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IN VITRO TESTING FOR ALLERGIC RHINITIS:
ECONOMIC AND QUALITY OF LIFE OUTCOMES

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
The Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

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ABSTRACT

Allergic rhinitis and associated co-morbidities such as sinusitis, conjunctivitis, and asthma can significantly decrease patient health related quality of life and impose substantial economic costs. The etiology for rhinitis is complex, therefore efficient management of patient symptoms requires a correct objective diagnosis. Diagnosis of allergic rhinitis is often made through patient history and physical exam, with skin prick or in vitro testing providing a physician with additional information concerning the patient’s allergic state. In this work, we investigated the sensitivity and specificity of certain in vitro tested allergens (i.e., cat and common ragweed) in the absence of a gold standard. In addition, the association between patient demographics, in vitro based disease classification and allergy-related medical charges, prescription charges, productivity, and quality of life were explored.

The population for this study (n = 330) included enrollees from a Midwestern managed care organization who had in vitro testing for inhalant allergies. In vitro laboratory results, along with medical and prescription claims associated with allergic rhinitis, were obtained from the managed care’s database. In addition to obtaining laboratory test results and claims data,
patients were asked to complete a survey containing severity of symptoms, productivity, and quality of life questions.

A total of 232 subjects returned surveys, yielding a 70% response rate. Of the 232 subjects, 170 returned useable surveys (51% response rate of total subjects). The sensitivity and specificity of in vitro allergy testing for cat were calculated to be 72.4% (credible interval: 66.0% - 78.3%) and 93.5% (credible interval: 91.8% - 95.0%), respectively. The sensitivity and specificity of in vitro allergy testing for short ragweed were estimated to be 47.9% (credible interval: 34.8% - 61.0%) and 98.5% (credible interval: 34.8% - 61.0%). In vitro test status, age, gender, race, and severity of symptoms did not significantly explain allergy-related medical or prescription charges, however, overall allergy work impairment was positively associated with symptom severity. Additionally, study subjects had lower overall mental quality of life when compared to the average U.S. population. Further research is needed to assess the direct impact in vitro allergy testing has on medical costs, productivity, and quality of life.
Dedicated to my mother,

Slavka Secnik
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td></td>
<td>ii</td>
</tr>
<tr>
<td>Dedication</td>
<td></td>
<td>iv</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td></td>
<td>v</td>
</tr>
<tr>
<td>Vita</td>
<td></td>
<td>vi</td>
</tr>
<tr>
<td>List of Tables</td>
<td></td>
<td>xii</td>
</tr>
<tr>
<td>List of Figures</td>
<td></td>
<td>xiv</td>
</tr>
<tr>
<td>Chapters:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Introduction</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1.1 Allergic rhinitis</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1.1.1 Epidemiology</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1.1.2 In vitro testing for allergic rhinitis</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1.1.3 Controversy surrounding in vitro testing for allergic rhinitis</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>1.2 Bayesian methods</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1.3 Purpose of the study</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>1.4 Brief review of data collection</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>1.5 Research objectives</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>1.6 Limitations</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>1.7 Organization of dissertation</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>References for chapter 1</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>2. Review of literature</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>2.1 Epidemiology</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>2.1.1 Overview</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>2.1.2 Prevalence</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>2.1.3 Associated variables</td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>
2.2 Etiology ................................................................. 24
  2.2.1 Overview ......................................................... 24
  2.2.2 Pollens .............................................................. 26
  2.2.3 Molds ............................................................... 26
  2.2.4 Mammals ......................................................... 27
  2.2.5 House dust mites ............................................... 27
  2.2.6 Insects ............................................................. 28

2.3 Diagnosis ............................................................. 28
  2.3.1 Overview ......................................................... 28
  2.3.2 Patient history and physical examination ................. 29
  2.3.3 Skin prick test .................................................. 31
  2.3.4 Intradermal test ............................................... 35
  2.3.5 In vitro blood test .............................................. 40
  2.3.6 Comparison of mRAST and PhRAST tests .................. 42
  2.3.7 Pharmacia CAP system ....................................... 45
  2.3.8 In vitro versus skin tests ..................................... 46

2.4 Management ......................................................... 51
  2.4.1 Overview ......................................................... 51
  2.4.2 Environmental controls ....................................... 51
  2.4.3 Pharmacotherapy .............................................. 53
  2.4.4 Immunotherapy ............................................... 59
  2.4.5 Anti-IgE therapy .............................................. 61

2.5 Quality of life ...................................................... 62
  2.5.1 Overview ......................................................... 62
  2.5.2 Allergy specific quality of life instruments ................. 63
  2.5.3 Generic quality of life instruments ......................... 65

2.6 Economic impact ................................................... 68
  2.5.4 Overview ......................................................... 68
  2.5.5 Productivity ................................................... 68
  2.5.6 Direct costs .................................................... 71

2.7 Summary .............................................................. 77

References for chapter 2 ............................................. 78

3. Methods .......................................................................... 89

  3.1 Research design ..................................................... 90
  3.2 Study population ................................................... 91
  3.3 Instrument development .......................................... 96
    3.3.1 Basic allergy information and demographics ............... 98
    3.3.2 Allergy symptom severity .................................. 98
    3.3.3 Quality of life ............................................... 99
    3.3.4 Productivity ................................................ 104
  3.4 Description of statistical procedures ............................. 105
    3.4.1 Bayesian statistics ............................................ 105
3.4.2 Linear regression ............................................................ 110
3.4.3 Logistic regression ........................................................... 112
3.4.4 One-sample T-test .......................................................... 113
3.5 Data analysis ................................................................. 113
3.5.1 Definition of terms for study variables ......................... 114
3.5.2 Study objectives and research questions ...................... 117
3.5.3 Objective 1 .................................................................. 117
3.5.4 Objective 2 .................................................................. 117
3.5.5 Objective 3 .................................................................. 119
3.5.6 Objective 4 .................................................................. 120
3.6 Conclusion ................................................................. 121
References for chapter 3 ...................................................... 123

4. Results ............................................................................... 128
4.1 Sample description ........................................................... 129
4.2 Research questions and analyses ..................................... 134
4.2.1 Objective 1 .................................................................. 134
4.2.2 Objective 2 .................................................................. 139
4.2.3 Objective 3 .................................................................. 145
4.2.4 Objective 4 .................................................................. 148
References for chapter 4 ...................................................... 154

5. Conclusions and recommendations ..................................... 155
5.1 Study overview ............................................................... 156
5.1.1 Background ................................................................. 156
5.1.2 Study methods ............................................................. 156
5.2 Research questions and discussion .................................. 158
5.2.1 Objective 1: analysis results and discussion ............... 158
5.2.2 Objective 2: analysis results and discussion ............... 162
5.2.3 Objective 3: analysis results and discussion ............... 165
5.2.4 Objective 4: analysis results and discussion ............... 167
5.3 Study limitations ............................................................ 170
5.4 Recommendations for future research ............................. 174
References for chapter 5 ...................................................... 177

Appendices:

A. Pre-notice survey letter .................................................. 182
B. First survey cover letter .................................................. 184
C. Postcard reminder ........................................................... 186
D. Second survey cover letter .............................................. 188
E. Telephone script ............................................................... 190
F. Mailed questionnaire ...................................................... 192
G. Institutional review board exemption .............................................. 204
H. Bayesian programming for estimation of disease prevalence and the parameters of a diagnostic test in the absence of a gold standard .... 206
I. Survey response rate ........................................................................ 215
J. Program input and output for parameter estimation of in vitro diagnostic allergy testing ........................................................... 217

Bibliography ...................................................................................... 220
<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Reported prevalence rates for allergic rhinitis in the United States</td>
</tr>
<tr>
<td>2.2</td>
<td>Worldwide reported prevalence rates for allergic rhinitis</td>
</tr>
<tr>
<td>2.3</td>
<td>Common allergens</td>
</tr>
<tr>
<td>2.4</td>
<td>Symptoms and signs of allergic rhinitis</td>
</tr>
<tr>
<td>2.5</td>
<td>Patient history to consider when evaluating a patient with rhinitis</td>
</tr>
<tr>
<td>2.6</td>
<td>Physical history to consider when evaluating a patient with rhinitis</td>
</tr>
<tr>
<td>2.7</td>
<td>Morrow Brown grading system for skin prick test</td>
</tr>
<tr>
<td>2.8</td>
<td>Grading system for intradermal skin tests</td>
</tr>
<tr>
<td>2.9</td>
<td>Example of skin end point titration (SET) skin test wheal response</td>
</tr>
<tr>
<td>2.10</td>
<td>Relative comparison between skin prick and intradermal testing</td>
</tr>
<tr>
<td>2.11</td>
<td>Standard CAP scoring system</td>
</tr>
<tr>
<td>2.12</td>
<td>Comparison of in vitro tests with other diagnostic standards</td>
</tr>
<tr>
<td>2.13</td>
<td>Oral drug therapy for allergic rhinitis</td>
</tr>
<tr>
<td>2.14</td>
<td>Non-oral drug therapy for allergic rhinitis</td>
</tr>
<tr>
<td>2.15</td>
<td>Summary of quality of life instruments used in allergic rhinitis research</td>
</tr>
<tr>
<td>2.16</td>
<td>Cost of allergic rhinitis</td>
</tr>
<tr>
<td>4.1</td>
<td>Subjects gender and race</td>
</tr>
<tr>
<td>4.2</td>
<td>Mean age of subjects</td>
</tr>
</tbody>
</table>
4.3 Subjects by gender................................................................. 132
4.4 Subjects by race................................................................. 132
4.5 Respondents by education and occupation......................... 133
4.6 Respondents allergy-related experience............................... 134
4.7 Probability ranges and coefficients of the beta prior densities for
the test parameters............................................................... 136
4.8 Results of in vitro testing in a managed care population......... 136
4.9 Posterior medians and lower and upper limits of the posterior 95%
credible intervals for the prevalence, sensitivities, specificities for
cat and short ragweed in vitro diagnostic tests...................... 138
4.10 Posterior medians and lower and upper limits of the posterior 95%
credible intervals for the positive and negative predictive value for
cat and short ragweed in vitro diagnostic tests..................... 139
4.11 Characteristics of non-prescription medical charges.............. 141
4.12 Characteristics of allergy specific prescription charges.......... 143
4.13 Characteristics of overall allergy work impairment............... 146
4.14 Final model of overall allergy work impairment................... 147
4.15 Final model of overall Mini-RQLQ scores............................ 150
4.16 SF-8 scores for in vitro allergy tested sample..................... 151
4.17 SF-8 summary difference scores adjusted for gender and age... 153
5.1 Characteristics of total allergy-specific medical charges......... 163
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Comparison of original RAST, Phadebas RAST, and modified RAST testing systems</td>
<td>45</td>
</tr>
<tr>
<td>2.2</td>
<td>Comparison of CAP with standard scoring method, CAP with alternative scoring method, and modified RAST testing system</td>
<td>47</td>
</tr>
<tr>
<td>4.1</td>
<td>In vitro allergy tested sample versus U.S. population on individual SF-8 items</td>
<td>151</td>
</tr>
<tr>
<td>4.2</td>
<td>In vitro allergy tested sample versus U.S. population on composite SF-8 items</td>
<td>152</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

The purpose of this dissertation is to investigate resource utilization, productivity, and quality of life (QOL) differences between patients who have positive or negative in vitro allergy test results. Additionally, through the use of Bayesian statistics, estimates of disease prevalence, sensitivity, and specificity of two in vitro allergens are assessed.

This first chapter begins with an overview of allergic rhinitis, a review of in vitro allergy testing, and a summary of the controversies concerning in vitro testing for allergic rhinitis. Thereafter, Bayesian statistical inference is introduced and is followed by the purpose of the study. A brief review of data collection methods is provided subsequently, and the empirical basis of this investigation is formally established by the presentation of study objectives and research questions. Next, study limitations are provided to establish the internal and external validity of this research and the chapter concludes by outlining the organizational structure of this dissertation.
1.1 Allergic Rhinitis

1.1.1 Epidemiology

Allergic rhinitis and associated co-morbidities such as sinusitis, conjunctivitis, and asthma can significantly decrease patient health-related quality of life and impose substantial economic costs.}\(^1\) Researchers have estimated that allergic rhinitis affects 20 to 40 million people in the United States annually.\(^4\)\(^5\) The direct annual costs of allergic rhinitis in the United States has been estimated to exceed well over one billion dollars.\(^4\)\(^\)\(^5\)\(^7\) Moreover, associated time lost from work or school may significantly and adversely affect productivity.\(^8\)\(^9\) Therefore, the considerable direct and indirect costs of allergic rhinitis represent enormous personal and social economic burdens.\(^10\)

Researchers have reported as few as half of those suffering from allergic rhinitis symptoms have a true immuno-modulated condition.\(^5\)\(^\)\(^11\) Notwithstanding current practice guidelines stressing the importance of adequate patient assessment, including medical history and physical exam, a major goal of this dissertation is to investigate the association of *in vitro*-based allergic rhinitis disease classification with quality of life, productivity, and medical resource utilization.

1.1.2 In Vitro Testing for Allergic Rhinitis

Since the early 1970's, practitioners have used allergy-specific *in vitro* measurement as a diagnostic tool for many immuno-mediated medical conditions.\(^12\) Other procedures to diagnose allergic rhinitis include the use of skin prick and intradermal tests to detect specific immunoglobulin E (IgE)
antibodies to various allergens. The Phadebas radioallergosorbent test (Phadebas RAST) was the first commercially available specific IgE measurement used to quantify serum specific IgE antibodies. The popularity and use of Phadebas RAST drastically increased throughout the 1970's. During the early 1980's, emerging controversy concerning the test's poor sensitivity (true positive test results compared to skin testing) motivated the development of several procedural and interpretive changes designed to increase the sensitivity of Phadebas RAST without significantly decreasing test specificity (true negative test results). The first product resulting from this research initiative was the modified radioallergosorbent test (mRAST). Subsequently, several versions of specific IgE measurements have become commercially available including the Pharmacia CAP System (CAP).

1.1.3 Controversy Surrounding In Vitro Testing for Allergic Rhinitis

Despite advances in quantitative in vitro IgE measurement, the American Academy of Allergy, Asthma, and Immunology (AAAAI) continues to recommend that specific allergen avoidance and treatment measures should be based on positive history of allergic rhinitis and diagnostic skin testing. Failure to acknowledge a more prominent role for in vitro testing may be attributed to the uncertainty caused by the varying performance levels among the several commercially available in vitro tests. The accuracy of in vitro blood test results depends on the sensitivity and specificity of the particular test. The sensitivity of a screening test is defined as the test's ability to accurately identify the disease probability given the person has the disease. Specificity is the
probability of a negative test result given the person does not have the
disease. Inaccurate testing or test procedures can lead to false positive or
false negative results. A false negative is a negative test result despite actual
disease presence. A test with a 95% sensitivity for an aeroallergen will produce
on average a false negative for 5% of those with true immuno-reactivity to this
allergen. A false positive is characterized as a positive test result without actual
disease presence. According to this test parameter, a 90% specificity means
that 10% of those not allergic to a given aeroallergen will produce a false
positive.

Obtaining an accurate diagnostic confirmation of allergic rhinitis may
deter unnecessary treatment recommendations including avoidance measures
and prescription regimes based on falsely classifying patients as disease
positive. Conversely, reduced patient incentive to pursue appropriate
avoidance measures or withholding potentially beneficial medications may
occur when incorrectly classifying patients as disease negative. Apart from
these medical consequences of misdiagnosis, ramifications of disease
misclassification can adversely affect patient productivity and quality of life.

Although the sensitivity and specificity of specific allergens used for in
vitro testing has been documented in the literature, the vast majority of
researchers use skin prick testing as the gold standard comparator. Using
skin prick test outcomes as a gold standard to compare in vitro allergy test
results is problematic because: 1) skin prick testing is not perfectly correlated
with clinical symptoms and, 2) errors made by the imperfect reference (i.e., skin
prick test) causes artificially low estimates of in vitro diagnostic performance. However, recent advances in statistical analyses—using Bayesian applications—allow for estimation of disease prevalence and the parameters of specific diagnostic tests in the absence of an recognized standard.

