoff is that test values that are close to the cutoff are treated the same as values that differ substantially from it.

To determine, the optimal cutoff for separating positive and negative results, an ROC curve is used which plots the TPR (sensitivity) on the Y axis, against the FPR (1-specificity) on the X axis. A 45-degree diagonal line from the intercept represents a situation in which the true- and false-positive are equal, and the test is worthless.

By using Bayes’ theorem and a ROC curve with our data, we were able to construct an equation to estimate LRs for each value of peanut sIgE. We identified a LR cutoff peanut sIgE level of 0.22 kU/L which corresponds to a LR of 1.0. This was comparable with other studies in the past that used 0.35 kU/L as a cut off shown in Table 2. Thus, by using our method, we were able to construct a statistically valid method of using peanut sIgE with the benefit of having dynamic cutoff value for sIgE.

The major limitation of our results is that our study was retrospective so only patients who underwent an OFC were included. The peanut-sIgEs were low because patients with high IgE levels were less likely to undergo oral food challenges. However, these data represent real world experience. We recognize that the number of patients involved in this analysis is relatively small and that the range of sIgEs is limited, however, the goal of our study was to demonstrate the feasibility of this

methodology. Ideally having food challenge outcome data in patients who underwent challenges despite large IgE values would be the best for this model and provide broader clinical utility. In the future, this could be done by expanding the study to multiple and larger institutions.

To determine the probability that a patient will have a SR following peanut ingestion, the pretest probability of having a reaction is needed. This takes into account the prevalence of peanut allergy in the patient's demographic (17)(18) modified by the history of prior ingestion (if any). The pretest probability can be converted into odds (defined as probability/(1-probability)) which is a ratio that can be multiplied by the LR to determine the posttest odds.

Another limitation of our approach is that given the posttest odds of peanut allergy, there is no consensus on what to do with the results since the primary goal is to decide whether to treat or not treat. Future studies will need to be done to determine when the probability is below a certain threshold (the no treat threshold), the patient can be advised to eat peanut (no treatment). When the probability is above that threshold, treatment (avoid peanut, carry epinephrine or possibly peanut oral immunotherapy) is recommended. When the probability is close to this threshold, a diagnostic or index test might change the recommendation by moving the probability across the decision threshold. Then the diagnostic test i.e. sIgE peanut (or series of tests) is used to determine the probability of peanut-induced anaphylaxis since that leads to specific treatment recommendations.

Overall, the purpose of a diagnostic test is to start with the pretest probability of a peanut reaction and, using the test results, determine a posttest probability that hopefully falls above or below the decision threshold so that a clear recommendation can be made. If the probability remains close to the threshold, another independent diagnostic test may be helpful. In this way, a series of tests can be used to alter the probability of a reaction until a recommendation to treat or to not treat can be made. This information can assist with shared decision making with patients to determine the best course of management.

There is still much work to be done in our field in creating a diagnostic method for diagnosis of peanut allergy. We were able to demonstrate a method by using Bayes' theorem and a ROC with our data to create a means in creating a dynamic cutoff for peanut sIgE. However, for this to become fully functional in predicting SR more research must be done on the pretest odds that include prevalence data and demographics.

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Tables

	No rxn (n=63)	Rxn (n=54)	Total (n=117)	P-value (rxn vs no rxn)
Sex				
Male	40 (63%)	34 (63%)	74 (63%)	0.95
Female	23 (37%)	20 (37%)	43 (37%)	
Age	7.27 ± 4.08	6.19 ± 4.18	6.69 ± 4.12	0.16
Personal History				
Eczema	24 (38%)	28 (52%)	52 (44%)	0.45
Asthma	20 (32%)	15 (28%)	35 (30%)	0.63
Initial Reaction				
No exposure	11	8	19	
No reaction	8	4	12	
Skin only	30	27	57	
GI only	4	1	5	
Skin and GI	5	4	9	
Respiratory	6	6	12	0.71
Peanut sIgE	1.32 ± 3.47	2.65 ± 5.41	1.88 ± 4.45	0.11
Total Range	<0.1 – 23.2	<0.1 – 35.7	<0.1 – 35.7	
No. with sIgE				
< 0.35	35	7	42	
0.35 - 1	12	19	31	
1.1 - 5	11	20	31	
5.1 - 10	1	5	6	
> 10	3	4	7	0.000043

Table 1: Characteristics of patients who underwent oral peanut challenge. Age and peanut-sIgE are mean ± Standard deviation. P-values for continuous variables were determined using paired T-test. Categories of initial reaction and peanut-sIgE were analyzed using chi-square. Sex and personal history were analyzed using the Z-score test for population proportions.

