Author's response to reviews

Title: Testing for Allergic Disease: Parameters Considered and Test Value

Authors:

Sheryl L Szeinbach (szeinbach.1@osu.edu)
Spencer E Harpe (seharpe@vcu.edu)
P Brock Williams (PBrockwil@aol.edu)
Hanaa Elhefni (hanaa.s.elhefni@bethesda.orcmacro.com)

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Author's response to reviews: see over
Comments Reviewer 1

Manuscript is some what too long and a bit difficult to read. It discusses the methodology very broadly and could be made shorter and more readable when leaving some of that away.

Thank you. Where possible we have condensed the methodology section and added more pertinent information to the manuscript as suggested.

Authors had decided to take IgE testing for the first choice in allergy testing for this study even SPT (skin prick tests) are as good and sometimes even better method and recommended in all mentioned guidelines like ARIA also for the first line allergy test. This should be address and explained why.

The following sentences were added to the manuscript.

Although ARIA suggests the SPT as a first line choice when further evaluation of patients is needed, interpretation of test results requires extensive training and experience. Thus, specific IgE testing was examined in this study as a practical choice for primary care physicians.

One very critical point is not discussed in the paper at all and that is the interpretation of the IgE results. When the results in IgE testing is e.g. allergy glass I (0.35-0.7 IU/l) the clinical significance of it is not clear. Physicians should be very cautious to make direct diagnosis without good clinical examination and medical history of the patient. With too much testing can also lead to false positive results and this can lead to significant restriction counselling without any real need for that. We want to endorse health, not allergy with testing and this should be discussed. When patientenst has allergic rhinitis or is suspected to have it, it is critical also to examine the nose and this should be address, too. Some one has to look into the nasal cavity to make differential diagnostics and exclude other reasons for rhinitis symptoms. Even patient would have AR he/she can still have also other reasons for chronic rhinitis.

We added the following information to address this issue. Another important aspect of training is the need to consider specific IgE blood test and SPT results in the context of patient history, especially when discrepancy exists between test results and symptoms. Diagnostic testing, per se, is no substitute for a thorough examination of patient symptoms, health status, and medical history. In summary, allergists and family physicians understand that test results coupled with the findings of a careful clinical examination serve as the foundation to establish a strategy for treatment, from which future health outcomes can be evaluated to determine the success of treatment.

Minor comments:
The supporter of the study is manufacturer for the IgE testing.

The following information was presented in the manuscript. In addition, there were no links or ties to any specific product in the manuscript. This study was supported by an unrestricted research grant from Phadia US Inc., Portage, Michigan.
Reviewer 2
- Minor essential revisions:
  Abstract versus methods section (instrument development: abstract mentions 9 patient profiles, methods section 11?)

  *The following change was made in the methods section for clarification.* A one-third fractional factorial design using repeated measures was chosen to minimize the number of profiles to 9 thereby attempting to avoid respondent fatigue. Two additional profiles were produced manually as holdout profiles for use in validation [21].

Discussion: add that this study is subject to some limitations: 1. response rate was quite low: only 50 out of 150 GPs after 2 invitations, 2. maybe the respondents had a specific interest in allergic rhinitis? It is not sure that the behaviour and opinions of the respondents is similar to that of the non-respondents and that of GPs in other geographical areas 3. data are collected from a survey and are based on self-reports and hypothetical patient profiles. It is well known that actual clinical practices may differ from answers in surveys.

  *The following changes were made.* Some limitations include a low response rate and a cross-sectional study representing one geographical region. In addition, family physicians may consider attributes that were not evaluated in this study when deciding to request specific IgE blood testing for patients suspected of having allergic rhinitis. Hypothetical profiles were developed for this study and may not include all aspects of information provided by patients to family physicians, reflect what happens in actual clinical practice, and represent the opinions of physicians in other geographical areas.

  - Discretionary revisions:
    Abstract, results, line 2: say family history instead of history

    Changed to read *family* history

    Symptom duration: why such long periods (minimum of 5 years?) chosen? It seems very unlikely that a GP would wait so long to decide to test for allergy.

    Introduction: add that the current guidelines for allergic rhinitis (ARIA, Bousquet et al.) recommend allergy testing to confirm diagnosis.

    *Good point - we added…..* From the study findings, family physicians can use symptom severity as a gauge in clinical practice to determine if patients should undergo detection and testing for allergic rhinitis or related conditions *perhaps much earlier during the process* of clinical evaluation, *especially in the presence of severe symptoms and a positive family history.*

    As a note, primary care physicians in the US under managed care may view testing as a more costly alternative to medication use, thereby postponing testing as long as possible. In addition, physicians may be reluctant to use SPT because of the training needed to
interpret test results, thus relying more on prescribed medication use. In the presence of mild symptoms, some physicians may opt not to test.

Reviewer 3 (Statistician)

Allergic rhinitis is very common in many western-type populations, and is responsible for moderate levels of disability among its victims. Correct diagnosis is always important for appropriate treatment, but these authors do not make a strong case in either direction for the costs – in morbidity, quality of life, or the resources used for testing – of errors in diagnosis. It is difficult, therefore, without considerable pre-existing background knowledge, to assess the importance of this research question.

Thank you. To bring the background material in the introduction back to the research question in the discussion, we added the following sentence and references.