1.2 Bayesian Methods

The most common statistical approach to analyze data is known as the frequentist or classical method. Classical statistical inference is characterized by hypothesis testing and the use of p-values. Frequentists use hypothesis testing to make statistical inferences about unknown parameters and rely on p-values to inform them as to whether or not the hypotheses can be rejected. Moreover, the use of classical statistical methods rely on the use of a single sample and testing whether or not the results are more extreme than would be found by chance. Information obtained from previous studies in the same area or on the same subject are not considered or included in this framework. In the Bayesian approach, however, information collected from a current study is used to update prior beliefs. Thus, in Bayesian analysis, prior beliefs are modified in light of new information. In order to update prior beliefs with the new study data, the following Bayes' theorem is used (Equation 1.1):

\[
Posterior \ belief = Prior \ belief \times likelihood \ function
\]

Equation 1.1: Bayes' theorem.
Bayes' theorem consists of three different components: prior belief, the likelihood function, and posterior belief. Prior beliefs concerning the unknown parameter of interest are obtained from previous studies or expert opinion. Prior information about an unknown parameter is assessed as a probability distribution, which informs the researcher the extent to which a belief can be attached to the values of the unknown parameter before observing the current data. The likelihood function is a model of how the current data relate to the unknown parameter. This function is an estimate of the probability of observing the outcome of interest for any given level of the parameter. Lastly, the posterior belief is obtained from the prior belief and the data currently available. Bayes' rule is used to estimate the posterior probability distribution of the parameter of interest based on the prior distribution and the likelihood function.

The basics of the Bayesian framework were presented here to identify the basic components of this technique and to provide background information concerning this method. Further information concerning how the Bayesian method will be used to estimate disease prevalence and the parameters of in vitro allergy testing are provided in Chapter Three.

1.3 Purpose of the Study

Recent advances in diagnostic testing technology have allowed physicians to order a blood test for patients suspected of having allergic rhinitis. One objective of this study is to estimate, in a managed care population, the
sensitivity and specificity of certain *in vitro* tested allergens in the absence of a gold standard. Previous studies have investigated the parameters of *in vitro* tested allergens using imperfect standards (e.g., skin prick tests, intradermal tests), thereby underestimating the sensitivity and specificity associated with these tests. Correctly estimating a test's sensitivity and specificity has important implications for the appropriate identification of patients with and without allergic rhinitis.

In addition to the estimation of *in vitro* allergen sensitivity and specificity in the absence of a gold standard, the relationship between *in vitro* based disease classification and medical charges, prescription charges, productivity, and quality of life measures are explored. Other researchers have investigated the impact of allergic rhinitis on medical costs, productivity, and quality of life. However, no known reports have been published concerning these outcomes in an *in vitro* allergy tested population. Thus, this study provides information concerning the association of *in vitro* testing and these patient outcomes.

1.4 Brief Review of Data Collection

All patients in a large Midwest managed care plan aged 18 years or older, and who had *in vitro* testing for allergic rhinitis between January 1, 1998 and December 31, 2000 were enrolled in the study. Patient health plan records were used to extract data pertaining to *in vitro* allergy test results, patient demographics, as well as medical and prescription charges associated with a
record of allergic rhinitis due to pollen, other allergens, or unspecified causes. Additional patient information was obtained directly from the patient through the use of a ten page mailed questionnaire.

1.5 Research Objectives

Accurate diagnostic test results are an important factor in patient diagnosis. Moreover, proper diagnosis of patients presenting with allergic rhinitis symptoms is essential to provide appropriate patient-specific therapy. Although researchers have compared in vitro allergy testing to many other standards, none have used Bayesian methods to estimate disease prevalence and in vitro test parameters.

Appropriate diagnosis of allergic rhinitis is imperative because the diagnosis and treatment of this condition costs the United States health care system billions of dollars each year. Despite the widespread prevalence and large expenditures for allergic rhinitis, no known study has investigated the comparative health care costs of patients classified as disease positive or negative according to in vitro allergy test results. Similarly, although some studies exist that report the impact of allergic rhinitis on productivity and quality of life, no known empirical study has simultaneously compared, in a managed care population, these measurements across individuals classified as disease positive or negative according to in vitro allergy test result status. Prescription and other medical allergy-linked charge data obtained from the health system
claims, along with quality of life and productivity information collected from a mailed survey instrument, constitute the data elements for the following study objectives.

**Objective 1**

To estimate the disease prevalence and the parameters of *in vitro* allergy tests in the absence of a gold standard.

**Research Questions Addressing Objective 1:**

1.1 What is the prevalence of allergy to specific allergies (i.e., cat, short ragweed) in this managed care population?

1.2 What are the sensitivity and specificity estimates of specific allergens (i.e., cat, short ragweed)?

**Objective 2:**

To examine variables associated with allergic rhinitis-linked prescription and non-prescription medical charges.
Research Questions Addressing Objective 2:

2.1 Are the following characteristics significant explanatory variables of allergy specific medical charges: *in vitro* allergy test status, age, gender, race, and severity of symptoms?

2.2 Are the following characteristics significant explanatory variables of allergy specific prescription charges: *in vitro* allergy test status, age, gender, race, and severity of symptoms?

Objective 3:

To examine the variables associated with overall work impairment as defined by the Allergy Specific Work Productivity and Activity Impairment (WPAI-AS).

Reilly and associates created the WPAI-AS questionnaire to obtain allergy specific work impairment measures. Other researchers have used this instrument in clinical trials to measure work and activity impairment in daily activities due to allergic rhinitis symptoms. Guided by the authors' published studies, the following research question will be evaluated in this study.
Research Question Addressing Objective 3:

3.1 Are the following characteristics significant explanatory variables of overall work impairment: *in vitro* allergy test status, age, gender, race, medication use, severity of symptoms?

Objective 4:

To evaluate the quality of life of patients who received *in vitro* testing for allergic rhinitis using generic and allergy specific quality of life instruments.

A commonly used allergy specific quality of life instrument, the Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ), developed primarily by Juniper and Guyatt, will be used as the disease specific quality of life instrument. Fourteen questions covering five different domains including activities, practical problems, nasal problems, eye symptoms, and other symptoms, comprise this instrument. It is with the use of disease specific instruments that small, but important changes, within a disease state can be obtained.

The SF-8 was developed to obtain a one to two minute survey questionnaire that would accurately reproduce the eight health concepts (general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role emotional) found in the SF-36 Health Survey. Unlike the disease specific Mini-RQLQ, the SF-8 is a generic quality of life instrument. The most important benefit from using a generic quality of life
instrument is the ability to compare quality of life across different medical conditions or across the average population. Although the SF-36 is a generic quality of life survey, researchers have successfully used this instrument to evaluate quality of life in patients with allergic rhinitis. No known study, however, has examined the use of the SF-8 in an \textit{in vitro} allergy tested population. Therefore, the SF-8 item responses in this study population will be compared to the reported national averages.

\textbf{Research Questions Addressing Objective 4:}

4.1 Are the following characteristics significant explanatory variables of overall Mini-RQLQ scores: \textit{in vitro} allergy test status, age, gender, race, medication use, and severity of symptoms?

4.2 What are the differences in SF-8 generic quality of life scores among patients who have had \textit{in vitro} testing and the general United States population?

\textbf{1.6 Limitations}

One limitation of the study is the use of data from only one managed care population located in a single geographic (Midwest) region. Thus, the generalizability of the study results to other populations (e.g., the non-insured, Medicaid-insured) or the same or differently insured populations in different regions.
regions of the United States must be undertaken with considerable caution. Other study limitations include the lack of access to physician notes concerning their medical decision making processes and patient progress. Additionally, because a significant number of patients self-medicate with over-the-counter allergy products, our ignorance of this treatment effect may have confounded the assessment of productivity, quality of life, and level of prescription drug use. Lastly, the use of claims-based health system records assumes but does not guarantee accurate and complete information.

1.7 Organization of Dissertation

The rest of this dissertation is comprised of four additional chapters. Chapter Two reviews the appropriate literature concerning the epidemiology, etiology, diagnosis, management, quality of life, productivity, and direct health care costs of allergic rhinitis. Chapter Three provides information concerning research design, instrument development, research hypotheses, sampling, data collection, and data analysis. The fourth chapter presents the data analysis results, descriptive statistics of the study sample, and answers to the research hypotheses. Lastly, Chapter Five includes a discussion of the data analysis results, reviews study limitations, and provides suggestions for future research.
REFERENCES FOR CHAPTER 1


33. Meltzer EO, Nathan RA, Selnar JC, Storms W. Quality of Life and Rhinitis Symptoms: Results of a National Survey with the SF-36 and RQLQ Questionnaires. Journal of Allergy and Clinical Immunology 1997; 99:s815-9.


CHAPTER 2

REVIEW OF LITERATURE

The objectives of this literature review are to strengthen the rationale for the study and provide background information concerning allergic rhinitis and \textit{in vitro} allergy testing. This review of the literature concerning allergic rhinitis has been organized into eight parts. Disease determinants, reviewed as epidemiology and etiology of allergic rhinitis, precede diagnosis and evaluation discussions. Management of allergic rhinitis is subsequently discussed. Thereafter, the literature on quality of life and the economic impact of this disease are explored. The chapter concludes with a summary of the preceding literature review.
2.1 Epidemiology

2.1.1 Overview

Rhinitis is defined as inflammation of the membranes lining the nose and is characterized by nasal congestion, itching of the nose, rhinorrhea, and sneezing.\(^1\) This condition is commonly accompanied by symptoms involving the eyes, ears, and throat. Patients with rhinitis are typically classified as having allergic rhinitis or non-allergic rhinitis. Rhinitis is designated as allergic if a causative allergen (e.g., dust, pollen, mold) can be identified.\(^2\) Lack of a known causal agent results in the condition labeled as non-allergic. Unfortunately, non-allergic rhinitis is a poorly defined disease condition with approximately half of the patients presenting with nasal conditions having this disorder.\(^1,3,4\) Because of the nature of this research project, allergic rhinitis will be the primary focus of this literature review.

Allergic rhinitis is classified as an immunoglobulin E (IgE) mediated inflammation of the mucous membranes in the ocular and upper respiratory tract.\(^5\) When an allergy sensitive individual inhales an allergen, the body's immune system responds by producing antibodies in the form of allergen specific IgE antibodies. These IgE antibodies then bind themselves to mast cells. Allergen re-exposure may then trigger the mast cell degranulation and histamine release.\(^6\) Histamine has long been known to cause allergic rhinitic symptoms including runny nose, watery eyes, itching, and swelling.
2.1.2 Prevalence

Allergic rhinitis is a frequently occurring disease, with prevalence estimates varying by disease definition and the population studied. Some prevalence study authors have unconditionally examined allergic rhinitis whereas others have limited their investigations to either seasonal (i.e., hay fever) or perennial allergic rhinitis. Additionally, studies have examined and reported on heterogeneous populations such as allergy clinics, a class of college freshmen, and United States national estimates. Reported prevalence rates of allergic rhinitis in the United States range from 5% to 42%, with the average reported prevalence in the mid-teens (Table 2.1). Worldwide prevalence rates range from approximately 1% to 28% (Table 2.2).

Because the onset of allergic rhinitis can occur at any age, prevalence rates of allergic rhinitis vary by the age of the study population. In 80% of the cases, allergic rhinitis develops before the age of 20 years. Hay fever prevalence rates are lowest for children under 5 years of age, rapidly increase during adolescence and early adulthood years, and then decline considerably beyond 35 years of age. During childhood, males are most likely to have allergic rhinitis, although this gender gap disappears during adulthood.
<table>
<thead>
<tr>
<th>Author</th>
<th>Prevalence</th>
<th>Study subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>VanArsdel &amp; Motulsky, 1959&lt;sup&gt;25&lt;/sup&gt;</td>
<td>12% hayfever</td>
<td>Questionnaire, 5,818 completed, to newly registered college students in Seattle, WA</td>
</tr>
<tr>
<td>Maternowski &amp; Mathews, 1962&lt;sup&gt;20&lt;/sup&gt;</td>
<td>13.4% allergic rhinitis</td>
<td>Questionnaire, 434 completed, to US students, from Ann Arbor, MI</td>
</tr>
<tr>
<td>Freeman &amp; Johnson, 1964&lt;sup&gt;19&lt;/sup&gt;</td>
<td>19% hay fever; 6% perennial allergic rhinitis</td>
<td>Mailed questionnaire to 2,627 8th and 12th grade students in Denver, CO</td>
</tr>
<tr>
<td>Smith &amp; Knowler, 1965&lt;sup&gt;15&lt;/sup&gt;</td>
<td>5% allergic rhinitis</td>
<td>Personal interview of 1,440 household in Iowa City, IA</td>
</tr>
<tr>
<td>McKee et al., 1966&lt;sup&gt;9&lt;/sup&gt;</td>
<td>16% seasonal allergic rhinitis</td>
<td>Questionnaire given to 1,000 consecutive adult patients at an allergy clinic in Palo Alto, CA</td>
</tr>
<tr>
<td>Hagy &amp; Settipane, 1969&lt;sup&gt;10&lt;/sup&gt;</td>
<td>19% allergic rhinitis</td>
<td>Questionnaire, 1,836 completed, to college freshmen from Brown and Pembroke College</td>
</tr>
<tr>
<td>Broder et al., 1974&lt;sup&gt;14&lt;/sup&gt;</td>
<td>8% allergic rhinitis diagnosed by physician</td>
<td>Personal interviews and physical exams of 9,226 residents of Tecumseh, MI</td>
</tr>
<tr>
<td>McMenamin, 1994&lt;sup&gt;18&lt;/sup&gt;</td>
<td>9% hay fever</td>
<td>1988 National Health Interview Survey(NHIS)</td>
</tr>
<tr>
<td>Wright et al., 1994&lt;sup&gt;17&lt;/sup&gt;</td>
<td>42% allergic rhinitis diagnosed by physician</td>
<td>Questionnaire given to parents of 747 six year old children from Tucson, AZ</td>
</tr>
<tr>
<td>Arrighi et al., 1995&lt;sup&gt;16&lt;/sup&gt;</td>
<td>9% physician diagnosis of hay fever; 24% hay fever symptoms without diagnosis</td>
<td>Mailed questionnaire, 1,602 completed, to parents of 5 to 8 year old children in the public school system of Seattle, WA</td>
</tr>
<tr>
<td>Malone et al., 1997&lt;sup&gt;12&lt;/sup&gt;</td>
<td>16% self-reported allergic rhinitis</td>
<td>1987 National Medical Expenditure Survey (NMES) of approximately 14,000 households</td>
</tr>
<tr>
<td>Nathan et al., 1997&lt;sup&gt;11&lt;/sup&gt;</td>
<td>14% self-diagnosed allergic rhinitis</td>
<td>Mailed questionnaire, 9,946 completed, to households in the United States</td>
</tr>
</tbody>
</table>

Table 2.1: Reported prevalence rates for allergic rhinitis in the United States (continue).
Table 2.1 (continued): Reported prevalence rates for allergic rhinitis in the United States.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Prevalence</th>
<th>Study subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strachan et al., 1997&lt;sup&gt;13&lt;/sup&gt;</td>
<td>6% (50&lt;sup&gt;th&lt;/sup&gt; percentile) of rhinoconjunctivitis in 6-7 year olds. 14% (50&lt;sup&gt;th&lt;/sup&gt; percentile) of rhinoconjunctivitis in 13-14 year olds.</td>
<td>Written questionnaire to parents of 257,800 6-7 years olds from 38 countries and 463,801 self-completed questionnaires to 13-14 year olds in 56 countries, including the United States</td>
</tr>
<tr>
<td>Crystal-Peters, et al., 2000&lt;sup&gt;8&lt;/sup&gt;</td>
<td>9% allergic rhinitis</td>
<td>1995 National Health Interview Survey (NHIS)</td>
</tr>
<tr>
<td>Malmberg, 1979&lt;sup&gt;23&lt;/sup&gt;</td>
<td>28% allergic rhinitis in university students; 13% allergic rhinitis in school children</td>
<td>Questionnaire given to 315 university students and to the parents of 319 children age 6-11 years old in schools in Helsinki, Finland</td>
</tr>
<tr>
<td>Sibbald &amp; Rink, 1991&lt;sup&gt;21&lt;/sup&gt;</td>
<td>24% rhinitis</td>
<td>Mailed questionnaire, 2969 completed, to patients of a general practice group in London, England</td>
</tr>
<tr>
<td>Strachan et al., 1997&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Range of 0.8% to 14.9% rhinoconjunctivitis in 6-7 year olds. Range of 1.4% to 39.7% rhinoconjunctivitis in 13-14 year olds.</td>
<td>Written questionnaire to parents of 257,800 6-7 years olds from 38 countries and 463,801 self-completed questionnaires to 13-14 year olds in 56 countries.</td>
</tr>
</tbody>
</table>

Table 2.2: Worldwide reported prevalence rates for allergic rhinitis.
2.1.3 Associated Variables

Genetic predisposition to atopy, defined as the propensity to allergic disease shown by elevated total or specific serum IgE, may be the single most important factor associated with the development of allergic rhinitis. A child with no atopic parents has a low risk (9 to 18%) of being atopic, whereas a child who has two atopic parents has a 70% risk of having the condition.\(^2,26\) Furthermore, an individual with a family history of atopic disease is more likely to have an earlier onset of allergic rhinitis when compared to others with no genetic history\(^24\). Although genetic predisposition to atopy has been found to play a major role in the development of allergic rhinitis, no significant racial or ethic differences has been found in the prevalence rates of this condition.

