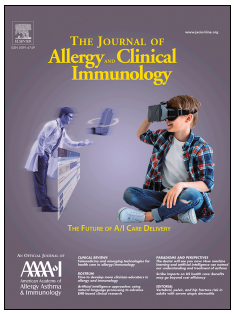
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Just Listen to Your Patient

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Word Count = 1,652

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- Disclosures
    - David Lang serves as a member of the Editorial Board for Allergy and Asthma Proceedings, Topic Editor for DynaMed, Associate Editor for J Asthma, and Delegate to National Quality Forum representing the American Academy of Allergy, Asthma, and Immunology.
    - John Oppenheimer has received financial support from DBV, TEVA, GlaxoSmithKline adjudication/data safety monitoring board, AstraZeneca, Novartis, and Sanofi; is Associate Editor of the Annals of Allergy, Asthma, and Immunology and AllergyWatch, an American Board of Internal Medicine (ABIM) Council Member and American Board of Allergy and Immunology Liaison to the ABIM, UpToDate Reviewer, American College of Chest Physicians Cough Guideline Committee Member, and WebMD Editor.
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Key Words: Ara h 2, In Vitro Testing, Likelihood ratio, Peanut Allergy, Skin Testing, Sensitivity, Specificity.

Abbreviations

Ara h - Arachis hypogaea

LR - Likelihood Ratio

PA Peanut Allergy

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The Practice Parameter on the Diagnosis of Peanut Allergy (PA) that appears in this issue of the JOURNAL (1) recommends a clinical pathway to determine the probability that a diagnosis of PA is present.

The process of diagnostic evaluation in which we commonly engage is comprised of four steps: (1) Performing a detailed history to arrive at a pre-test probability of PA; (2) Determining whether to perform a diagnostic test, and if so which test to perform; (3) Using the test results to determine a post-test probability; (4) Deciding -- with the patient -- what action (i.e., treatment / no treatment / further testing) to pursue based on that probability.

The first step can be conceptualized as depicted in Figure 1. The probability of PA can range from 0 to 100 percent. That range can be partitioned into different actions by probability thresholds either for testing or for treatment (2).

Three Sisters

Imagine three sisters who are one year apart in age arrive for consultation, each concerned that she has PA:

- Sister A had a reaction that occurred 3 weeks ago. She was at a picnic, and ate one bite from a peanut butter cookie. Pruritus of her mouth and throat developed promptly. Within 10 minutes she experienced generalized flushing and urticaria, a sensation of “throat closing”, and lightheadedness. Upon arrival at a nearby Emergency Department, her vital signs were: HR= 110, RR = 30, BP = 80/40. She received

intramuscular epinephrine and intravenous saline. Prior to discharge, her vital signs were: HR= 70, RR = 16, BP = 110/70.

- Sister B experienced adverse reaction six months ago, consisting of nausea, abdominal cramping, and "feeling dizzy" within 30 minutes after eating a portion of a peanut butter sandwich. She has subsequently avoided peanut ingestion, but believes she may have had peanut in restaurant meals without untoward reaction.
- Sister C requests evaluation for PA because of the reaction histories of her sisters. She reports never having an adverse reaction following peanut ingestion but has avoided peanuts in recent months pending further evaluation.

The above histories lead you to assign a different pre-test probability of PA for sisters A, B, and C as illustrated in Figures 2a, 2b, and 2c. Referring to Figure 1, we would place our "pre-test probability" on the far right for sister A, and on the far left for sister C. In other words, sister A is above our *treatment threshold*, while sister C is below our *testing threshold*. Sister B is between these thresholds. More on these thresholds and the three sisters momentarily…

Suppose we change our scenario for Sister A. Instead of eating a peanut butter cookie at the picnic, she was stung by a yellow jacket and following this experienced the reaction described above. Her history of a systemic reaction after exposure to a known allergen fulfills the criteria for a diagnosis of anaphylaxis (3). Although she is above the threshold for treatment based on history alone, we still need to perform diagnostic testing for sister A to confirm presence of venom-specific IgE and direct her prescription for venom

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immunotherapy. We can anticipate that skin and/or serum specific IgE testing will be positive for yellow jacket and perhaps other venoms.