Given the economic burden of allergic rhinitis on society and the research evidence that supports an inverse relationship between health status and specific IgE antibody levels [32-34], current guidelines should be repositioned and possibly modified to allow family physicians to have a more active role in specific IgE blood testing.

The authors focus entirely on the clinical factors associated with physicians’ decision to order IgE tests. There is no attempt at a decision-theoretic analysis of the responses, no attempt to quantify prior or posterior probabilities and no attempt to account for the likelihood ratio characteristics of the IgE test itself. As a statistician, I see this as a lost opportunity for this manuscript.

A panel of n=50 physicians was assembled – with a disappointing response rate of only 33%, which raises questions of representativeness – and each was presented with nine clinical scenarios, and a binary response was elicited to indicate an intention to order IgE tests. A factorial experimental design was used to balance clinical factors within and between respondents. This is an appropriate design.

Your suggestion would be great for a large study with claims data and data from medical records where the exact values for specific IgE test results may be available. The notion of data collection using a revealed preference approach compared to a stated preference approach as used in this study is also interesting. However, we did not have access to information (i.e., patient medical records) at this level during this study. Obtaining information from physicians is particularly challenging.

With 448 observations, our statistical analysis was robust, and the results were consistent with findings from studies (e.g., Polasa et al. Respiratory Research 2005, 6:153) that used a compositional approach (conjoint is viewed as a de-compositional approach to data analysis in that we are breaking down the final preference decision, from the profiles, to obtain the part-worth contribution of each attribute) in the data analysis. The following changes were added to the limitation section to address the concerns about representativeness.

Some limitations include a low response rate and a cross-sectional study representing one geographical region. In addition, family physicians may consider attributes that were not
evaluated in this study when deciding to request specific IgE blood testing for patients suspected of having allergic rhinitis. Hypothetical profiles were developed for this study and may not include all aspects of information provided by patients to family physicians, reflect what happens in actual clinical practice, and represent the opinions of physicians in other geographical areas.

The statistical analysis methods used are not well described. The principal analysis, so-called ‘conjoint analysis’ appears to be a straightforward multiple regression approach (although the cited reference [14] addresses mainly a reliability question, rather than the parameter estimation attempted in this paper). Although the binary outcome (yes/no to ordering tests) would usually call for logistic modelling, there is some confusion in this manuscript, with the terms used:
“some form of regression” (p 7);
“a linear or logistic regression” (p 7);
“a random effects linear model” (p 9);
“the random effects logit model” (p 9);
“random effects logistic regression model” (p 22).

**Good points - we made the following changes:**

1. *Yes, conjoint analysis uses some type of multiple regression approach for the analysis.* Reference 14 was replaced with the following reference, which is more applicable to the study objectives and readership. 14. Mark TL, Swait J. Using stated preference and revealed preference modeling to evaluate prescribing decisions. *Health Econ* 2004, 13: 563-573.
2. We changed all wording to the “random effects logistic regression model” to be consistent throughout the manuscript.

The confusion is not resolved by the authors’ interpretation of the reported regression coefficients. On p 10, the coefficient for ‘symptoms > 20 yrs’ is reported as “coefficient = 2.494”, with the interpretation of “a 2.49% increase in likelihood to consider specific IgE blood testing for every ‘one unit’ increase in symptom severity”. But if the model is logistic, then these coefficients are log(odds ratio); they cannot be interpreted as proportional increases in risk of the outcome. Indeed, why have not odds ratios been reported in Table 2, if the model is indeed logistic? And why have the authors chosen orthogonal parameterisation for the categorical predictors reported in Table 2, which is contrary to Stata’s default indicator parameterisation? These certainly cannot be interpreted as proportional increases in risk of outcome. Finally, how (and why?) was the coefficient of 2.49 converted to a percentage of 2.49%?

We were not sure if coefficients or the OR would be better for the readership. Your comments have definitely convinced us that the OR is the best approach. The percentage should not be there – thanks. The following changes were made in that all coefficients were exponentiated to odds ratios. Changes were made in the abstract and the results and now read…. Symptom severity had the greatest impact on physician decisions to test patients for allergic rhinitis (OR, 12.11; 95% CI, 7.1-20.7). Thus, one would expect that physicians would be 12.11 times more likely to consider the specific IgE blood test for patients with high symptom severity compared to patients with low symptom severity.
Other attributes such as length of symptoms and both parents having a history of allergic rhinitis significantly influenced physician decisions to test (OR, 1.46; 95%CI, 0.96-2.2; OR, 1.44; CI, 0.95-2.2, respectively).

The authors also seem to believe that the Wald chi-square test (pp 9-10) is a test of the contrast that four estimated coefficients are equal. This is not true. The Wald statistic tests the hypothesis that all estimated coefficients are simultaneously zero, not that they are equal to each other.

*Right, this information was not presented clearly. The following changes were made.*

The hypothesis for this study was that the estimated part-worth values or coefficients, exponentiated to odds ratios in this study, for each of the four profile attributes were simultaneously equal to zero.

In both situations, other parameter estimates were significant indicating the hypothesis that the coefficients were simultaneously equal to zero was rejected regardless of the presence of the symptom severity.

Once again, we greatly appreciated the helpful comments and suggestions provided by the reviewers.