Recently, researchers have found an association between socio-economic status and the prevalence of allergic rhinitis. Allergic rhinitis has been reported to be more prevalent in higher socio-economic groups and among those considered to be in professional social classes\(^2\). Furthermore, a strong inverse relationship exists between hay fever prevalence rates and the number of younger children in the family, with first born offspring being at greatest risk.\(^1,27\)

Environmental pollution has been hypothesized to enhance allergic sensitization to aeroallergens (i.e., airborne allergens). Authors of a widely cited epidemiologic study conducted in Japan have reported an increased prevalence of seasonal allergic rhinitis in patients living near motorways\(^24\). Conversely, two large studies have found higher allergic rhinitis prevalence
rates in cities with lower—compared to higher—pollution levels. Given these conflicting findings, the evidence to support a causal hypothesis linking allergic rhinitis to environmental pollution is somewhat dearth.

Notwithstanding these allergic rhinitis risk factors, there are several known co-morbid conditions. Hay fever has been documented as a “known predictor and correlate of asthma incidence.” Researchers have documented the prevalence of asthma among hay fever subjects to be between 13% to 38%. Conversely, the prevalence of hay fever among asthmatics is reported to be 28% to 50%. One other condition which often coincides with allergic rhinitis is eczema. The prevalence rate of allergic rhinitis in subjects with eczema was stated to be 29% in twins in a Swedish study. In summary, there tends to be an increased prevalence of allergic rhinitis in young individuals, those with a family history of atopy, in first born children, and in higher socio-economic classes.

2.2 Etiology

2.2.1 Overview

Understanding allergic rhinitis etiology can help physicians and patients construct patient-specific environmental control measures to help alleviate symptoms. Identification of allergens also assists allergists in providing patient-specific immunotherapy. Pollen, mold, animals, house dust mites, and insects comprise the main categories of common allergens (Table 2.3).
<table>
<thead>
<tr>
<th>Common Allergens</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pollen</strong></td>
<td>Birch, oak, beech, chestnut, hazel, maple</td>
</tr>
<tr>
<td><strong>Tree</strong></td>
<td>Ragweed, sage, cocklebur, Russian thistle</td>
</tr>
<tr>
<td><strong>Weed</strong></td>
<td>Bermuda, Johnson, Orchard, Timothy, Kentucky bluegrass</td>
</tr>
<tr>
<td><strong>Grass</strong></td>
<td><em>Alternaria alternaria, Aspergillus fumigatus, Cladosporium herbarum</em></td>
</tr>
<tr>
<td><strong>Mold</strong></td>
<td>Cat, dog, mouse, rat, guinea pig, rabbit, cow, horse</td>
</tr>
<tr>
<td><strong>Mammalian</strong></td>
<td><em>Dermatophagoides pteronyssinus, Dermatophagoides farinae</em></td>
</tr>
<tr>
<td><strong>House Dust Mites</strong></td>
<td>American cockroach, German cockroach</td>
</tr>
<tr>
<td><strong>Insects</strong></td>
<td>Fire ants, bees, paper wasps, yellow jackets, hornets</td>
</tr>
</tbody>
</table>

Table 2.3: Common allergens.

Individuals who suffer from allergic rhinitis and experience symptoms may be classified according to the persistence of symptoms —throughout the year (perennial) or just part of the year (seasonal). Perennial allergies are often associated with allergens found indoors such as house dust mites, pet dander, cockroaches, and mold. In the United States, tree pollen is abundant in the spring, grass pollen peaks late spring or summer, and weed pollen occurs late summer or fall. Moreover, outdoor mold levels often reach their highest levels.
in summer and fall.$^{30}$ Thus, knowledge concerning the time frame for peak allergen levels in one’s local area can help allergy suffers prepare for the season that most affects them.

2.2.2 Pollens

Pollen allergens originate from trees, weeds, or grasses. The most dominate allergen source for tree pollens originates from the order Fagales.$^{31}$ Trees belonging to the order Fagales include birch, alder, hazel, oak, beech and chestnut. Maple and juniper trees are of lesser importance in the elicitation of allergic symptoms in the United States.

Weeds are another important source for pollen production.$^{32}$ In North America, ragweed pollen is one of the key sources of allergenic proteins from midsummer through late autumn. Other weeds commonly implicated in pollen-induced allergic rhinitis include sage, Russian thistle, and cocklebur. During the spring and summer months grass pollens are a major source of airborne allergens.$^{33}$ The pollen structure of grass is spheroidal and measures 20 to 50 μm in diameter. Though there are hundreds of different types of grasses only a few are known to cause allergic disease (e.g., timothy, Kentucky bluegrass).

2.2.3 Molds

Besides pollen, mold is another common allergen.$^{34}$ Mold can grow on many materials with sufficient moisture and thus is found both indoors and outdoors. The most common indoor molds are Aspergillus and Penicillium whereas Alternaria and Cladosporium are predominate outdoor environments.$^{34,35}$ Aspergillus fumigatus and Cladosporium herbarum are
considered some of the most common causes of mold allergies. Although there is an outdoor seasonal-peak spore pattern, most patients with mold allergies have perennial symptoms caused by mold in their home or work environments.

### 2.2.4 Mammals

Owing to close proximity, some mammalian species, (e.g., livestock, pets, or laboratory animals) can cause allergy in some patients. Cats, dogs, and guineas pigs are common household pets often associated with allergic reactions. Epidemiologic studies of laboratory workers who handle common laboratory animals (e.g., mice, rats and rabbits) suggest up to 38% of these individuals develop measurable specific IgE levels. Although allergies to cows and horses has been reported in individuals who commonly come in contact with these animals, no known prevalence estimates have been reported.

### 2.2.5 House Dust Mites

Worldwide, the most predominate house dust mite are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Dust mites can play an important role in asthma. Cutaneous sensitivity to mite allergens has been documented in the majority (50 to 90%) of asthmatics. Because house dust mites extract water vapor from the air, they require humid and warm conditions (humidity 70 to 90%) in order to complete their life cycle. Dust mite allergens can be detected in many areas of the home, but beds provide ideal living conditions. Mite allergens can also be found in mite bodies and secretions. Mite fecal particles contain the greatest amount of mite allergen and can easily become airborne because of their small size.
2.2.6 Insects

Another potential source of allergens comes from insects. Two common types of cockroaches in the United States are the German and American cockroach. In urban areas, 40% to 60% of patients with asthma have specific IgE antibodies to cockroach allergens. Stinging insects (e.g., wasps, bees) do not cause allergic rhinitis symptoms but can be of great concern to patients who are severely allergic to the insects venom. Reactions to a sting can are classified as: 1) local cutaneous reaction, 2) large local reaction and 3) allergic systemic reaction.

2.3 Diagnosis

2.3.1 Overview

Allergic rhinitis can occur at any age but most patients develop their symptoms prior to twenty years of age. Common signs and symptoms of allergic rhinitis include sneezing, congestion, and red and itchy eyes. Presentation of allergic rhinitis, however, may vary considerably (Table 2.4). Obtaining information concerning the pattern of allergic symptoms can help provide clues concerning the causes of a patients’ allergies and help distinguish between seasonal and allergic rhinitis.
### Table 2.4: Symptoms and signs of allergic rhinitis [Source: Lagnese and Kelsen, 1999]

<table>
<thead>
<tr>
<th>Symptons</th>
<th>Nasal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritation</td>
<td>Loss of sense of smell</td>
<td>Cough</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Itching</td>
<td>Decreased sense of taste</td>
</tr>
<tr>
<td>Puffiness</td>
<td>Mucosal edema &amp; congestion</td>
<td>Headache</td>
</tr>
<tr>
<td>Redness</td>
<td>Postnasal drip</td>
<td>Otitis media</td>
</tr>
<tr>
<td></td>
<td>Sneezing</td>
<td>Sinusitis</td>
</tr>
<tr>
<td></td>
<td>Water rhinorrhea</td>
<td>Sore throat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Throat clearing and hoarseness</td>
</tr>
<tr>
<td>Signs</td>
<td>Erythema</td>
<td>Cobblestone pharynx</td>
</tr>
<tr>
<td></td>
<td>Nasal obstruction</td>
<td>Sinus tenderness</td>
</tr>
<tr>
<td></td>
<td>Pale mucosa</td>
<td>Retracted tympanic membrane</td>
</tr>
<tr>
<td></td>
<td>Polyps</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White secretions</td>
<td></td>
</tr>
</tbody>
</table>

2.3.2 Patient history and physical examination

Experienced clinicians typically make the diagnosis of allergic rhinitis based on careful patient history in combination with physical examination. A history of the patient’s general medical condition should be taken along with detailed questioning concerning the patient’s symptoms (Table 2.5). Not only is it important to inquire as to the when and where allergy symptoms occur, physicians should ask how symptoms of rhinitis impact the patient’s quality of life. For example, rhinitis can impact one’s ability to concentrate, sleep or both.
### Table 2.5: Patient History to Consider in the Evaluation of Rhinitis

<table>
<thead>
<tr>
<th>Points to Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms:</strong> magnitude, duration, timing in relation to exposure, effect on daily living</td>
</tr>
<tr>
<td><strong>Triggers/seasonality</strong></td>
</tr>
<tr>
<td><strong>Environment, including home, job and school or day care for children</strong></td>
</tr>
<tr>
<td><strong>History of other allergic symptoms (e.g., asthma, conjunctivitis, eczema)</strong></td>
</tr>
<tr>
<td><strong>Past medical history, including trauma</strong></td>
</tr>
<tr>
<td><strong>Feeding history in young children</strong></td>
</tr>
<tr>
<td><strong>Past treatment experience</strong></td>
</tr>
<tr>
<td><strong>Current treatment</strong></td>
</tr>
<tr>
<td><strong>Family history, including allergic diseases</strong></td>
</tr>
<tr>
<td><strong>Review of symptoms</strong></td>
</tr>
</tbody>
</table>

Table 2.5: Patient history to consider when evaluating a patient with rhinitis [Source: Dykewicz, Fineman, et. al., 1998].

A physical examination of the nose should be performed for all patients with rhinitis. Specifically, a physician should examine the appearance of the nasal mucous membranes, determine if the nasal passageways are open, look for causes of nasal obstruction, such as polyps, and note the quality and quantity of nasal discharge. Besides examination of a patient's nose, an assessment may also include a review of the ears, eyes, throat and lungs (Table 2.6).
Elements of Physical Examination to Consider in the Evaluation of Rhinitis

| General observations: facial pallor, ‘allergic shiners’, mouth breathing and nasal crease |
| Eyes: evidence of conjunctivitis, accentuated lines or folds below the margin of the inferior eyelid |
| Nose: presence or absence of external deformity, nasal mucosal swelling, nasal polyps, deviated septum, discharge, blood, and septal perforation. |
| Ears: look for abnormalities of tympanic membranes |
| Mouth: observe for high arched palate associated with chronic mouth breathing, tonsilar hypertrophy, and halitosis |
| Neck: lymphadenopathy, thyroid enlargement |
| Chest: signs of asthma |
| Skin: eczema, skin dryness, dermographism |

Table 2.6: Physical history to consider when evaluating a patient with rhinitis [Source: Dykewicz, Fineman, et al., 1998].

2.3.3 Skin Prick Test

Despite the prominent role of patient history in making the diagnosis of allergic disease, skin or *in vitro* test results may be needed to 1) establish an allergic basis for the patient’s symptoms, 2) confirm suspected causes, or 3) assess the degree of sensitivity to a specific allergen. Allergist most commonly utilize skin prick and intradermal skin tests to detect specific IgE antibodies to various allergens. Scratch testing for inhalant sensitivities has been in practice since the 1870’s, when Charles Blackley first performed the procedure on himself. He abraded a quarter inch of skin on both of his forearms and then applied pollen to one of the scratched areas. After a few minutes, the area where he had placed the pollen began to itch and swell while
the other arm showed no visible reaction. Hence, the scratch test is performed by scraping the epidermis and dropping or rubbing concentrated antigen (e.g., 1:10 w/v) in the abraded area. The weight/volume system (w/v) explains how the extract was prepared. A 1:10 w/v allergen extract is prepared by taking 1 gram of source material (e.g., cat dander, house dust mite, ragweed pollen) in 100 milliliters of appropriate buffer. After applying the concentrated allergen to the scratched skin and waiting 15 to 20 minutes, the test area is examined for a wheal-and-flare reaction signifying a positive response.

The scratch test has several advantages and disadvantages. The scratch test is easy to perform and relatively painless. In addition, this type of procedure is extremely safe because epicutaneous testing does not involve a large amount of antigen challenge to the patient. A problem with the scratch test is that the actual scratching of the skin promotes local irritation which gives rise to potential false positive results. Furthermore, this type of testing strategy is very difficult to reproduce. The irreproducibility of the test is due to the frequency of false positives and also because the amount of antigen introduced is impossible to control. Due to these major disadvantages, the American Medical Association no longer recommends the use of scratch testing for diagnostic purposes.43

Lewis and Grant, in 1924, were the first to describe skin prick testing.44 Skin prick tests are usually done on the volar surface of the forearm but can also be done on a patient's back. First, the patient's skin is wiped with 70% ethanol and then a drop of allergen extract, typically as 1:10 or 1:20 w/v
solution, is placed on the skin with a dropper or glass applicator. These drops are placed at least 2 cm apart in order to allow accurate measurements of potential allergic reactions. A disposable hypodermic needle or lancet is then passed through the extract drops and punctures the epidermal layer of the skin. In order to prevent cross-contamination of the allergens through the use of the same needle, either a new needle is used to test each extract or the needle is wiped with sterile gauze between tests. Approximately 8 - 12 skin tests can be performed on an adult forearm. In order to give the extracts time to penetrate the epidermal layer, the drop of allergen remains on the skin or is wiped away after a few minutes.

Two skin prick controls, a positive and a negative control, are concurrently tested. In the United States, the typical positive control is histamine. The purpose of a positive control is to detect allergic reaction suppression due to medications (e.g., anti-histamines, steroids) or disease. A standard histamine response would produce a wheal-and-flare reaction in the range of 2 to 7 mm. The usual negative control solution is comprised of the diluents used to preserve the allergen extracts. The use of a negative control will help identify patient reaction to the test diluent. Furthermore, this control will detect any reactivity caused by the minor skin trauma associated with the testing procedure.

Ten to fifteen minutes after performing the skin prick test, the test area is examined for wheal-and-flare (wheal denotes the raised area of skin and the flare indicates erythema) reactions. The Morrow Brown method is commonly
used to assess the wheal-and-flare reaction (Table 2.7). This standardized
scoring method uses the prick histamine control as a comparator for the other
reactions. A scale is established with the histamine control graded as a 3+
and the negative diluent is graded as zero. Wheal-and-flare reactions greater
than the histamine control are graded as 4+, reactions two thirds the size of the
histamine control are graded 2+, and reactions one third the size of the
histamine control are graded as 1+. An alternative to the Morrow Brown scoring
method is the following simple criterion: reactions over 3 mm in wheal diameter
and over 10 mm in flare diameter are indicative of clinical allergy. The larger
the skin test reaction, the more likely it is for the allergen to be clinically
significant.

<table>
<thead>
<tr>
<th>Size</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>One third of histamine control</td>
<td>+</td>
</tr>
<tr>
<td>Two thirds of histamine control</td>
<td>++</td>
</tr>
<tr>
<td>Same size as histamine control</td>
<td>+++</td>
</tr>
<tr>
<td>Larger than histamine control</td>
<td>++++</td>
</tr>
</tbody>
</table>

Table 2.7: Morrow Brown grading system for skin prick test [Source: Anon, 1993]

Although the skin prick test is simple, fast, and relatively painless, many
technical elements can effect the test results. First, if the allergen extracts are
placed too proximal, test reactions cannot be separated visually. Second,
bleeding caused by the needle or lancet may lead to false-positive results.
Alternatively, inadequate penetration of the skin by the needle may lead to false-negative results. Lastly, spreading of the allergen solutions during testing or while wiping away the allergen solutions may lead to inaccurate conclusions.

2.3.4 Intradermal Test

Another common allergy skin test, introduced in 1908 by Mantoux, is the intradermal method. Normally, a patient is first screened using the prick test and then has intradermal skin tests for any negative skin prick tests results. Intradermal testing is usually used after skin prick testing because the skin prick test is less reproducible and has more false negatives with fewer false positives (less sensitive) compared to the intradermal skin test. Conversely, the intradermal skin test is more reproducible and provides fewer false negatives but more false positives (more sensitive) results.