It is also standard of care to perform a diagnostic test to confirm Sister A has PA. However, based on the high pre-test probability, even if the test is negative, the post-test probability would still be quite high such that a diagnosis of PA would not be ruled out. The next step would be to perform a test regarded as the reference standard – oral food challenge (1).

According to previously published management recommendations based on best evidence (4), sister C, who in our altered scenario is seeking evaluation for stinging insect allergy based on family history, would not be a candidate for venom testing because her pre-test probability is below the testing threshold. From a broader perspective, this and previously published Practice Parameters are intended, at least in part, to reduce clinical variation (5). Much of the well-documented variation in physician behavior in ordering diagnostic tests can be attributed to differences in individual action thresholds (6,7). We currently have no data for our specialty that allow us to determine the *performance gap* that exists between Practice Parameter-based management and normative care as it is actually occurring. However, the authors believe we can be relatively certain that were we to be able to accurately make such determinations we would find the performance gap for diagnostic evaluation of sister C would be narrow in the context of hymenoptera venom anaphylaxis, but not so narrow in the context of PA and allergy to other foods.

For the evaluation of a patient with suspected PA, as is the case with evaluation of a patient with suspected stinging insect allergy, when the

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probability of PA is very low, a patient can be advised to continue or resume eating peanut as desired; *no diagnostic testing is warranted*. When the probability of PA is very high, a patient should be advised to avoid ingestion of peanut based on history, and to carry epinephrine in case of accidental ingestion. When the certainty PA is present is below the testing (or above the treatment) threshold, the post-test probability will not change remarkably even if the result of the test is positive (or negative). When the probability of PA is intermediate, our management recommendation is uncertain. It is in this situation that a diagnostic test has utility for providing additional information that can significantly influence post-test probability for PA being present/not present, and lead to appropriate management recommendations. Our "pre-test probability" for sister B is intermediate and falls in between our *testing threshold* and our *treatment threshold*. It is for patients such as sister B that diagnostic testing is most useful.

Estimating the probability of PA

To determine what action to recommend and whether to order a test, it is necessary to estimate the probability thresholds for testing and treatment (8). These estimates depend on the efficacy and safety of treatment, the potential for harm/burden associated with each test, and the likelihood ratio (LR) for the test that can be ordered. Practice variation can be minimized if providers make these determinations consistently. The use of varying thresholds or practice behavior that does not conform to this threshold model will lead to unnecessary variation in practice (6).

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When the pre-test probability of PA is in between the testing and treatment thresholds, a diagnostic test can be used to change treatment recommendations by adjusting the post-test probability across a threshold. By sequentially using independent tests to refine the probability of PA, an objective method for making a clinical decision can be achieved.

The most useful characteristic of a test determining the post-test probability is its LR. In the case of PA, the LR is the likelihood that a given test result would be expected in a patient with PA compared to the likelihood that the same result would be expected in a patient without PA (7). The advantage of the LR as a measure of diagnostic test performance is that it can be used mathematically to convert pre-test odds to post-test odds of PA. In addition, if there is more than one independent test (e.g., history, skin or in-vitro test, oral food challenge), the post-test odds of one independent test can serve as the pre-test odds for the next test (i.e., pre-test odds x LR1 x LR2 = post-test odds). In addition, LRs are not dependent on the population prevalence of the disease, as this is already accounted for in the pre-test odds, unlike positive and negative predictive values which may vary based on disease prevalence in the population being studied.

Ara h 2: more optimal specificity and positive LR

Putting this all together, how does the Practice Parameter on the Diagnosis of PA (1) aid us in evaluation and management of sister B, whose pre-test probability is in between our testing and treatment thresholds? The Parameter communicates the performance characteristics of our currently available testing tools, shown in Table 1. An important message from the Parameter is that the utility of these tests is

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optimized in combination with a pre-test probability of PA derived from a detailed history.

Note that both skin and in vitro testing have higher sensitivity in identifying patients with PA. However, in identifying the one "best test" for the diagnosis of PA, the parameter has prioritized the more favorable combination of sensitivity and specificity shown for Ara h 2, which leads to a positive LR that can more substantially influence our post-test probability. The specificity of the other two diagnostic tests is poor, and would lead to a substantial rate of false positive tests. Several aspects of this recommendation for Ara h 2 are important to note: (1) the Forest Plots presented in the Parameter demonstrate substantial heterogeneity; (2) the conditional nature of this recommendation implies that further research is very likely to have an important impact on the estimates shown in Table 1, and in the future this recommendation may change; (3) a potential risk of relying upon Ara h 2 as a stand-alone test is that an allergic individual may be sensitized to components other than Ara h 2 and thus could be missed if this was the only component tested.