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Study	TP	FP	FN	TN	Sens	Spec	LR+	LR-
Beyer 2015 (19)	77	17	13	103	0.86	0.86	6.0	0.17
Dang 2012 (20)	81	7	19	93	0.81	0.93	11.6	0.20
Ebisawa 2012 (21)	23	3	5	28	0.82	0.90	8.5	0.20
Gray 2016 (22)	22	8	2	12	0.92	0.60	2.3	0.14
Keet 2013 (23)	23	10	3	25	0.88	0.71	3.1	0.16
Klemans Broekman 2013 (24)	33	6	22	33	0.60	0.85	3.9	0.47
Klemans Otte 2013 (25)	43	15	4	38	0.91	0.72	3.2	0.12
Kukkonen 2015 (26)	58	11	3	30	0.95	0.73	3.5	0.07
Lieberman 2013 (27)	85	5	21	56	0.80	0.92	9.8	0.22
Martinet 2016 (28)	45	0	3	35	0.94	1.00	ND	0.06
Schots 2016 (29)	27	7	4	14	0.87	0.67	2.6	0.19
Suratannon 2013 (30)	16	7	3	14	0.84	0.67	2.5	0.24
Current Study	44	10	26	37	0.63	0.79	3.0	0.47

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310 Table 2: Comparison with LRs of the current study using a positive/negative cutoff of 0.35 for
 311 peanut sIgE with other studies that also used 0.35 as the cutoff for peanut sIgE. TP=true
 312 positives, FP=false positives, FN=false negatives, TN=true negatives. Sens=sensitivity,
 313 Spec=specificity, LR+=Likelihood ratio of an IgE value > 0.35, LR-=likelihood ratio of an IgE value
 314 < 0.35. ND=not defined because there were no FPs.

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Legends for Figures

Figure 1: Bayes' Theorem can be used to estimate the posttest odds of a reaction given the pretest odds and test results. $P(A|B)$ is the likelihood of the disease (A) given the test results (B). $P(B|A)$ is the likelihood of the test results (B) given the disease (A). $P(A)$ and $P(B)$ are the unconditional probabilities (ie: prevalence) for the disease and for the test results. For this study, $P(A)$ = the prevalence of peanut allergy and $P(B)$ is the probability of a given sIgE result.

Figure 2: Decision-making algorithm for diagnostic test for peanut allergy using Bayesian statistics. The pretest odds represent an estimate of the prevalence of peanut allergy in the patient's demographic. Tests can include history of ingestion, skin tests or in-vitro tests. The posttest odds of a reaction can be converted to a probability of a reaction which is used to decide on treatment.

Figure 3: Count of patients with peanut sIgE by whether they reacted to an OFC. The categories represent peanut sIgE in whole unit categories.

Figure 4: Typical sigmoid curve showing $\text{Log}(\text{peanut-sIgE})$ vs probability of reaction.

Figure 5: ROC curve for peanut-sIgE and challenge result (left). Polynomial regression was used to estimate an equation for the curve. The first derivative of that equation was used to estimate the slope of the curve for each $1 - \text{Specificity}$ value. Peanut-sIgE vs. LR for each IgE value (right). A LR value of 1 is associated with a sIgE value of 0.22kU/L.