Intradermal skin tests are usually performed on the arm using sterile tuberculin syringes. A volume between 0.01 and 0.05 ml of 1:100 to 1:1000 w/v concentration of extract is injected in the superficial layers of the skin. Enough extract is administered to raise an initial wheal or bleb (a large flaccid vesicle) approximately 3 mm in size. Similar to the skin prick procedure, a positive and negative control are also administered. The ensuing wheal-and-flare reactions are read approximately 15 to 20 minutes after administration. The wheal-and-flare results are reported on scale from 0 to 4+ (Table 2.8).
<table>
<thead>
<tr>
<th>Grade</th>
<th>Wheal (mm)</th>
<th>Erythema (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 4</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>+ -</td>
<td>5 - 10</td>
<td>5 - 10</td>
</tr>
<tr>
<td>1 +</td>
<td>5 - 10</td>
<td>11 - 20</td>
</tr>
<tr>
<td>2 +</td>
<td>5 - 10</td>
<td>21 - 30</td>
</tr>
<tr>
<td>3 +</td>
<td>10 - 15</td>
<td>31 - 40</td>
</tr>
<tr>
<td>4 +</td>
<td>&gt; 15</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

Table 2.8: Grading system for intradermal skin tests [Source: Yunginger, 1997].

As with any testing method, errors can occur when actually performing traditional intradermal testing. Similar to skin prick testing, if the test sites are too close together, false positive results can be observed. Excessive extract concentration is another cause of false-positive test results. A false-negative test result could occur if the injection is given incorrectly and therefore, no bleb is formed. An additional inaccurate test result may take place if the volume injected is too large (i.e., greater than 0.05 ml). Lastly, too many injections performed at the same time may induce systemic reactions.

Rinkel developed a second modified method to intradermal testing, called skin end point titration (SET). This technique involves the use of a series of single intracutaneous skin tests of various dilutions to evaluate the degree of allergen sensitivity. The patient begins with an injection of the most dilute allergen solution. If the test is negative, the patient is then tested with the next least concentrated solution and so forth. The most dilute solution required
to produce a reaction is considered the end point. This technique differs slightly from the single intradermal testing procedure earlier described; typical intradermal methods involve only a single injection per allergen tested.

For an example of a SET testing procedure, assume a patient receives a 0.01 ml injection of 1:312,000 w/v allergen extract. Also assume that if the wheal remains the same size or grows by less than 2 mm, it is considered a negative response—indicating that the patient is not sensitive to that particular allergen concentration. Say that the most dilute injection produces a wheal 4 mm in size (Table 2.9). The subsequent dilutions (1:62,500 and 1:12,500) also produce a wheal 4 mm in size. When the allergen concentration reaches 1:2,500 w/v, the wheal increases to 5 mm. Because the wheal size did not increase by 2 mm, it is considered a negative response. The next injected concentration (1:500) results in a 7 mm wheal and therefore is considered the end point.

<table>
<thead>
<tr>
<th>Concentration (w/v)</th>
<th>Wheal Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:20</td>
<td>11 mm</td>
</tr>
<tr>
<td>1:100</td>
<td>9 mm</td>
</tr>
<tr>
<td>1:500</td>
<td>7 mm</td>
</tr>
<tr>
<td>1:2,500</td>
<td>5 mm</td>
</tr>
<tr>
<td>1:12,500</td>
<td>4 mm</td>
</tr>
<tr>
<td>1:62,500</td>
<td>4 mm</td>
</tr>
<tr>
<td>1:312,000</td>
<td>4 mm</td>
</tr>
</tbody>
</table>

Table 2.9: Example of skin end point titration (SET) skin test wheal response [Source: Anon, 1993].
This intradermal skin test technique produces highly reproducible wheals and allows a standardized method of scoring. However, the SET is time consuming, initially complicated, and involves a large number of test injections compared to the tradition intradermal skin testing method. Nevertheless, SET can be very useful in determining the starting point for immunotherapy.

Although similar, there are some differences between skin prick and intradermal tests (Table 2.10). The skin prick test produces more false negatives than the intradermal test. Despite this fact, the skin prick test has a few advantages over the intradermal test (e.g., speed, simplicity, interpretation of results, safety). Most importantly, the skin prick test is considered to be better correlated with symptoms. Because of these reasons, the U.S. Joint Council of Allergy, Asthma and Immunology recommend skin prick tests as the primary test for diagnosis of IgE-mediated allergic disease. Furthermore, the U.S. Joint Council of Allergy, Asthma, and Immunology states that "the evaluation of inhalant allergy may require up to 70 skin prick tests followed by up to 40 intracutaneous tests, which are ordinarily performed when prick/puncture tests are negative."
<table>
<thead>
<tr>
<th>Description</th>
<th>Prick Test</th>
<th>Intradermal Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplicity</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Speed</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Interpretation of positive and</td>
<td>+++++</td>
<td>++</td>
</tr>
<tr>
<td>negative reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discomfort</td>
<td>+</td>
<td>+++++</td>
</tr>
<tr>
<td>False-positive reactions</td>
<td>Rare</td>
<td>Possible</td>
</tr>
<tr>
<td>False-negative reactions</td>
<td>Possible</td>
<td>Rare</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Detection of IgE antibodies</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Safety</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Testing of infants</td>
<td>Yes</td>
<td>Difficult</td>
</tr>
</tbody>
</table>

Table 2.10: Relative comparison between skin prick and intradermal testing [Source: Demoly, et al., 1998].

Thus, with inhalant allergies, skin tests reportedly represent the primary and most effective diagnostic method. There have been no reported fatalities and the overall risk of an adverse reaction is 0.04% for systemic reactions. It is important to remember however, that the following factors can affect skin test response: age of patient (skin test reaction increases from infancy to adulthood but then declines after the age of 50), test site (upper back is more reactive than forearm), quality of extracts, presence of dermatographism, use of medications (e.g., antihistamines, tricyclic antidepressants, hydroxyzine). Notwithstanding the many advantages of skin testing for allergic disease, not all patients can be availed to these methods. For example, patients with dermatographism or severe skin eczema cannot be skin tested. Moreover, certain drugs can interfere with the performance of skin tests: antihistamines
inhibit the wheal-and-flare reaction, as do topical corticosteroids. Most allergy clinics do not recommend any skin or intradermal testing during pregnancy. Also, *in vivo* testing may be impossible in those patients who have life threatening anaphylaxis to allergens. However, there is another test method available for the diagnosis of allergic rhinitis (c.f., *in vitro* testing).

### 2.3.5 In Vitro Blood Test

*In vitro* allergy blood tests have been used since the late 1960's. Wide et al. developed in 1967 a radioimmunoassay, called the radioallergosorbent test (RAST), to detect specific IgE antibodies in serum. Test development included evaluating this new assay on 29 and 22 patients who had responded and not responded to a previous allergy challenge, respectively. The RAST test was able to detect levels of specific IgE antibody in 28 of the 29 respondents whereas 21 out of the 22 non-respondents had no detectible levels of specific IgE antibody. Hence, the overall test sensitivity and specificity were both 96%. The sensitivity of a test is defined as the probability that the test is positive given that the person has the disease. The specificity of a test is the probability that the test is negative given that the person does not have the disease.

The basic principles for the RAST test, which still hold true today for other similar IgE specific *in vitro* blood tests, were described by Osguthorpe as including the following four steps: 1) the soluble allergens can be bound to solid phase supports to create a stable immunosorbent particle that acquires the antigenicity of the allergen, 2) the passively created immunosorbent (insoluble allergen) on incubation with a test serum will react with specific antibody to form
the solid phase complex, 3) the anti-human IgE serum raised in another species and radiolabeled with iodine-125 will react with antigenic determinants on the Fc portion of the IgE antibody bound to the allergen-coated immunosorbent, and 4) the greater the amount of radioactivity remaining bound to the immune complex (disk), the more specific IgE present in the serum sample under test. Radioactive counts larger than 2 times the nonspecific background binding were considered positive.

This technical explanation of basic immunologic principles of the RAST test is laden with jargon and may therefore not be accessible to those outside this field of study. Hence, a less scientific way to describe the process is as follows: 1) blood is drawn from the patient, 2) collected serum is incubated with specific allergens that are anchored to a solid phase material -usually on a paper disc, 3) specific IgE is in the serum will bind to the allergen on the solid phase, 4) serum is washed away from the solid phase and hereby allowing only IgE specific antibodies to remain attached to the solid phase, 5) radioactive or fluorescent labeled anti-IgE antibodies are introduced, 6) labeled anti-IgE antibodies attach to the specific IgE antibodies, and 7) non-attached labeled antibodies are removed through washing. The final result of this process is the ability to quantify the labeled antibodies — a measurement directly proportional to the amount of allergen specific IgE in the blood sample.

The first commercially available in vitro allergy test that was used to measure serum specific IgE antibodies was called the Phadebas radioallergosorbent test (PhRAST). This assay used radiolabeled iodine-125
for its labeling and a gamma counter to measure the amount of bound specific IgE.\textsuperscript{52} With the availability of the PhRAST system, physicians were finally able to perform \textit{in vitro} allergy tests in their office.

\textbf{2.3.6 Comparison of mRAST and PhRAST Tests}

Although the use of PhRAST greatly increased in the 1970's, controversy over the test's poor sensitivity began to emerge later that same decade.\textsuperscript{53} The debate over the PhRAST centered around its allergy scoring system. In order to provide physicians with a reference standard, four reaginic reference standards were established: standard A was taken from patients highly sensitive to birch pollen, standard B was a five fold dilution of standard A, standard C was a five fold dilution of standard B, and standard D was a two fold dilution of standard C. In the Phadebas RAST scoring system, each of the standards were given an arbitrary number of Phadebas RAST units (PRUs) ranging from 1 PRU for standard reference D to 50 PRUs for standard reference A. Patients who had bound radioactivity less than the standard reference D were considered to have nondetectable levels of specific IgE antibodies and thus were considered to have negative test results. Thus, the PhRAST was intended to be highly specific (i.e., to give few false positive results). However, when the PhRAST test results were compared to skin testing, a large number of false negative results were documented. This disagreement between the Phadebas RAST test and skin tests was noted by physicians and caused some criticism regarding the tests' poor sensitivity. To address physician concerns, the manufacturer of PhRAST decided to revise the
test's scoring system by diluting all the reference standards by one-third. This dilution of the reference standards placed reference standard D's cut-off point at 0.35 PRU. Consequently, a PRU is equivalent to the response given by 0.35 IU/ml of IgE.\(^5^4\) Despite efforts to increase the sensitivity of the PhRAST by modifying the scoring system, the new cut-off point did not solve the sensitivity problem. Moreover, another change to the PhRAST test created the Phadezym RAST test. The Phadebas RAST was a system that used a radioactive tracer in the assay as the marker, and typically the results were measured in counts (i.e., gamma emissions). Phadezym RAST was launched when the radioactive marker was replaced with an enzymatic marker producing a colorimetric response and then the results were measured on a spectrophotometer. The other assay components, such as paper disc stayed the same.

Several procedural and interpretive changes were made to increase the sensitivity of PhRAST without significantly decreasing the specificity of the test results. These changes resulted in the development of the modified radioallergosorbent test (mRAST) by Naleguff and Fadal in 1979.\(^5^3\) These two researchers integrated several procedural changes into the PhRAST test to increase its sensitivity without significantly decreasing specificity. Initial changes included: increased volume of sera to ensure that the paper discs stayed moist (from 50 to 100 mL), longer incubation time (from 3 to 18 hours),
and transfer of paper discs into a clean tube in order to prevent any
measurement of extraneous radioactivity prior to counting the bound
radioactivity.\textsuperscript{52}

The mRAST test had a nonspecific IgE binding rate of 500 counts. Thus,
test results below this level were considered to be negative. Counts ranging
between 500 and 750 were considered equivocal – any detectible level of IgE in
the sera could be considered clinically insignificant. Counts ranging higher than
750 were divided into 5 different classes ranging from Class 1 to 5. Each class
represented a five fold increase in the amount of specific IgE. The mRAST was
tested in several clinical trials, compared to PhRAST, and was found to have
increased sensitivity without significant loss of specificity. Consequently, the
mRAST test became gold standard to which a majority of the new in vitro tests
would be compared. The mRAST test is still widely used today. Figure 2.1
provides a comparison of the original RAST, PhRAST and mRAST.
### 2.3.7 Pharmacia CAP System

After the introduction of mRAST, the same test technologies were used to develop different versions of *in vitro* assays (e.g., MAST, Alastat), another advancement in assay development lead to the creation of the Pharmacia CAP System (CAP) in 1988. This test system uses a flexible hydrophilic polymer encased in a capsule instead of the paper disc used in other *in vitro* tests. This flexible hydrophilic polymer, called ImmunoCAP, allows additional allergen to be added and exposes more binding sites to the assay.

The CAP test measures the amount of bound IgE through the fluorescent enzyme reagent. Test results below 0.35 kU/L indicate a negative result.

Thus the CAP system uses a fluorometer instead of a gamma counter or a

---

<table>
<thead>
<tr>
<th>Original RAST</th>
<th>2X</th>
<th>5X</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongly Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phadebas RAST</th>
<th>.35</th>
<th>.70</th>
<th>3.5</th>
<th>17.5</th>
<th>PRU's</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified RAST</th>
<th>500</th>
<th>750</th>
<th>1600</th>
<th>3600</th>
<th>8000</th>
<th>18000</th>
<th>Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.1: Comparison of original RAST, Phadebas RAST, and modified RAST testing systems [Source: Nalebuff, 1992].
spectrophotometer found in the PhRAST or Phadezym RAST, respectively.

The standard CAP scoring system is divided into seven class ranges (Table 2.11).

<table>
<thead>
<tr>
<th>Specific IgE Class</th>
<th>Greater Than or Equal to</th>
<th>Less Than</th>
<th>Level of Allergen Specific IgE Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>Cal- 100.0</td>
<td></td>
<td>Very High</td>
</tr>
<tr>
<td>V</td>
<td>Cal- 50.0</td>
<td>Cal- 100.0</td>
<td>Very High</td>
</tr>
<tr>
<td>IV</td>
<td>Cal- 17.5</td>
<td>Cal- 50.0</td>
<td>Very High</td>
</tr>
<tr>
<td>III</td>
<td>Cal- 3.5</td>
<td>Cal- 17.5</td>
<td>High</td>
</tr>
<tr>
<td>II</td>
<td>Cal- 0.7</td>
<td>Cal- 3.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>I</td>
<td>Cal- 0.35</td>
<td>Cal- 0.7</td>
<td>Low</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>Cal- 0.35</td>
<td>Absent or Undetectable</td>
</tr>
</tbody>
</table>

Table 2.11: Standard CAP Scoring System.

2.3.8 In Vitro versus Skin Tests

Although the standard CAP (CAP-STD) scoring system is the most widely used, an alternative scoring method (CAP-ASM) is also available to report CAP data (Figure 2.2). The CAP-ASM was developed to imitate the mRAST scoring system. This alternative scoring method increases test sensitivity but results in a slight decrease in specificity.
Whereas some researchers have compared in vitro testing to skin testing, others have investigated the precision and accuracy among different in vitro allergy tests. Szeinbach et al. sent random anonymous serum samples to six different laboratories to compare the IgE specific test results among the various in vitro testing methods utilized at each laboratory. Analysis of over 7,000 useable assays indicated significant variability across the reported laboratory results for identical samples. More specifically, laboratories using a modified RAST procedure demonstrated significantly different results when analyzing identical samples. The CAP system did not have this problem. These researchers also found that several in vitro allergy test methods could not differentiate between serum samples that had significantly different specific
IgE antibody concentrations. Debate surrounded these reported findings; the Pharmacia CAP system, however, consistently performed well compared to the ideal assay standard.

Given the different scoring methods and procedures to detect allergen-specific IgE (i.e., skin prick tests, intradermal, and in vitro testing), no research had convincingly demonstrated the comparability of in vitro and skin test results. Kelso et al. (1991) performed a comparison between skin prick tests and three different in vitro tests (PhRAST, mRAST, and CAP). Study subjects with rhinitis and/or asthma, between the ages of 10 and 75 years, were enrolled from an allergy clinic. Patients whose disease history was considered due to any of five allergens (cat, Dermatophagoides pteronyssinus, Alternaria, June grass, and short ragweed) were skin prick tested. If one or more skin prick tests was evaluated as positive, they were enrolled in the study. One hundred and four patients with the conditions described above were included in the study. Clinic employees and family members who had no history of rhinitis and/or asthma also volunteered to undergo skin prick testing. If the skin prick test results of this group were negative, they were enrolled in the study as a control. Twenty four control patients were obtained in this manner. The comparison of the three different tests results are shown in Table 2.12. Overall, the mRAST had the highest sensitivity (90%), while the PhRAST had the highest specificity (99%).
<table>
<thead>
<tr>
<th></th>
<th>Kelso* (n = 128)</th>
<th>Kam† (n = 49)</th>
<th>Kam‡ (n = 96)</th>
<th>Boccagni§ (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>PhRAST</td>
<td>62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>mRAST</td>
<td>90%</td>
<td>79%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>CAP</td>
<td>74%</td>
<td>79%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>PhRAST</td>
<td>99%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>mRAST</td>
<td>87%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>CAP</td>
<td>96%</td>
<td>91%</td>
<td>94%</td>
</tr>
</tbody>
</table>

* Compared to skin prick test. Tested five allergens.
† Compared to skin prick test. Tested six allergens.
‡ Compared to intradermal test. Tested four allergens.
§ Compared to clinical history and skin prick test. Tested nine allergens.
|| Phadebas RAST test.
‖ Phadezym RAST test.