William Osler famously said: "Just listen to your patient, (s)he is telling you the diagnosis" (9). Step one, as a "screening test" for diagnosis of PA, is a comprehensive history. For step two, to confirm or rule out the diagnosis in properly selected patients (such as sister B), we do not currently have a "perfect" test. The Practice Parameter on the Diagnosis of PA recommends Ara h 2 as the test with the most optimal performance characteristics; however, step two should proceed only in accordance with the threshold approach to clinical decision-making displayed in Figure 1 -- after we have listened.

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Legends

Figure 1: This graphic illustrates the relationship between testing threshold, treatment threshold, and probability that a condition is or is not present, which influences whether testing is appropriate to be performed.

Figure 2a: This graphic illustrates the clinical situation in which a patient such as Sister A provides a history associated with a pre-test probability that is exceeds the treatment threshold.

Figure 2b: This graphic illustrates the clinical situation in which a patient such as Sister B provides a history associated with a pre-test probability that is in between the testing threshold and the treatment threshold; in this instance a diagnostic test is indicated to confirm or rule out a diagnosis to determine whether treatment is warranted.

Figure 2c: This graphic illustrates the clinical situation in which a patient such as Sister C provides a history associated with a pre-test probability that is below the testing threshold.

Table 1: Mean estimates (95% CI) for sensitivity and specificity, and calculated positive and negative likelihood ratios are displayed for skin testing, serum specific IgE, and Ara h 2 for diagnosis of peanut allergy (1). Both skin and in vitro testing have poor specificity and positive likelihood ratios that are associated with a low impact on post-test probability. The positive and negative likelihood ratios for Ara h 2 would each be associated with a moderate impact on post-test probability.

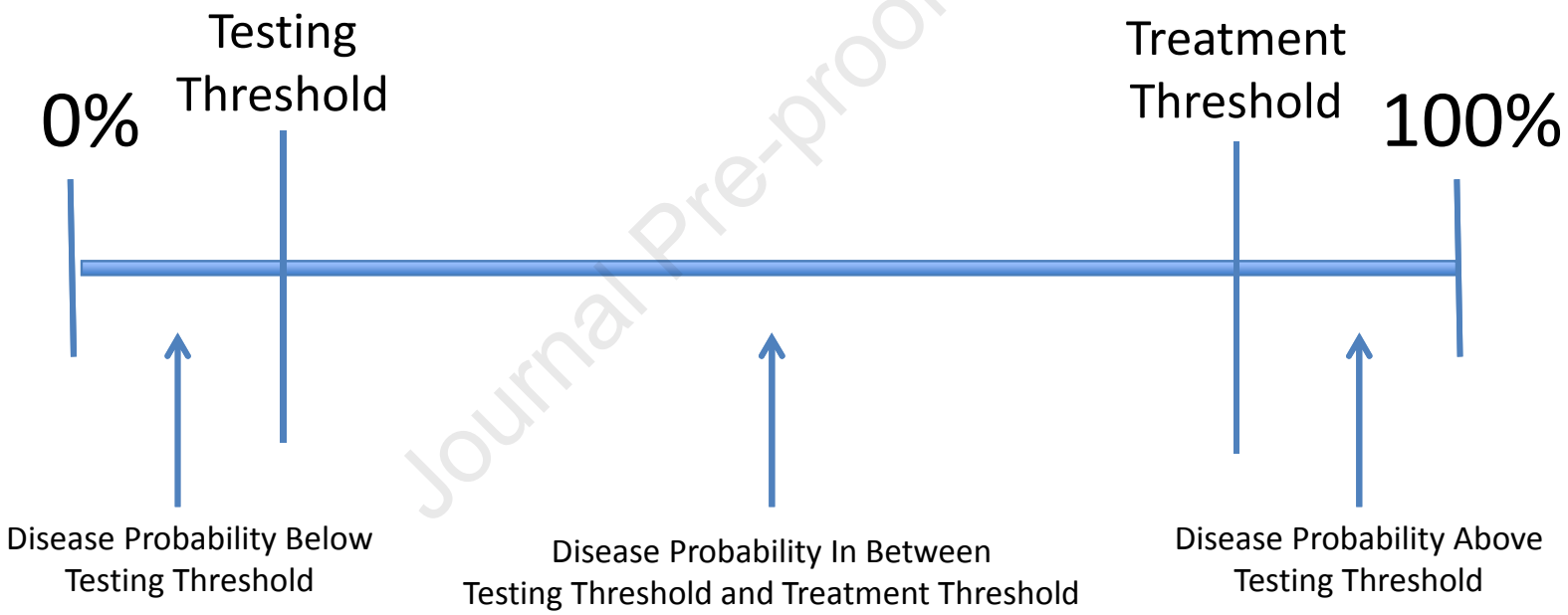
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	Sensitivity	**Specificity**	**Positive LR**	**Negative LR**
Skin Test	97% (93-99)	46% (29-65)	1.8	0.06
Serum Specific IgE	95% (91-97)	38% (28-48)	1.5	0.13
Ara h 2	86% (81-89)	84% (79-89)	5.4	0.16