Figure 6: A Fagan Nomogram showing how to use LRs to convert from pretest probability to posttest probability for various values of pretest probability. The pretest probabilities used are estimates of the probability of a reaction given that a patient tolerates peanut (arbitrarily estimated at 0.1%), the prevalence in an unselected population (1.5%) (1), the prevalence in patients ages 5-11 months with eczema and/or egg allergy from the LEAP study (17%) (30) and the probability in a patient with a clear history of peanut allergy (arbitrarily estimated at 99%). The likelihood ratios correspond to sIgE values of 0.1 (0.67) and 10 (2.57).

Numbered Figures

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

The diagram illustrates the components of the formula $P(A|B) = \frac{P(B|A)P(A)}{P(B)}$. Three blue arrows point from the text labels below to the corresponding terms in the formula: one from 'Posttest Probability' to $P(A|B)$, one from 'Likelihood Ratio' to $P(B|A)$, and one from 'Pretest Probability' to $P(A)$.

Posttest Probability Likelihood Ratio Pretest Probability

Figure 1

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<u>Initial Probability</u>	<u>History of Ingestion</u>	<u>Diagnostic tests</u>	<u>Probability of a Rxn</u>	<u>Treatment Decision</u>
Prevalence in group	None	None	How much ingested	Eat peanut
Age	No reaction	Prick skin test	Form of the food	Avoid peanut/carry epinephrine
Sex	Reaction characteristics	slgE to peanut	Reaction characteristics	Oral food challenge
Ethnicity	• Severity	slgE to components		
Race	• Symptoms	slgE/IgE ratio		
Location of origin	• Objective vs subjective	Basophil activation		
Other factors	How long ago?	Other tests		
				Modifying factors
				Age
				Vulnerability
				Anxiety
				Eagerness to eat peanut

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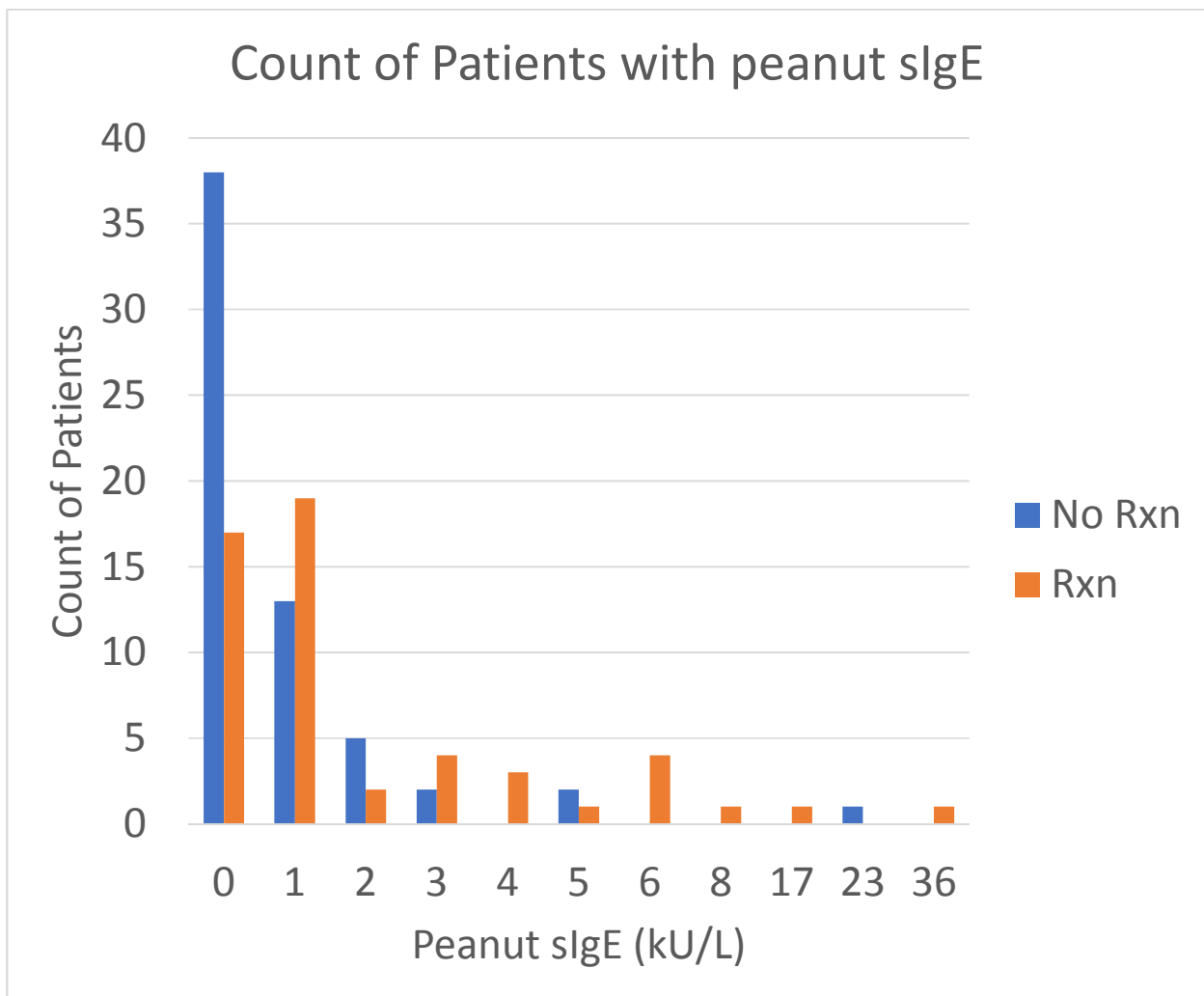
Pretest Odds X LR1 X LR2 = Posttest Odds → Decision Analysis