Table 2.12 Comparison of in vitro tests with other diagnostic standards.

Kam et al. (1994) compared in vitro skin tests with skin prick and intradermal skin tests. Ninety-six allergic patients, age 3.5 to 16 years, were recruited from an allergy clinic. All 96 patients had intradermal tests and 49 of these 96 were randomly selected to receive the skin prick test. The four allergens (Dermatophagoides pteronyssinus, Aspergillus fumigatus, Candida albicans, and short ragweed) were used for the intradermal tests and six allergens (Dermatophagoides pteronyssinus, Aspergillus fumigatus, Candida albicans, short ragweed, Bermuda grass, and cockroach mix) were used for the skin prick tests. The performance of the in vitro assays relative to the
intradermal testing indicated the CAP system had the highest overall sensitivity (86%) and specificity (94%) among the in vitro tests. When comparing the in vitro tests to the skin prick tests, the Phadezym RAST had the highest specificity (94%) and CAP system had the best sensitivity (79%).

Further investigation into the comparability of in vitro assays and skin prick tests were conducted by Boccagni et al. Forty-two adults, aged 17 to 68 years, underwent skin prick and in vitro tests for nine aeroallergens (Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat epithelium, Cynodon dactylon, Lolium perenne, Phleum pratense, Holcus lanatus, Parietaria officinalis, and Betula verucosa). Twenty-three subjects were known to have aeroallergen allergies and the remaining 19 served as sex and age matched controls. The researchers reported the highest sensitivity (94%) and specificity (100%) to the CAP test.

High in vitro skin test correlation may, however, not be associated with the clinical utility of in vitro testing because skin testing is not perfectly correlated with clinical symptoms. When comparing skin and in vitro test results in the same patient, "one must consider that different environmental factors as well as pharmaceutical therapies may have different effects on in vitro results compared with in vivo parameters." For example, antihistamines, age,
hormones, and the site of injections can influence skin tests results. Thus, the
two test results may be substantially different even when performed with the
highest possible standards.

2.4 Management

2.4.1 Overview

Although diagnostic assessment of allergic rhinitis remains controversial,
there are only three recognized approaches to allergy care: avoidance,
pharmacotherapy, and immunotherapy. Allergen avoidance should be the
first step in the management of treating an allergic rhinitis patient. Patient-
specific environmental control measures are guided by the implicated
allergen(s). Researchers have shown complete avoidance of the allergen can
be curative.

2.4.2 Environmental Controls

When a patient is allergic to house dust mites, allergists usually
recommend environmental controls first for the bedroom because of the large
amount of time spent there. Pillow and mattress encasement with material
impermeable to dust mists, as well as washing bed lines every week in hot
water, will reduce exposure to dust mites. Furthermore, synthetic pillows are
preferred to those made of feather or down. Carpets and upholstered furniture
also harbor these mites and removal of these reservoirs should be evaluated.

Because house dust mites thrive in humid conditions, dehumidification will
lessen the mite-appeal of areas such as bathrooms and kitchens.
Alleviating the allergic rhinitic from general housekeeping, such as dusting and vacuuming, will reduce exposure to house dust mites. Important to note is that vacuuming does not directly remove house dust mites because they attach themselves to fibers in furniture and carpets, although it does remove fecal pellets. Environmental control of dust mites should be given special attention because it is the most important cause of allergy in the domestic environment.

Pets are the second most important cause of perennial rhinitis. Dander, salivary, and urine proteins from cats, dogs, hamsters, rabbits, and guinea pigs are major sources of allergenic proteins. Approximately, 45% of US households contain one or more animals. The most effective manner to eliminate allergies caused by pet dander is the removal of the offending animal. If this is not a viable alternative, confining the pet to an uncarpeted portion of the home should be considered. Special attention should be given to preventing the pet from being allowed in the bedroom. Using an electrostatic air purifier or high-efficiency particulate air (HEPA) filter can help remove pet dander and thus help eliminate allergy symptoms. If the pet allergy is caused by a cat, weekly cat washings may decrease the amount of airborne allergen.

For patients suffering from pollen allergies, HEPA filters can be used as a preventive measure. Changing filters on heating and air condition units approximately every month is encouraged. Furthermore, patients with seasonal allergies should stay indoors as much as possible during periods of high pollen.
counts and turn on the air conditioning rather than opening windows. After being outdoors, taking a shower is recommend in order to remove pollen from the hair and skin.

Symptoms from mold allergies can be experienced indoors or outdoors. Avoiding outdoor activities which increase exposure to molds, such as leaf raking or spreading mulch, can help alleviate symptoms. Using bleach or a disinfectant to retard or eliminate mold from damp areas (e.g., bathroom, basement) is recommended. The use of a dehumidifier can decrease mold growth, however the use of a vaporizer is discouraged. Unsuspecting household plant owners may be surprised to discover that plants can harbor mold and therefore should be eliminated or minimized.

2.4.3 Pharmacotherapy

If environmental control measures result in little or no symptom improvement for the patient, pharmacotherapy may be needed. Drug therapy for allergic rhinitis can be divided into five groups: antihistamines, decongestants, corticosteroids, mast cell stabilizers, and anticholinergics. Oral antihistamines are first-line drug therapy for mild to moderate seasonal or perennial allergic rhinitis. Antihistamines antagonize histamine-H1 receptors on target cells in the respiratory mucosa. Normal activation of H1 receptors increases vascular permeability, increases the production of mucus, and activates sensory nerves to induce reflexes such as sneezing. Thus, the use of antihistamines prevents this cascade of physiological events. Because antihistamines compete with histamine for receptors, they are most effective
prior to the onset of symptoms or prior to allergen exposure. They are good at preventing and relieving sneezing, rhinorrhea, and nasal pruritus but have minimal effects on nasal congestion.

Although recently a third generation antihistamine class has been introduced, the antihistamine drug group is commonly subdivided into first and second generation antihistamines based on their propensity to induce sedation. First generation antihistamines cross the blood-brain barrier and therefore cause sedation and have anticholinergic effects (e.g., dry mouth, constipation, urinary retention). The sedation caused by this group of drugs can be a concern to many patients. The drowsiness that can be caused by these medications are of concern to drivers and operators of heavy machinery. Research has found work performance and productivity is decreased, while the risk of on the job injury increases in patients taking first generation antihistamines. Moreover, the use of sedating antihistamines can impair children’s learning ability and impact academic performance. Despite these increased risks, these drugs are still widely used because many of these drugs are easily available over-the-counter (Table 2.13 and 2.14).

The newer generation antihistamines have improved clinical effectiveness and patient tolerance. Second generation antihistamines are more costly than their first generation counterparts and are currently only available by prescription. The use of two second generation antihistamines,
astemizole and terfenadine, were associated with life-threatening cardiotoxicities resulting in their withdrawal from the market. Other drugs within this group have not been associated with this serious medical problem.

<table>
<thead>
<tr>
<th>Drug Class and Generic Name</th>
<th>Trade Name</th>
<th>Available OTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral first-generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triprolidine</td>
<td>Actifed, Actigen</td>
<td>Yes</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Chlor-Trimeton, Aller-Chlor</td>
<td>Yes</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benadryl, Genahist</td>
<td>Yes</td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>Dimetane, Diamine</td>
<td>Yes</td>
</tr>
<tr>
<td>Clemastine</td>
<td>Tavist</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenindamine</td>
<td>Nolahist</td>
<td>Yes</td>
</tr>
<tr>
<td>Azatadine</td>
<td>Optimine</td>
<td>No</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Phenergan</td>
<td>No</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>Semprex</td>
<td>No</td>
</tr>
<tr>
<td>Oral Second Generation</td>
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<td></td>
</tr>
<tr>
<td>Loratadine</td>
<td>Claritin, Claritin-D</td>
<td>No</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Allegra</td>
<td>No</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Zyrtec</td>
<td>No</td>
</tr>
<tr>
<td><strong>Decongestants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral: alpha-adrenergic receptor agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Sudafed, Rhinosyn</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>Propagest</td>
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</tr>
<tr>
<td>Phenylephrine</td>
<td>Neosynephrine;</td>
<td>Yes</td>
</tr>
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</table>

Table 2.13: Oral drug therapy for allergic rhinitis.
<table>
<thead>
<tr>
<th>Drug Class and Generic Name</th>
<th>Trade Name</th>
<th>Available OTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intransasal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelastine</td>
<td>Astelin</td>
<td>No</td>
</tr>
<tr>
<td><strong>Decongestants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intransasal: catecholamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naphazoline</td>
<td>Privine</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxymetazoline</td>
<td>Afrin</td>
<td>Yes</td>
</tr>
<tr>
<td>Xylometazoline</td>
<td>Otrivin</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
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<td></td>
</tr>
<tr>
<td>Intransasal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>Beconase, Vancenase</td>
<td>No</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Rhinocort</td>
<td>No</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Nasalide, Nasarel</td>
<td>No</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Fionase</td>
<td>No</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Nasonex</td>
<td>No</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Nasacort, Nasacort AQ</td>
<td>No</td>
</tr>
<tr>
<td><strong>Other treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intransasal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn</td>
<td>Nasalcrom</td>
<td>Yes</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Atrovent</td>
<td>No</td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
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<td></td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Acular</td>
<td>No</td>
</tr>
<tr>
<td>Olopatadine</td>
<td>Patanol</td>
<td>No</td>
</tr>
<tr>
<td>Lodoxamide</td>
<td>Alomide</td>
<td>No</td>
</tr>
<tr>
<td><strong>Inhalant</strong></td>
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<td></td>
</tr>
<tr>
<td>Cromolyn</td>
<td>Intal</td>
<td>No</td>
</tr>
<tr>
<td>Nedocromil</td>
<td>Tilade</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2.14 Non-oral drug therapy for allergic rhinitis.
Notwithstanding their effectiveness in relieving many allergy symptoms, antihistamines do not effectively relieve nasal congestion. To treat the symptoms of congestion, many physician recommend the use of oral or intranasal alpha-adrenergic agonists. These medications cause vasoconstriction of the nasal blood vessels thereby reducing nasal congestion; these products, however, do not affect sneezing, rhinorrhea or nasal pruritus. Intranasal decongestants should be used for no more than 5 days consecutive days; longer use may lead to rebound vasodilatation and congestion (i.e., rhinitis medicamentosa).

Oral decongestants can be used in place of intranasally administered products. These products, however, have several side-effects including increased blood pressure, heart rate, intraocular pressure, anxiety levels, and nervousness. These products, therefore, are contraindicated for patients with arrhythmia, angina, hypertension, glaucoma, hyperthyroidism and diabetes.

Intranasal corticosteroids are the most effective treatment available for allergic rhinitis symptoms. Intranasal administration minimizes their systemic side effects and their local anti-inflammatory properties make them clinically effective. Topical corticosteroids are effective in decreasing nasal blockage, itching, and sneezing in both allergic and non-allergic rhinitis. Local nasal irritation, sneezing, and headache may occur with nasal administration but are rarely associated with systemic side effects. The use of oral corticosteroids is
recommended for a 3 to 7 day period to treat severe nasal symptoms, however, longer term oral therapy is not recommended because of the risk of serious systemic side effects (e.g., immunosuppression, diabetes).

The fourth class of drugs to treat allergic rhinitis is mast cell stabilizers. Cromolyn sodium, a mast cell stabilizer, inhibits the degranulation of sensitized mast cells thereby preventing the release of histamine. Therefore, cromolyn sodium is useful in preventing and relieving all allergic rhinitis symptoms. Physicians recommend starting to use this medication prior to the onset of the allergy season in order to obtain maximum benefit. Because cromolyn sodium has no known drug interactions and has a good overall safety profile, the product achieved over-the-counter availability.

Ipratropium bromide is an anticholinergic nasal spray that antagonizes the action of acetylcholine at cholinergic receptors—it has no effect on histamine. Cholinergic hyperactivity in allergic rhinitis patients has been associated with vasodilation. Nasally administered ipratropium may reduce rhinorrhea, it does not affect nasal congestion, nasal pruritus or sneezing. The most common adverse effects of this drug are headache and nasal dryness.

Although patients with allergic rhinitis may have their allergy symptoms under control using a single medication, combination drug therapy may be necessary for some patients. For example, antihistamines relieve itching, sneezing, and rhinorrhea but decongestants are necessary to help with the
symptom of nasal congestion. Alternatively, patients who have mild symptoms can be treated with cromolyn sodium prior to allergen exposure and then use an antihistamine to relieve symptoms as needed.

2.4.4 Immunotherapy

Despite all of the different types of drug therapy currently available, patients may elect another mode of treatment for inhalant allergies—immunotherapy.\textsuperscript{75} If immunotherapy treatment is given to properly selected patients and correctly administered it can provide long-term allergy relief. Patients who are acceptable candidates for this therapy should have proven allergies to one or more allergens which are not easily avoided and are not adequately controlled by drug therapy.\textsuperscript{78} Because of the cost and significant time commitment necessary to complete a full course of immunotherapy, patients should be highly motivated prior to beginning any treatment. Contraindications for the initiation of immunotherapy is the absence of allergies, the presence of human immunodeficiency virus (HIV), pregnancy, and beta-blocker therapy.\textsuperscript{29,62}

Immunotherapy involves the subcutaneous injection of patient specific allergen extracts. The injections are given in order to increase tolerance to allergens so that environmental exposure to these allergens produces little or only mild symptoms. Injections are initially given once or twice a week, with the allergen concentration increasing with each injection.\textsuperscript{62} Standardized allergen vaccines are crucial for successful immunotherapy treatment. Currently available allergens available in the United States include: house dust mite (\textit{D}.}
farinae, D. pteronyssinus), cat hair, short ragweed, and grass pollens. Once
the maximum tolerated dose is reached, periodic maintenance injections are
given every week for the first year of treatment. Thereafter, injections are given
every two weeks until reaching a total of 3 years of immunotherapy. At this
point, many patients may discontinue treatment, although some patients may
continue therapy for up to five years. The American Academy of Allergy,
Asthma and Immunology recommends all immunotherapy injections be
performed in a physicians office or similar health care setting rather than at
home because of safety considerations (e.g., risk of anaphylaxis, puncture
wounds).

The efficacy of specific immunotherapy for pollen, ragweed, birch, house
dust mite, and cat dander has been documented in clinical trials. Moreover,
immunotherapy is the only therapeutic approach that provides long-term,
permanent relief for patients. Patients who are highly sensitive to allergens are
most likely to benefit. Typically after 3 to 5 years of appropriate
immunotherapy treatment, approximately 45% to 80% of patients can
discontinue therapy and still experience little to no allergy symptoms. While
only limited clinical data is available concerning the duration of immunotherapy
efficacy, researchers have suggested beneficial effects persist for up to six
years after discontinuing therapy. The cost of immunotherapy, per person-
year, in a health maintenance organization setting, for the treatment of allergic
rhinitis has been estimated to be four hundred and sixteen dollars.
2.4.5 Anti-IgE Therapy

A novel approach to treating allergic rhinitis, that is not yet available, is anti-IgE therapy. This new product causes substantial reductions in circulating IgE levels by complexing with unbound IgE thereby blocking this antibody before it binds to mast cells, basophils, and eosinophils. Genentech Inc., Novartis Pharmaceuticals Corporation, and Tanox, Inc. are developing Xoliar® (Anti-IgE Humanized Monoclonal Antibody) for allergic asthma and seasonal allergic rhinitis. Currently, Xoliar® is awaiting FDA approval, with FDA approval forecasted in 2002 or 2003.

Anti-IgE therapy has been tested as a treatment alternative for moderate to severe allergic asthma. Patients who received anti-IgE therapy every two weeks had greater improvements in their daily asthma symptom score and quality of life compared to those who received placebo. No significant differences in the incidence of side effects were reported among the groups. One concern, however, with this new therapy is the unknown effects on the immune system of long-term administration.

Anti-IgE has been tested in Europe for the treatment of pollen-induced seasonal allergic rhinitis. The reported clinical trial results showed that the drug was well tolerated and effective in preventing and controlling seasonal allergic rhinitis. At this time, the cost per dose has not been released. This novel therapeutic approach may change physician prescribing patterns and increases the number of different therapeutic options available to patients.
2.5 Quality of Life

2.5.1 Overview

Quality of life (QOL) is defined as the "subjective value a person places upon satisfaction with his or her life." Quality of life can be divided into four broad domains: physical and occupational function, psychological state, social interaction, and somatic sensation (i.e., the problems that the patients experience as a result of the symptoms themselves). Significant effort has been made in the past 15 years to investigate health related quality of life (HRQOL) in a variety of disease states. Specifically, HRQOL is the "value assigned to duration of life as modified by the impairments, physical, social and psychological functional states, perceptions and opportunities that are influenced by disease, injury, treatment, or policy". The use of QOL instruments in clinical trials or practice is vital when the goal of health care is not only to prolong lives but to also improve patients' quality of life.