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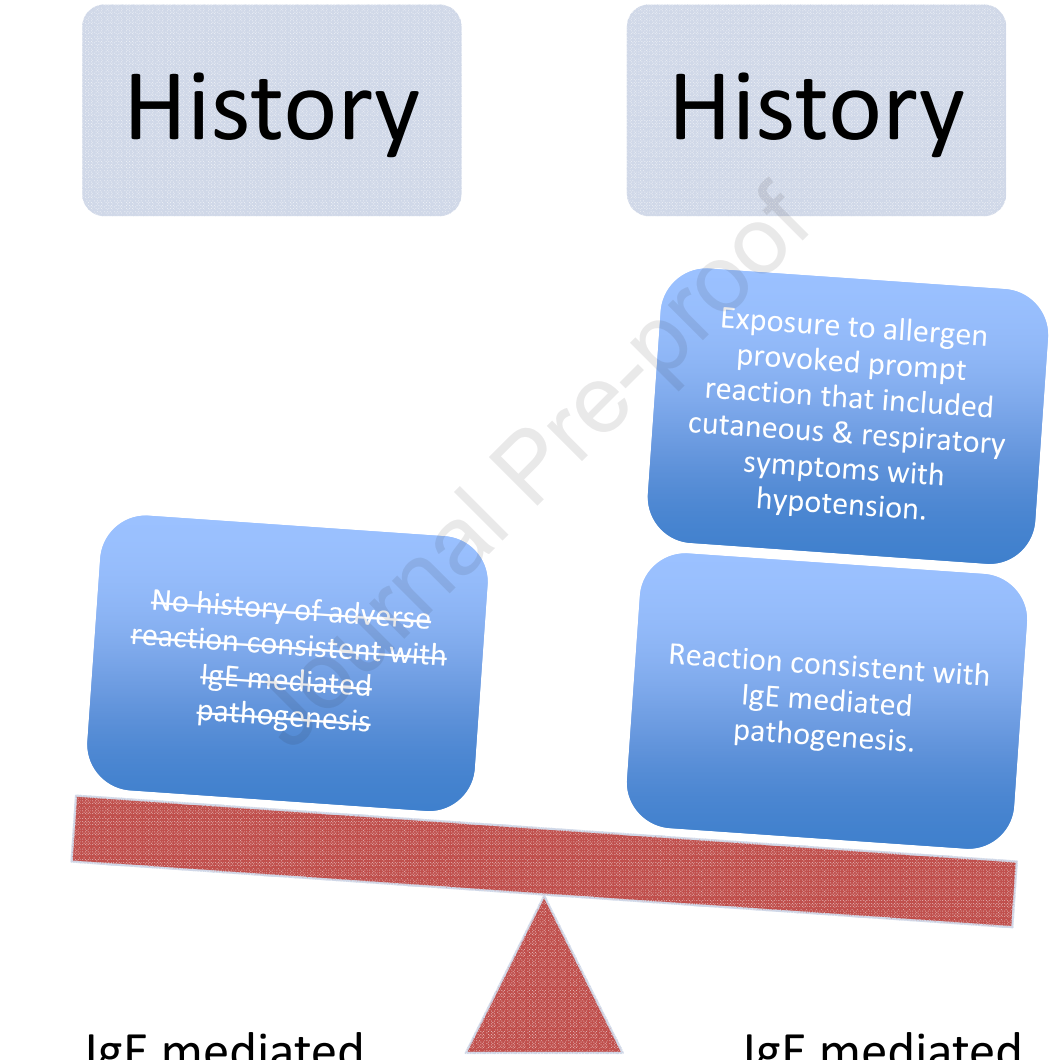