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356 Figure 2

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360 Figure 3

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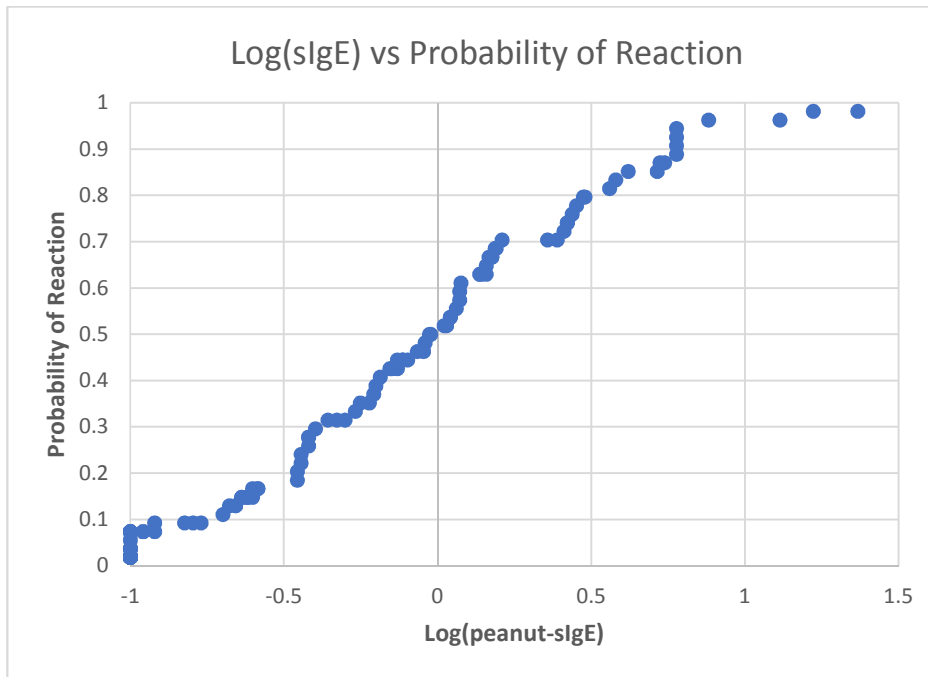