There are two types of quality of life instruments: specific instruments that focus on problems associated with a particular condition, population, or specific function and generic instruments that provide a summary of quality of life and can be applied to all medical conditions. The most important benefit from using a generic quality of life instrument is the ability to compare across different medical conditions. However, because measurements are broad in scope, they may not include specific questions that are relevant to a particular disease state. Hence, it is with disease specific instruments that small, but important changes, within a disease state can be obtained. Unfortunately, the
use of such instruments does not allow for comparisons across conditions. The use of both generic and disease specific QOL instruments have been validated in allergic rhinitis patients.

2.5.2 Allergy Specific Quality of Life Instruments

Allergic rhinitis can cause several functional impairments such as nasal and ocular symptoms, sleep impairment, activity limitations, and emotional disturbances. Moreover, adults with allergic rhinitis can have condition-associated non-nasal symptoms such as poor concentration or headache. Hence, it is not surprising to find researchers investigating how allergic rhinitis affects quality of life. This is especially important because nasal symptoms are only moderately correlated with a rhinitis QOL questionnaire.

A recently developed quality of life instrument for allergic rhinitis is the Allergy Outcome Survey (AOS)(Table 2.15). The AOS developers constructed the survey to be a non-comprehensive evaluative instrument for symptoms (3 items) and medication usage (3 items) in allergic rhinitis. To date, use of the AOS has been published in only one clinical study to measure the impact of immunotherapy.
<table>
<thead>
<tr>
<th>QOL Instrument</th>
<th>Questions</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOS</td>
<td>-6 scored items -2 domains: symptoms &amp; medication usage</td>
<td>-Specific for allergic rhinitis -Contains medication usage section</td>
<td>-Not widely used -No comparative population data available</td>
<td>-AOS total score is moderately correlated with RQLQ total score -Recall time frame of 4 weeks, and 1 year</td>
</tr>
<tr>
<td>Mini-RQLQ</td>
<td>-14 items -5 domains: activity limitations, practical problems, nose symptoms, eye symptoms, &amp; other symptoms</td>
<td>-Specific for allergic rhinitis -RQLQ has 28 items, Mini-RQLQ has half that number</td>
<td>-Mini-RQLQ, unlike the RQLQ, does not allow patient to identify activities which are limited because of their condition</td>
<td>-High correlation between RQLQ and Mini-RQLQ -Recall time frame of 1 week</td>
</tr>
<tr>
<td>SF-8</td>
<td>-8 items -8 domains: general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, &amp; role emotional</td>
<td>-SF instruments versions highly recognized and validated -Comparative population data available</td>
<td>-Many not adequate on problems specific for allergic rhinitis</td>
<td>-High convergent correlation on concepts between SF-8 and SF-36 -Has 3 different recall versions (4 week, 1 week and 24 hours)</td>
</tr>
</tbody>
</table>

Table 2.15: Summary of quality of life instruments used in allergic rhinitis research.
A more common allergy related QOL instrument is the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) developed primarily by Juniper and Guyatt. The principle aim of the instrument development was to produce a questionnaire capable of measuring change over time in rhinoconjunctivitis patients. Originally a list of 91 health-related items concerning rhinoconjunctivitis was created. After item reduction, 28 questions covering seven different domains (sleep, non-hay-fever symptoms, practical problems, nasal problems, eye symptoms, activities, and emotions) were kept and included in the final questionnaire. Patients filling out the questionnaire are asked to respond to each item on a scale from 0 (not troubled) to 6 (extremely troubled). Thus, an overall high score indicates poor health status. The original RQLQ has been modified and now there are five different modified versions of the instrument. More specifically, they include: 1) Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S), 28 items), 2) Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ, 14 items), 3) Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ, 23 items), 4) Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (Adol-RQLQ, 25 items), and 5) Rhinitis Quality of Life Questionnaire (24 items).

2.5.3 Generic Quality of Life Instruments

A generic quality of life instrument that has been used in many different disease states and translated into numerous languages is the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). The SF-36 was originally derived from a health care insurance experiment conducted by the
Rand Corporation in the 1970's. This instrument was created to be used to measure QOL in a wide range of medical conditions and is able to estimate relative burden of minor versus serious medical and psychiatric conditions.\textsuperscript{107} The SF-36 uses 36 questions to assess 9 different health domains dealing with physical and mental conditions including 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) social functioning, 5) general mental health, 6) role limitations due to emotional problems, 7) vitality, 8) general health perceptions and 9) change in health.\textsuperscript{108,109} Responses to the SF-36 are tallied so that the higher score indicates a better health state. The raw scores are then adjusted to a scale ranging from 0 to 100. These transformed scores can then be compared to SF-36 scores the general US population. The SF-36 has been modified from the original version and now several other versions are available, specifically SF-6, SF-8, SF-12. The SF-8 and SF-12 both measure the same 8 domains as the SF-36, while the SF-6 does not include a measure of vitality.\textsuperscript{110}

Although the SF-36 is a generic instrument, it has been used to measure QOL in patients with allergic rhinitis.\textsuperscript{107,111} Bousquet et. al. performed a study where their goals were to verify that the SF-36 was sensitive enough to detect QOL impairments in patients with perennial allergic rhinitis.\textsuperscript{111} Healthy volunteers and allergic rhinitis patients in France, with moderately severe or severe symptoms, were recruited to complete the SF-36. The questionnaire was scored and analyzed using standard techniques. Patients in the rhinitis group had significantly lower scores in eight of nine domains (except change in
health) of the SF-36 when compared to the healthy controls. This was an important study because it was the first which showed that "perennial allergic rhinitis impairs the QOL of patients with moderate to severe rhinitis compared with healthy subjects".  

Meltzer et. al. carried out a United States population based study using the SF-36 and RQLQ on patients with nasal and/or ocular symptoms for \( \geq 31 \) days in the previous 12 months and randomly selected controls. When comparing the SF-36 health profiles between the subjects and controls, the study subjects had significantly lower scores than the controls on seven of nine domains (excluding role emotion and change in health). Moreover, the patients with nasal and/or ocular symptoms had lower mean values than to the general US population. On the allergic rhinitis specific questionnaire, RQLQ, the overall quality of life scores were significantly different between the study subjects and controls, 3.81 and 3.55 respectively. Again indicating that subjects with nasal and/or ocular symptoms had a poorer health status than the control group. Thus, research has shown individuals with allergic rhinitis suffer overall lower QOL because of their condition. This decrease in QOL has been shown to effect individuals in their home, work and school environment which can influence their ability to perform daily activities and impair their productivity.
2.6 Economic Impact

2.6.1 Overview

Research concerning the impact of allergic rhinitis has documented significant impact on QOL.97,98,107 However, researchers have also begun to investigate the impact of allergic rhinitis on productivity and the health care system.112-115

2.6.2 Productivity

A group of researchers from California used a population based survey to evaluate the impact of asthma and rhinitis on work loss and productivity.112 Study subjects were identified through random digit dialing limited to area codes in Northern California. A total of 300 individuals with either physician diagnosed asthma or rhinitis completed the entire interview. Among the 175 individuals in the rhinitis group, 65% reported hay fever and 72 of the 125 subjects with asthma indicated a physician diagnosis of rhinitis. Work loss and effectiveness were obtained for the four weeks prior to the telephone contact. In both groups lost work days in the past month due to illness was common (~20%). However, when focusing on decreased work productivity, significantly more rhinitis patients reported reduced job effectiveness (36%) compared to 19% of the asthmatics reporting reduced job effectiveness. Thus, the authors conclude that the “data suggest that rhinitis, which is more common than asthma, may actually have a bigger impact among those who stay in the labor force ‘working through’ their symptoms.”116
Notwithstanding the condition-associated impact on work productivity, the treatment of allergic rhinitis with first generation antihistamines has been shown to cause sedation and poor work performance.¹ Cockburn et. al. investigated the effect of antihistamines on worker productivity through the linking of a health claims database and daily output records of insurance claim processors.¹¹⁴ They found an 8% reduction in daily work output after workers received first generation sedating antihistamines; workers who received a non-sedating antihistamine were found to be 5% more productive. Thus, differences of up to 13% in productivity were found to be associated with the differential use of antihistamine products.

Ross estimated the cost associated with lost productivity and the use of first generation antihistamines in the United States.¹¹⁷ To calculate the cost of lost productivity due to first generation antihistamines, Ross 1) calculated the prevalence of allergic rhinitis in the workforce by type of employment using US Health Department of Health and Human Services survey data, 2) assumed 3.5 days/year/worker were lost to impaired productivity caused by the antihistamines (based upon McMenamin’s 1994 work), and 3) multiplied by the average daily wage by employment category. According to this algorithm, lost productivity from treating allergic rhinitis with sedating antihistamines was valued at $3.8 billion dollars annually (Table 2.16).

The productivity loss due to sedating antihistamines and allergic rhinitis was estimated using the 1995 National Health Interview Survey (NHIS) and other published surveys by Crystal-Peters.⁸ The NHIS is a annual, nationwide
household survey of health care utilization in the Unities States. Data collected concerning the general health of the household (e.g., acute and chronic conditions, restricted work days, and number of lost work days) were obtained through telephone interviews. Researchers analyzed the information obtained from this survey and found an estimated 3.5 million work days lost each year due to allergic rhinitis. Additionally, those who did go to work with this condition reported a total of nearly 3 million lost work days due to decreased productivity while on the job. Using wage data from the Bureau of Labor Statistics (BLS) with the lost work day estimates, the productivity associated with the diagnosis of allergic rhinitis was estimated to be $601 million in 1998 dollars. Costs associated with the use of sedating antihistamines were calculated under the following two assumptions: 1) 82% of allergy sufferers using some type of medication to treat their symptoms, of which 52% use sedating antihistamines and, 2) the average worker's productivity is diminished by an average of 25% for 14 work days per year. Under these assumptions and using the 1995 NHIS data, the estimated productivity loss associated with sedating antihistamine use was $4.6 billion (1998 dollars) per year.

Another way of measuring changes in productivity, besides interviews and analysis of claim data, is through the use of a questionnaire. Reilly has created the Work Productivity and Activity Impairment (WPAI) questionnaire to obtain quantitative values concerning the number of days and hours missed from work and the effect of a health condition on productivity. The WPAI has been used in a clinical trials concerning drug therapy treatment for allergic
Researchers in one clinical trial found an overall decrease in work impairment when comparing patients who took a second generation nonsedating antihistamine compared to those who took placebo. No significant differences, however, were found between the treatment group and the control group in the percentage of work time missed or in classroom impairment measures. Similarly another clinical trial using the WPAI to measure productivity in patients with allergic rhinitis found no effect on actual missed hours or sick days. This later study, however, did find a significant difference in self-rated productivity while at work.

The original WPAI was constructed as a generic productivity instrument (i.e., used to measure the effect of general health and symptom severity on work productivity and regular activities). Reilly subsequently created a nine item allergy specific WPAI instrument (WPAI-AS) thereby extending her previous work to a symptom specific condition. Reilly et al.'s work in instrument validation found that moderate to severe allergy symptoms were "associated with a high degree of impairment at work, at other activities, and in the classroom."  

2.6.3 Direct Costs

McMenamin investigated the indirect and direct costs associated with hay fever using two national surveys, the 1988 National Health Interview Survey National Health Interview Survey (NHIS) and the 1985 National Ambulatory Medical Care Survey (NAMCS). As described earlier, the NHIS is an annual, multi-purpose health survey conducted by the National Center for Health
Statistics (NCHS), Centers for Disease Control and Prevention (CDC). Data collected for the 1988 NHIS consisted of two main parts: 1) items concerning basic health and demographic information (Core questionnaire), and 2) one or more sets of questions (called Supplements) on current health topics. The NAMCS data on ambulatory medical care covers outpatient office visits for physicians engaged in direct patient care excluding specialties of anesthesiology, pathology, and radiology specialists. The NAMCS survey has been conducted in 1973-81, in 1985, and annually since 1989. Thus, both surveys were necessary to construct the allergic rhinitis cost analysis—NHIS data provided prevalence data while the NAMCS supplied the types of physician treatment to patients with hay fever.

Indirect cost included in this estimation included productivity loss due to hay fever in both the work force and at home. NHIS data on respondents with hay fever reported 3.4 million work days lost due to allergic rhinitis. Besides lost work days, data concerning reduced activity days were also included in the indirect cost analysis—at a value 25% of average wages. Costs of parental productivity losses from a child's school absences due to hay fever were not included. The total indirect cost of hay fever was reported to be over $600 million in 1990 dollars.
<table>
<thead>
<tr>
<th>Article</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMenamin, 1994&lt;sup&gt;18&lt;/sup&gt;</td>
<td><em>Indirect cost</em></td>
<td>$639 million&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Lost work days and reduced productivity at work or home</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Direct cost</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTC and prescription medication</td>
<td>$276 million&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Physician visits</td>
<td>$881 million&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><em>Total cost</em></td>
<td>$1.8 billion&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ross, 1996&lt;sup&gt;117&lt;/sup&gt;</td>
<td><em>Indirect cost</em></td>
<td>$3.8 billion&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Due to sedating antihistamines</td>
<td></td>
</tr>
<tr>
<td>Malone et al., 1997&lt;sup&gt;12&lt;/sup&gt;</td>
<td><em>Indirect cost</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lost work days</td>
<td>$37 million&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>School absenteeism</td>
<td>$13 million&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Restricted activity days</td>
<td>$17 million&lt;sup&gt;‡&lt;/sup&gt;</td>
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<tr>
<td></td>
<td><em>Direct costs</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prescription medication</td>
<td>$184 million&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Hospital and ER</td>
<td>$106 million&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Medical office or clinic visits</td>
<td>$418 million&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><em>Total cost</em></td>
<td>$775 million&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ray et al., 1999&lt;sup&gt;120&lt;/sup&gt;</td>
<td><em>Direct cost</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prescription medication</td>
<td>$1,498 million&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Hospital, surgery and ER</td>
<td>$2,133 million&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Physician office visits</td>
<td>$2,299 million&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><em>Total cost</em></td>
<td>$5.9 billion&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Crystal-Peters, et al, 2000&lt;sup&gt;8&lt;/sup&gt;</td>
<td><em>Indirect cost</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lost work days</td>
<td>$497 million&lt;sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Reduced productivity at work</td>
<td>$104 million&lt;sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Due to sedating antihistamines</td>
<td>$4.6 billion&lt;sup&gt;</td>
</tr>
<tr>
<td></td>
<td><em>Total cost</em></td>
<td>$5.2 billion&lt;sup&gt;</td>
</tr>
</tbody>
</table>

* In 1990 dollars  
† In 1994 dollars  
‡ In 1987 dollars  
§ In 1996 dollars  
|| In 1998 dollars  

Table 2.16: Cost of allergic rhinitis.
Direct costs of hay fever were primarily derived from the NAMCS data. Analysis of the 1985 NAMCS data suggest a total of 9.8 million visits for which the physician recorded a diagnosis of hay fever. Physician visits were valued at $70.70 and the value of time and travel costs to the physicians office was $15. Using these cost estimates, the annual cost of physician visits for hay fever was $881 million (1990 dollars). McMenamin, however, did not base the costs of hay fever specific medication on the NAMCS or NHIS data. Instead, medication cost estimates were derived from the United States National Health Accounts and totaled $276 million. Overall, the annual cost of hay fever was estimated to be $1.8 billion dollars.

Malone et al. estimated the indirect and direct costs of allergic rhinitis with 1987 National Medical Expenditure Survey (NMES) data. The 1987 NMES was a national probability sample that surveyed 14,000 households and over 36,000 non-institutionalized individuals in the United States. The NMES data included measures of medication use, ambulatory medical visits, emergency room and hospital visits, restricted activity days, and the number of days missed from work or school attributable to allergic rhinitis.

Malone compiled indirect costs of lost work productivity, school absenteeism, and restricted activity days. Lost work days were calculated for persons over the age of 18 years and were based on their average daily wage rate. Costs associated with school absenteeism were based the lost wages of a parent missing work to take care of a child with allergic rhinitis. Conservative estimates where made by assuming only children under 13 years of age
required parental care taking and by taking the lower of the two wage rates for dual income households. Restricted activity days were defined as times when the study subject was unable to engage in normal activities for at least half the day. Cost estimates were conservative and days lost were valued at 25% of the person's daily salary. All costs were reported in 1987 dollars.

A total of 811,000 lost work days were attributed to allergic rhinitis and 824,000 lost work days were attributed to parents staying home to care for their children with allergic rhinitis. The cost associated with these lost work days were $37 and $13 million, respectively. Over 4 million days were classified as restricted activity days attributable to allergic rhinitis. Productivity losses associated with these restricted days were estimated to be $17 million. Overall, total indirect cost totaled over $67 million.