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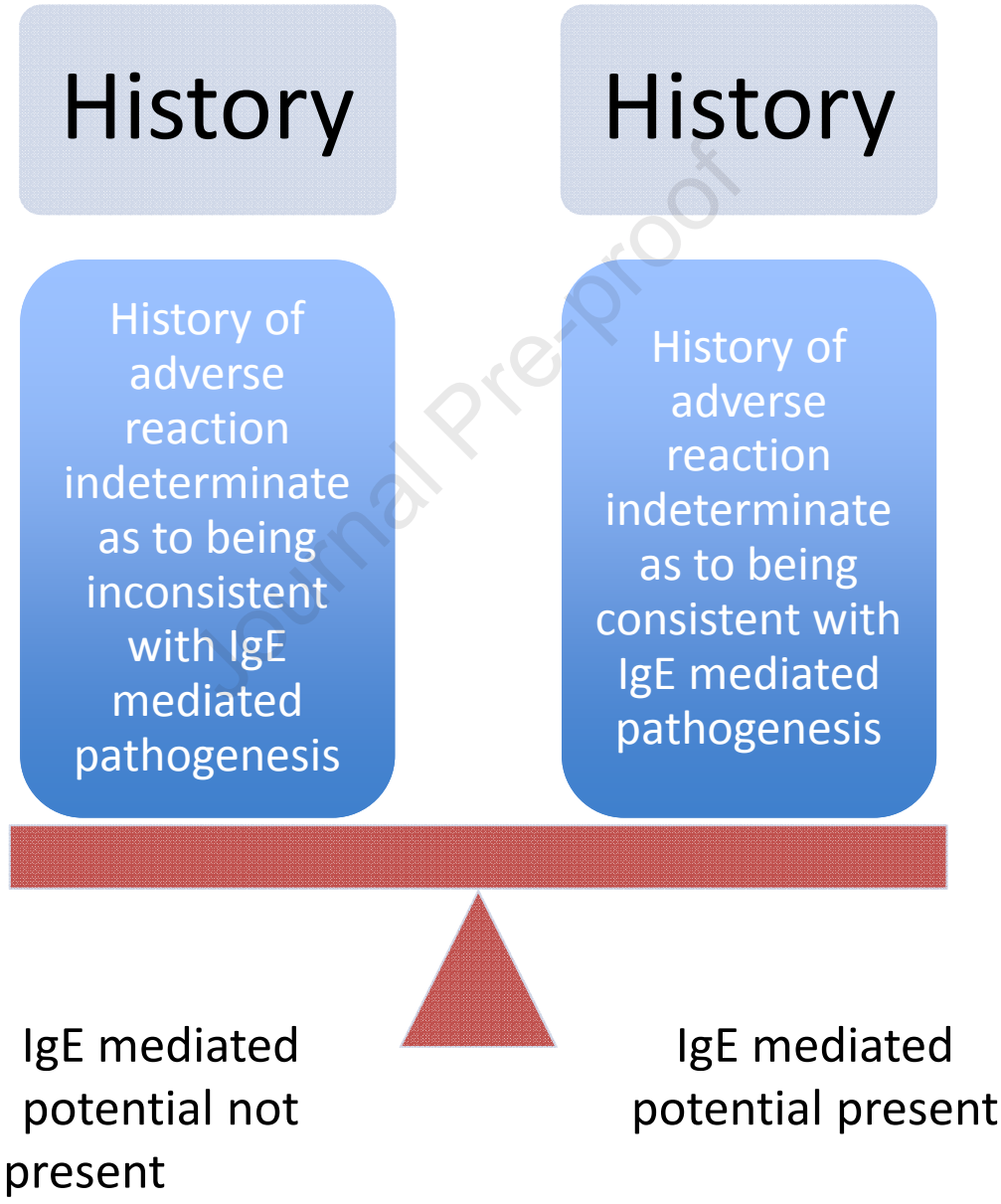
Probability Above Treatment Threshold