Figure 4

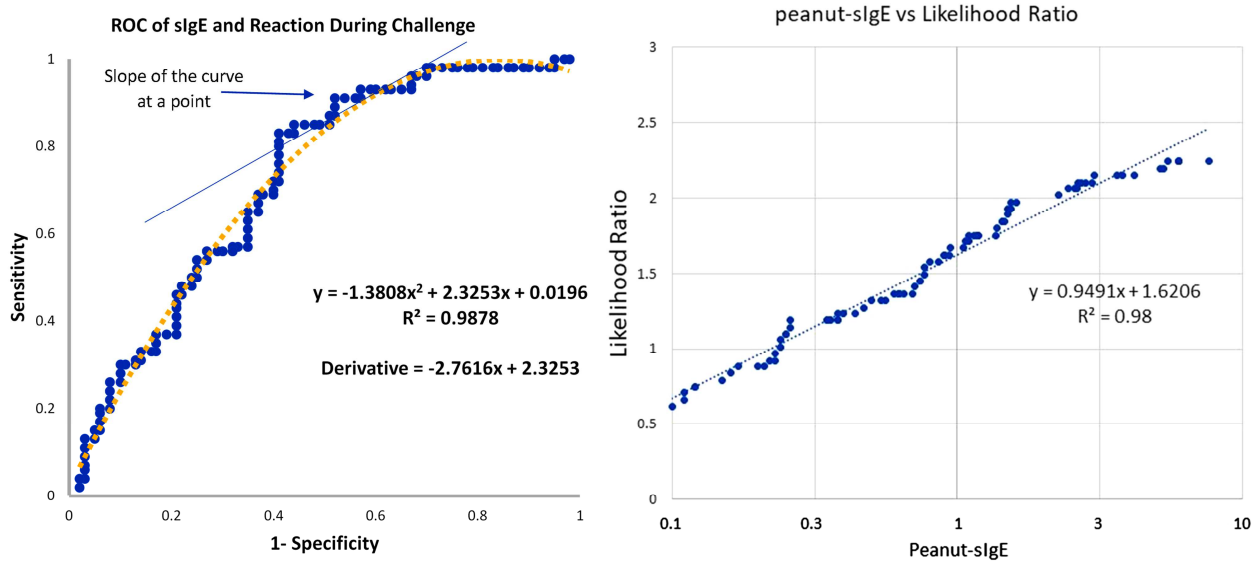
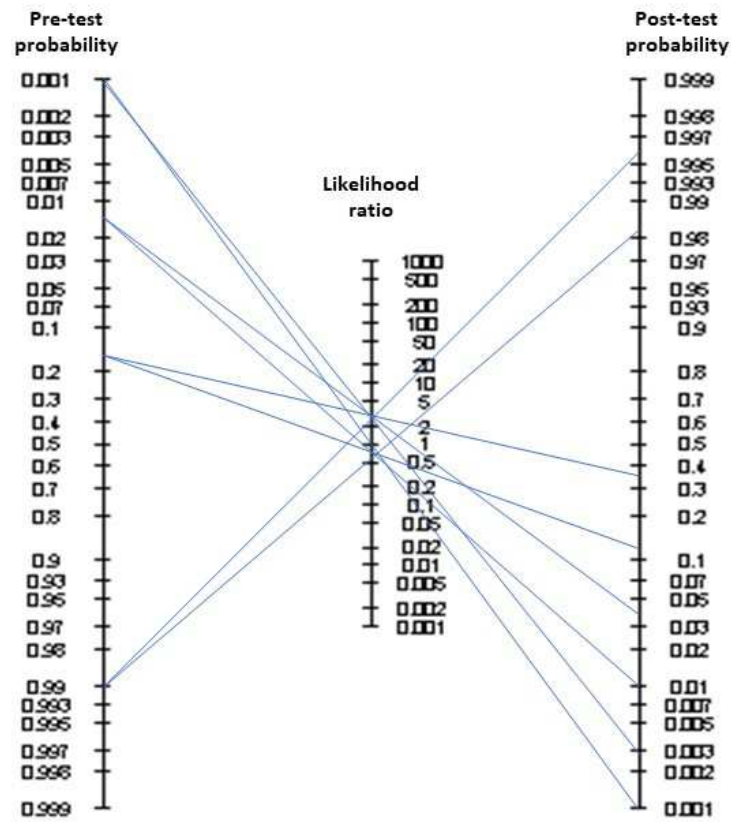


Figure 5



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375 Figure 6