The NMES data also provided medical care resource utilization and costs associated with the diagnosis and treatment of allergic rhinitis. Over 11 million allergy prescriptions accounted for $184 million. Sixteen million visits to medical providers for the treatment of allergic rhinitis were documented in the NMES data. The cost of these medical office and clinic visits total $418 million. Additional direct medical costs, represented by outpatient and emergency department visits, totaled over $106 million. Total direct cost of all the medical care resources used for allergic rhinitis was approximately $707 million. Thus, the sum of direct and indirect costs of allergic rhinitis was $775 million with over 90% of the total costs associated with direct medical care.
While McMenamin and Malone et al. report the cost of allergic rhinitis as a primary diagnosis, neither study estimated the cost of this disease when another comorbid condition was the primary diagnosis. Not accounting for the fact that allergic rhinitis is a predisposing factor for the development and exacerbation of such conditions as asthma and sinusitis may have underestimated the national costs associated with allergic rhinitis. Ray et al. investigated the health care costs of treating allergic rhinitis, as a primary or secondary diagnosis, using various national health survey data sets combined with the qualitative Delphi technique. Costs attributable to allergic rhinoconjunctivitis as a primary diagnosis totaled over $1.8 billion in 1996 dollars. This value is very comparable to costs reported by Malone et al. and McMenamin. Direct costs, however, totaled $5.9 billion when including both primary and secondary diagnoses of allergic rhinoconjunctivitis. More importantly, this large estimate would have been ever greater had productivity losses associated with this condition been included.

Thus, in the United States allergic rhinitis is associated with billions of dollars each year. Yet despite all the research reported on costs associated with allergic rhinitis, no known study has investigated the medical, prescription, or productivity costs associated with in vitro tested cases of allergic rhinitis. Hence, research is needed to ascertain the costs associated with an in vitro tested population.
2.7 Summary

Allergic rhinitis is a condition affecting millions of Americans each year. Researchers have found patients with this condition report a lower quality of life compared to healthy subjects. The direct and indirect economic impact of this disease in the United States totals billions of dollars each year.

Given the substantial costs associated with the diagnosis of allergic rhinitis, it is reasonable to confirm this diagnosis with *in vitro* or *in vivo* testing. This review of the allergy literature did not find any published studies investigating the effect of *in vitro* testing on patient quality of life or productivity. Nor were any articles identified that reported on direct or indirect costs associated with an *in vitro* tested population. The purpose of this dissertation, therefore, is to examine the association of allergic rhinitis *in vitro* test results with allergy related prescription and non-prescription medical charges, quality of life, and productivity. Moreover, estimates of disease prevalence, along with the sensitivity and specificity of two specific *in vitro* allergens are assessed.
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CHAPTER 3

METHODS

This chapter reviews the research design and methods of this study. The chapter begins by presenting the study design and instrument development. A description of the study population and data collection procedures is then provided. Thereafter, a brief review of statistical procedures is given. A list of the research questions, hypotheses, and planned analyses concludes the chapter.
3.1 Research Design

A cross-sectional observational design was used in this study. In a cross-sectional observational study, data is collected at a single point in time.\textsuperscript{1,2} Furthermore, a cross-sectional study entails a non-directional or backward design of the study population —after the subjects are selected from the study population, the participating study subjects are examined or questioned concerning their disease status or other variables of interest.\textsuperscript{3} The study was observational, rather an experimental, because no attempt was made to randomize subject selection or subject assignment into a treatment or control group. An observational study is useful when “it is not feasible to use controlled experimentation or to assign subjects at random to different procedures.”\textsuperscript{4}

Cross-sectional studies are especially practical for studying conditions which are quantitatively measured.\textsuperscript{5} Moreover, the cross-sectional design is particularly useful for describing characteristics of a target population and is often used by administrators to plan health services and programs. A disadvantage of a cross-sectional study is that such a study is not appropriate when investigating rare diseases or diseases with short durations. Further, this study design does not allow assessment of causal effects and only allows a researcher to investigate associations between variables.
3.2 Study Population

The target population for this study included enrollees in a Midwestern managed care organization who had in vitro testing for inhalant allergies. The managed care organization, the Health Alliance Plan (HAP), was located in Detroit, Michigan and serves more than 4,000 employer groups and more than 500,000 members. HAP’s origins date back to the mid-1950’s when industrial leaders in the Detroit area began seeking an alternative to traditional health insurance. In 1996, HAP expanded and affiliated with the Henry Ford Health System.

On January 1, 1998, HAP began using the Pharmacia Immuno-CAP system for in vitro allergy testing. A researcher at Henry Ford Health Systems, Suzan Kucukarslan, PhD, reviewed automated laboratory reports and provided a list of all patients, within the health plan, who had in vitro CAP inhalant allergy testing. Patients were included in the study if: 1) they had an in vitro inhalant test battery between January 1, 1998 and December 31, 2000 and were over 18 years in age and 2) were continuously enrolled in HAP in the year 2000. Pregnant patients were excluded because the safety of taking prescription allergy medication during pregnancy has not been established by the Food and Drug Administration (FDA). Additionally, general medical practice standards do not recommend beginning immunotherapy in a pregnant patient.
the study involved a census of all patients within the health plan that met inclusion criteria, no sample size calculations were required to establish a population sample.

Once all patients who had in vitro allergy testing where identified, medical and prescription insurance claims were extracted from the Henry Ford Health System databases. Laboratory information obtained included test date, test code description, numeric test results, non-numeric test results, and ordering physician. The inhalant in vitro allergy panel consisted of tests for the following twelve allergens: *Alternaria* Alternaria (mold), *Aspergillus fumigatus* (mold), cat, dog, cocklebur (weed), dust mite, plantain (weed), birch, maple, oak, bluegrass, and ragweed.

All data were reviewed and limited to only claims associated with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 477.0, 477.8, 477.9, indicating allergic rhinitis due to pollen, other allergen, or cause unspecified, respectively. Medical and prescription claims included all claims processed by Henry Ford Health System in the year 2000 coded under the diagnosis codes of 477.0, 477.8, or 477.9. Medical claims included such items as physician office visits, immunotherapy solutions, administration of immunotherapy injections, skin testing, and in vitro allergy testing. Prescription drug claims included allergy medication such as oral antihistamines, antihistamine eye drops, decongestants, and intranasal corticosteroids. Over-the-counter allergy medications taken by the study subjects were not captured by the insurance claims data base.
However, because the survey was sent in August, during the fall allergy season, claims data were reviewed for charges dated during the months of June, July, and August. To obtain an average monthly charge amount, the total monthly charges associated with allergy related medical services, each of the three months charges were summed and then divided by three. June and July where included in these calculations because of the possibility of patients visiting their physician prior to the actual onset of symptoms. Additionally, allergy-related charges accrued prior to June were not considered because it would further limit the number of study subjects who could be included in the medical cost analysis. Similarly, prescription allergy claims were reviewed for the months of June, July, and August. However, because data regarding actual days supply of medication was available, accurate estimates of prescription allergy charges associated with the month of August were calculated. For example, if a patient received a ninety day supply of an oral antihistamine in June, charges associated with the 31 days of August were included in the prescription cost analysis. Besides providing information concerning outpatient, hospital, and pharmacy claims, the database included patient demographic information (e.g., age, gender, and race).

After compiling medical and prescription claims data by patient medical record numbers, the names and postal-addresses of these enrollees were matched with the utilization records in order to complete the second phase of data collection —a ten page mailed questionnaire. Survey implementation followed the ‘Tailored Design Method’ outlined by Dillman. The Tailored
Design Method is a set of procedures to elicit high response rates when conducting self-administered surveys. This method emphasizes the importance of multiple mailings; a total of five contacts were made to the study subjects. The first four contacts were sent by first class mail to the study subjects, and the final contact was made to non-respondents in the form of a telephone call. In order to increase response rate and to appeal to our study subjects, all letterhead and outgoing envelopes were imprinted with the Henry Ford Health Systems logo.

A brief pre-notice letter was sent to the respondents a few days before the mailed questionnaire (Appendix A). The letter informed the study subjects of the purpose of the study, how they were selected to participate, and notified them of when they should expect to receive the survey. This first mailing was sent out the last week of July, 2001.

The second mailing consisted of a manila envelope with the health-system return logo and contained four items: cover letter, questionnaire, business class return envelope, and incentive (Appendix B). The cover letter solicited the subjects for their help, indicated how they were chosen to participate, and conveyed the reason for the study. The study subjects were informed they did not have to participate in the study. If they chose not to participate, however, they were asked to return the questionnaire unanswered. Furthermore, study subjects were assured that if they did complete the questionnaire, their responses would be kept confidential. The cover letter concluded by thanking the respondents for their time and provided information...
on who they should contact if they had any questions concerning the study.
Enclosures of a business return envelope and token of appreciation, in the form of a two dollar bill, were included to help increase response rate and to thank subjects in advance for their assistance. Additionally, the business return envelope was imprinted with an individual identification number to allow for the matching of survey respondents to their medical records. The survey packet was sent by first-class mail on August 6, 2001.

To remind individuals about the survey, a postcard follow-up was sent four days after mailing the original survey packet (Appendix C). The postcard was designed to notify study subjects concerning the mailed questionnaire and once again inform them how they were chosen to participate. Individuals who had already returned the survey were thanked and those who had not done so were asked return the survey today. The postcard concluded with an invitation to call for a replacement questionnaire if one was either not received or discarded.

The fourth contact was sent to only those study subjects who had not yet responded (Appendix D). This contact consisted of a cover letter, a replacement questionnaire, and a business class return envelope. The cover letter informed the recipient that their completed questionnaire had not yet been received and then explained why their response was important. The letter again stated that participation to complete the survey was voluntary and their responses would be kept confidential. Moreover, if the participants did not wish to participate, they were asked to return the survey unanswered. The letter
concluded by once again thanking them for their participation and informed them who they should contact if they had any questions. The replacement survey and business reply envelope were identical to previous mailings except that the imprinted individual identification number on the return envelope was positioned in the opposite corner of the mailing label so that a distinction could be made between those responding to the first versus the second mailing. This final mailed packet was sent two weeks after the first mailed survey, on August 21, 2001.

The fifth and final contact to non-respondents was through a telephone call (Appendix E). At this time, respondents were not asked to complete the survey on the telephone. Rather, the telephone contact was initiated to answer questions or concerns regarding the project and encourage them to complete and return the survey. The telephone calls were made from Henry Ford Hospital in Detroit, Michigan and were completed in two days (August 23 and August 24, 2001).

3.3 Instrument Development

Instrument development to measure severity of symptoms, quality of life, productivity, and demographics of patients who had in vitro allergy testing were developed from published and validated instruments, the allergy literature, input provided by department graduate students, and dissertation committee members. A panel knowledgeable in research methodology, consisting of Pharmaceutical Administration faculty and graduate students, assessed the
questionnaire prior to survey implementation. The allergy questionnaire consisted of the following topic areas: allergy symptom severity, quality of life, productivity, basic allergy information, and demographics (Appendix F).

After review by the panel, a preliminary version of the survey instrument was field tested in a small group of allergy sufferers. The purpose of the field test was to identify poorly worded or confusing questions and to identify the average time it took to complete the survey. Subjects for the field test were recruited by having the principal investigator sit in the waiting room of two different private allergy practices located in Columbus, Ohio during the month of March, 2001.

The field study instrument consisted of nine pages of questions printed on white paper and stapled in booklet form measuring 8.5 x 11”. Sixteen subjects were recruited from one allergy practice and 29 additional patients were obtained from the second physician practice. Of the 45 subjects who completed the questionnaire, 13 were male and 32 were female. The average time needed to complete the survey was 11 minutes, with a time range of completing the entire survey between 6 and 25 minutes. Overall, when asked pilot study subjects found the survey questions, responses, and directions understandable. Very little modification was necessary between the pilot survey and the final mailed version. Minor modifications included a spelling correction and the inclusion of a general quality of life instrument (SF-8).
Prior to study implementation, the research proposal and questionnaire were reviewed by the Behavioral and Social Sciences Institutional Review Board of The Ohio State University. The Institutional Review Board granted approval of the research project (Appendix G).

### 3.3.1 Basic Allergy Information and Demographics

Portions of the survey which did not include items from validated instruments consisted of questions concerning allergy history and patient demographics. Basic background history concerning the patient’s experience with allergies were included in the questionnaire (e.g., items 1-5, 53-58). Demographic variables age, race, and gender were not asked on the survey because that data was available in the claims database. Other demographic information not available in the claims database were included as items on the questionnaire. Such items included questions concerning employment status, occupational history, and educational background.

### 3.3.2 Allergy Symptom Severity

Allergy symptom severity questions were obtained from published work where the allergy symptom severity responses were used to screen patients in clinical trials. The allergy symptom severity questions were comprised of five items concerning the following five symptoms over the past week: sneezing, runny nose, itchy nose, palate and/or throat, itchy, watery and/or red eyes, and nasal congestion. Each symptom was rated by the patient on the
following 5-point scale: 0, absent (symptom not present); 1, mild (symptom present but not annoying or troublesome); 2, moderate (symptom frequently troublesome but not interfering with either normal daily activity or sleep); 3, severe (symptom sufficiently troublesome to interfere with normal daily activity or sleep) and 4, very severe (symptom so severe as to warrant an immediate visit to the physician). A total symptom score (TSS) can be calculated by summing the five individual symptom scores. Thus, the TSS may be used as a continuous measure, ranging from a low of zero to a high of 20. Alternatively, the TSS could be transformed into a discrete variable (e.g., mild versus severe allergy symptoms).

3.3.3 Quality of Life

One generic and two disease specific quality life instruments were included in the mailed questionnaire. The multipurpose short-form survey of health status (SF-8) 4-week recall version was the generic quality of life instrument included in the survey instrument. This generic instrument was selected because of its widespread use and its ability to be used for comparing specific populations to the general United States population. Although the SF-8 is available with three different versions, 24 hr-recall, 1-week recall, and 4-week recall, the later version was used because the U.S. population norms based on age and gender are currently only available for the 4-week recall version.
Although no known studies have used the SF-8 to measure quality of life in allergic rhinitis, the SF-36 has been used in researching outcomes in allergic rhinitis patients. \(^{10,15-18}\) The SF-8 was developed from the SF-36 and covers each of the eight different health concepts using a single item measure. Even though none of the SF-8 items are identical to those in the SF-36, each of SF-8 scales is scored on the same metric as the SF-36. Therefore, it is possible to compare and interpret results for one in relation to the other.\(^{13,19}\) Although the main advantage of the SF-8 is its shorter length, a disadvantage of scores estimated from this abbreviated version is that they are less precise than the SF-36.

The eight health concepts, in the order in which they appear in the questionnaire include: general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role emotional. Response categories differ across the scales, with five or six responses per item. SF-8 scoring options include an 8-dimension health profile, as well as summary measures of the physical and mental components of health. The scales are recorded so that a higher response value is indicative of better health. The SF-8 scales and summary measures are scored using norm-based scoring (NBS) algorithms.\(^{13}\) NBS methods were adopted to yield means of 50 and standard deviations of 10 in the general U.S. population. For example, the mean SF-8 social functioning scale score in the general U.S. population is 48.54. Scores above and below 48.54 are above and below average, respectively, in the
general U.S. population. Permission to use the SF-8 was obtained from QualityMetric Incorporated in April 2001 in the form of a single-user non-commercial license agreement.

The Mini-Rhinoconjunctivitis Quality of Life (Mini-RQLQ) was one of two disease specific quality of life instruments used in this study. The Mini-RQLQ is a shorter and simpler version of the original 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Although the original RQLQ was developed to assess functional impairments in adults with pollen-induced rhinoconjunctivitis, the instrument was later fully validated for patients with perennial rhinitis. Clinical trials and population-based studies have used either the RQLQ or Mini-RQLQ to evaluate quality of life in perennial or seasonal allergic rhinitis sufferers.

The RQLQ was developed to measure the functional (physical, emotional, and social) problems that are troublesome to adults with rhinoconjunctivitis. The Mini-RQLQ consists of 14 items covering five different areas, or domains: activity limitations (3 items), practical problems (2 items), nasal problems (3 items), eye symptoms (3 items), and other symptoms (3 items). Response categories for each of the items range from 0 (not troubled) to 6 (extremely troubled). Individual items within the Mini-RQLQ are equally weighted, with summary scores that are expressed as the mean score per item for each of the domains. The overall quality of life score is estimated from the mean score of all the items. Therefore, both the domain and overall quality of life scores range from zero to six.
In order to be able to judge whether a particular change in Mini-RQLQ score represents an important improvement or deterioration, or whether it represents a trivial change, Juniper and colleagues investigated the minimal important difference in RQLQ scores. In this case, minimal important difference was defined as the "smallest difference in score in the domain of interest that patients perceive as beneficial that would mandate, in the absence of troublesome side effects and excess cost, a change in the patient's management."²⁶ For the rhinoconjunctivitis quality of life questionnaire, an average change in score of 0.5 per item per domain and for the overall quality of life score has been shown to be the minimal important difference.²⁷ Permission to use the Mini-RQLQ for this dissertation work was obtained from Elizabeth E. Juniper in January 2001.