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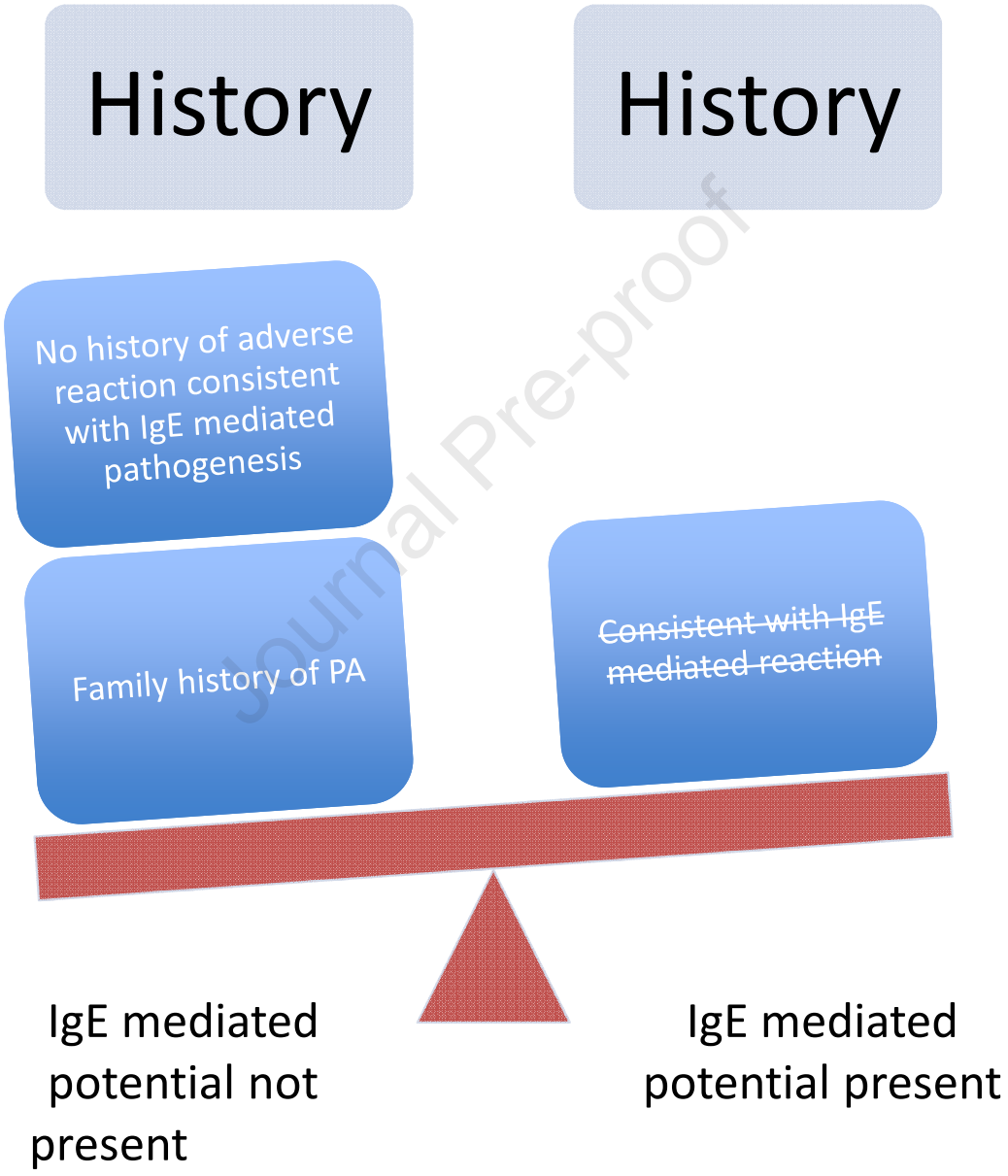
Probability In Between Testing & Treatment Thresholds



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Probability Below Testing Threshold



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