The second allergic rhinitis specific outcomes survey which was included in the mailed instrument was the Allergy Outcome Survey (AOS). The AOS is a patient-based condition-specific survey that is brief, reliable, and useful for evaluating patients with allergic rhinitis. Because the AOS was only recently developed, data concerning the AOS has only been reported in two known publications.¹⁸,²⁸ Despite the limited number of studies using the AOS, the instrument has been validated and has been found to be reliable.²⁸
The AOS is intended as an non-comprehensive evaluative instrument for symptoms and medication usage in allergic rhinitis. The survey consists of a total of seven items, with each item consisting of five different response options. Scoring procedures include separate measures of symptoms and medication usage, as well as a total AOS score.

All items are asked so that higher number responses indicate greater severity of allergy. However, when computing the symptom and medication subscale, all response choices must be recoded so that high scores indicate little or no allergy symptoms or little or no allergy medication use, respectively. The allergy symptom subscale is obtained from responses to the first three questions on the survey, whereas the medication usage subscale is derived from the next three questions. All six questions are used to calculate the AOS total subscale. The last question from the survey is not included in the scoring algorithm.

The final step in scoring the AOS requires transforming each subscale score to a standardized score. The transformation procedure changes all the subscales into a percentage of the total possible points that could be scored (Equation 3.1).

\[
\text{Transformed} = \left( \frac{\text{Sum Recoded Value} - \text{Lowest Possible Recoded Sum}}{\text{Subscale Possible Recoded Range}} \right) \times 100
\]

Equation 3.1: Subscale Transformation Algorithm for the AOS
Once transformed, higher values on the allergy symptoms and medication usage scale indicate little or no allergy symptoms or little or no allergy medication use, respectively. Similarly, higher transformed total AOS values denote higher levels of functioning for an allergic rhinitis patient. Permission to use the Allergy Outcome Survey was obtained from Jacquelynnne Corey and Richard Gliklich in January 2001.

3.3.4 Productivity

Productivity of the study sample was assessed using the Work Productivity and Activity Impairment Questionnaire: Allergy Specific (WPAI-AS). The Work Productivity and Impairment (WPAI) instrument is a questionnaire used to measure the effect of general health and symptom severity on work productivity and regular activities. The WPAI-AS is an allergy specific version of the WPAI. The instrument has been tested and found to be both valid and reliable. Clinical trials have used the WPAI-AS to investigate the effect allergy medication has on daily activities and work productivity.

The WPAI-AS is comprised of nine questions which assess the effect allergies have on an individual’s ability to work, attend classes, and perform regular daily activities within the past seven days. Domains measuring impairment in the workplace include percent time missed due to allergies and percent impairment while working due to allergies. WPAI-AS outcomes are usually expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. Overall work impairment scores,
consisting of actual lost days of work and impairment while at work due to allergies, can be estimated for each subject who is employed for pay at the time of filling out the survey. Margaret Reilly gave permission to use the WPAI-AS for this research in January, 2001.

### 3.4 Description of Statistical Procedures

This section contains a brief review of statistical procedures which were used in this study. General statistical procedures used included Bayesian statistics, linear regression, logistic regression, and one-sample t tests.

#### 3.4.1 Bayesian Statistics

Bayesian analysis is a mathematical technique used to update a prior state of knowledge with current data. Bayes' theorem is the basic tool of Bayesian analysis and provides the basic mathematical formula for this technique (Equation 3.2).

$$p(\theta | y) = \frac{p(y | \theta) p(\theta)}{p(y)}$$

Equation 3.2: Bayes' Theorem

Where $\theta$ is the unknown parameter, $y$ is the observed data, $p(\theta)$ is the belief about $\theta$ before seeing the current data, $p(y)$ is the probability of the observed data, and $p(\theta | y)$ is the posterior density of $\theta$.  

105
Bayes' theorem consists of three different components: prior belief, the likelihood function, and posterior belief. Prior beliefs concerning the unknown parameter of interest are obtained from previous studies or expert opinion. Prior information about an unknown parameter is assessed as a probability distribution, which informs the researcher the extent to which a belief can be attached to the values of the unknown parameter before observing the current data. The likelihood function is a model of how the current data relate to the unknown parameter. This function is an estimate of the probability of observing the outcome of interest for any given level of the parameter. Lastly, the posterior belief is obtained from the prior belief and the data currently available. Bayes' rule is used to estimate the posterior probability distribution of the parameter of interest based on the prior distribution and the likelihood function. Thus, the posterior distribution contains updated beliefs about the parameters of interest after taking into account the information provided by the currently available data.

Bayesian statistics can be especially useful when evaluating the sensitivities and specificities of a diagnostic test when no gold standard is available. Comparing a diagnostic test result to another imperfect comparator result causes artificially low estimates of diagnostic performance. Moreover, when a gold standard is not available, it is often tempting to assume that one of the available testing methods is error free. However, when assuming one test is error free, such an assumption biases the estimated error rates in the test comparator.
Joseph et al. have demonstrated how Bayesian methods can be used to estimate disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. The following is a review of Joseph’s approach to estimate disease prevalence and other parameters of diagnostic testing.

Although diagnostic tests can be used to interpret disease severity through use of quantitative measurements (e.g., iron levels to diagnosis severity of anemia, glucose levels to evaluate degree of hyperglycemia), often such tests are used to provide a positive or negative presence of a condition (e.g., pregnancy, chlamydia). Given that diagnostic test results can be considered in terms of two possible outcomes, positive or negative, the assumption is that the proportions of positive test results is considered as $p$. Because there are only two possible outcomes, prior information concerning the diagnostic test is in the form of a beta density ($\alpha, B$) is assumed (Equation 3.3).

$$\text{Beta (} \alpha, B \text{) density } \propto p^{(\alpha-1)} (1 - p)^{(B-1)}$$

Equation 3.3: Beta Density

The beta family of distribution is characterized by a positive density region ranging from 0 to 1 and requires the specification of $\alpha$ and $B$ to distinguish its shape. Alpha ($\alpha$) and beta ($B$) values of the beta distribution are calculated through previous knowledge of the mean and standard deviation of parameter of interest (e.g., sensitivity, specificity) (Equation 3.4 and 3.5):
\[ \alpha = \frac{(\mu (\sigma + \mu^2 - \mu))}{\sigma} \]

Equation 3.4: Alpha of Beta Density

\[ B = \frac{((\mu - 1) (\sigma + \mu^2 - \mu))}{\sigma} \]

Equation 3.5: Beta of Beta Density

where \( \mu \) is the mean and \( \sigma \) is the variance.

Whereas the beta distribution consists of the prior information, the likelihood function contains the data from the current study. Assuming a sample of \( n \) patients and there are \( s \) positive test results and \( f \) number of negative test results, then \( s + f = n \). Because there are only two possible outcomes, \( s \) or \( n \), and \( p \) is the proportion of positive tests, the likelihood of \( p \) is a binomial distribution (Equation 3.6).

\[ \text{Likelihood of } p \propto p^s (1-p)^f \]

Equation 3.6: Likelihood of Proportion of Positive Tests
By Bayes theorem, the posterior distribution is proportional to the product of the likelihood function and the prior distribution (Equation 3.7). Thus, because the prior distribution is in the form of a beta distribution and the likelihood function is a binomial distribution, the posterior distribution is also a beta distribution.

\[ p^s (1 - p)^f p^{(\alpha - 1)} (1 - p)^{(\beta - 1)} = p^{(\alpha + s - 1)} (1 - p)^{(\beta + f - 1)} \]

Equation 3.7: Posterior Distribution

However, actual estimation of the posterior distribution in the absence of a gold standard is analytically intractable and necessitates the use of the Gibbs sampler. The Gibbs sampler is a technique for sequentially sampling from a collection of conditional distributions. In diagnostic testing, the Gibbs sampler algorithm is used to obtain random samples of sensitivity and specificity pairs. These random samples are then used to obtain the means, standard deviations, and interval estimates for each parameter of interest.

Joseph et. al. uses the equations and methods described above to estimate the population prevalence, along with the sensitivity and specificity of a test. Moreover, using the statistical techniques outlined in his article, positive and negative predictive values can also be estimated. Positive predictive value is defined as the proportion of individuals screened positive by the test who actually have the disease. Negative predictive value is defined as the proportion of individuals screened negative by the test who do not have the
disease. Positive and negative predictive values are dependent upon the
disease prevalence within the population and thus are useful when one is
interested in the likelihood of a correct classification of individual subjects within
a specified population.\textsuperscript{39} Whereas positive and negative predictive values are
influenced by the prevalence rate of the disease, sensitivity and specificity are
not.\textsuperscript{43} S-Plus programming for Bayesian estimation of disease prevalence and
parameters of diagnostic tests (Appendix H).

3.4.2 Linear Regression

Regression analysis is a statistical method which is used to examine the
relationship between a single dependent variable (Y) and one or more independent
variables (X). The existence of a statistical relationship between the dependent and
independent variable(s) does not imply any causal pattern between the variables,
rather, only provides information concerning the association between the
independent and dependent variables. When only one independent variable is
used in the model, this technique is called simple linear regression and can be
stated as an equation of a line (Equation 3.1):

\[ Y = \beta_0 + \beta_1 X + e \]

\textit{Equation 3.1}
When more than one independent variable is used to predict a single dependent variable, the statistical method is called multiple linear regression.\textsuperscript{3} Multiple linear regression can be expressed as (Equation 3.2):

\[
Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + e
\]

Equation 3.2

where \(Y\) is the dependent variable, \(\beta_0\) is the intercept, \(\beta\) is a parameter or regression coefficient, \(X\) is the independent or explanatory variable, and \(e\) is the random error or residual term. A regression coefficient for a given independent variable represents the average change in \(Y\) that is associated with a one-unit change in that variable, while holding all other independent variables constant.\textsuperscript{44} The intercept is a constant value which is included in the model to improve the accuracy of prediction. The portion of the score on a dependent variable not explained by the independent variables is the error or residual term.

Regression models are used to predict values of the dependent variable from known values of the independent variables. Regression coefficients and intercept values are calculated to minimize errors in predicting the dependent variable. To minimize the errors in predicting the dependent variable, the principle of least squares is used. The principles of least squares is a method...
in which the predicted dependent variable is calculated so that the sum of the
squared errors of prediction is minimized. The resulting combination of the
intercept, coefficients, and error term produces the best fit line for the data.

The proportion of the variance in the dependent variable explained by
the linear combination of the independent variables is expressed as the
coefficient of determination (R^2). The assumptions of linear regression models
include linearity, constant variance of the residuals (i.e., no heteroscedasticity),
and normally distributed residuals.

3.4.3 Logistic Regression

Logistic regression is similar to linear regression but is suited for models
where the dependent variable is binary or dichotomous. An important
difference between the two statistical procedures is that logistic regression uses
the binomial, not normal, distribution for the error terms. Additionally, the
conditional mean of the regression equation must be formulated to always be
some number between 0 and 1. Whereas the least squares method is used to
estimate parameters in linear regression, the maximum likelihood method is
used to estimate the parameters of the model in logistic regression. The same
procedures used to guide linear regression analysis are used in building a
logistic regression model.
3.4.4 One-sample T-Test

The one-sample t-test is used to test whether the mean of a single sample differs from a hypothesized population value. The formula for the one-sample t-test is:

\[ t = \frac{X_s - X_p}{s / n^{1/2}} \]

Equation 3.3

where \( X_s \) is the sample mean, \( X_p \) is the population mean, \( s \) is the standard deviation, and \( n \) is the total number of cases. The one sample t-test follows the Student's t distribution and has \( n - 1 \) degrees of freedom. The null hypothesis for the one-sample t-test is that the data were sampled from a population with a known mean value.

3.5 Data Analysis

The data analysis section begins by first providing study definitions concerning each research variable. Thereafter, the study objectives are provided along with null hypotheses, if appropriate. Following each study objective, data analysis plans are provided.
3.5.1 Definition of Terms for Study Variables

Prevalence: The number of existing cases of a disease or health condition in a population at some designated time.⁴³

Sensitivity: The probability of a positive test result given the person has the disease.⁴⁹

Specificity: The probability of a negative test result given the person does not have the disease.⁴⁹

Allergy specific medical charges: Medical claims obtained included all medical related claims processed by Henry Ford Health System in the year 2000. All data were reviewed and limited to only claims associated with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 477.0, 477.8, 477.9, indicating allergic rhinitis due to pollen, other allergen, or cause unspecified, respectively.⁸ Moreover, medical charge data were calculated to obtain a monthly average charge amount based upon charges for the months of June, July, and August of 2000. Thus, an average monthly charge value was used to reflect allergy specific medical charges.
Allergy specific prescription charges: Prescription claims obtained included all allergy related prescription drug claims processed by Henry Ford Health System in the year 2000. Prescription charge data were calculated to obtain August's charge amount based upon claims indicating days supplied for the months of June, July, and August. Adjusted August prescription allergy claims data were used to evaluate allergy prescription charges.

Overall allergy work impairment: A dichotomous variable defined as having had no work impairment or having had some allergy work impairment as classified by the WPAI-AS work impairment questions. The overall allergy work impairment measure includes lost days from work, as well as allergy-related impairment experienced while at work.

Physical composite SF-8 scores: Physical summary scores obtained from the SF-8 survey, where higher values indicate better general quality of life status.

Mental composite SF-8 scores: Mental summary scores obtained from the SF-8 survey, where higher values indicate better general quality of life status.

Age: Age of the study subject as of January 1, 1998.

Gender: Gender of the subject.
Race: Classified as either White or Other.

In vitro test status: Categorized as either having a fall allergy or not having a fall allergy. Subjects were classified as having a fall allergy if they had a positive test result for any of the following allergens: Alternaria Alternaria (mold), Aspergillus fumigatus (mold), cat, dog, cocklebur (weed), dust mite (Dermatophagoide Farinae), plantain (weed), and common ragweed. Subjects who were not allergic to any tested allergen or allergic to only spring allergens (i.e., birch, maple, oak, and bluegrass) were classified as not having a fall allergy. The decision to classify specific allergies as occurring during the fall season were based upon the allergy literature and consultation with an allergist. The research focused on fall allergies versus no allergies or spring allergies because the survey was sent during the fall allergy season.

Severity of symptoms: The total symptom score (TSS) calculated by summing the five individual symptom scores. The TSS may range from a low of zero to a high of 20, with higher values indicating more severe allergy symptoms.

Medication use: The medication usage value from the Allergy Outcome Survey. Values range from 0 to 100, with higher values indicating little or no allergy medication use.
Overall Mini-RQLQ scores: Overall quality of life score is estimated from the mean score of all the items of the Mini-RQLQ. The overall Mini-RQLQ score ranges from zero to six, with higher values indicating greater quality of life impairment.

3.5.2 Study Objectives and Research Questions

3.5.3 Objective 1

To estimate the disease prevalence and the parameters of in vitro allergy tests in the absence of a gold standard.

Research Question 1.1: What is the prevalence of allergy to specific allergies (i.e., cat, short ragweed) in this managed care population?

Research Question 1.2: What are the sensitivity and specificity estimates of specific allergens (i.e., cat, short ragweed)?

Analysis: Analysis of both research questions was performed using statistical programming developed by Joseph et al.40

3.5.4 Objective 2:

To examine variables associated with allergic rhinitis-linked prescription and non-prescription medical charges.
Research Question 2.1: Are the following characteristics significant explanatory variables of allergy specific non-prescription medical charges: in vitro allergy test status, age, gender, race, and severity of symptoms?

Null Hypothesis 2.1: Allergy specific medical charges are not associated with the following variables:

   a) in vitro allergy test status
   b) age
   c) gender
   d) race
   e) severity of symptoms.

Research Questions 2.2: Are the following characteristics significant explanatory variables of allergy specific prescription charges: in vitro allergy test status, age, gender, race, and severity of symptoms?

Null Hypothesis 2.2: Allergy prescription charges are not associated with the following variables:

   a) in vitro allergy test status
   b) age
   c) gender
   d) race
   e) severity of symptoms.

Analysis: For hypothesis 2.1, an allergy specific medical charges model will be estimated with allergy specific medical charges as the dependent variable and with in vitro allergy test status, age, gender, race, and severity of symptoms.
considered as independent variables. For hypothesis 2.2, an allergy specific prescription charges model will be estimated with allergy specific prescription charges as the dependent variable and with in vitro allergy test status, age, gender, race, and severity of symptoms considered as independent variables.

3.5.5 Objective 3:

To examine the variables associated with overall work impairment as defined by the Allergy Specific Work Productivity and Activity Impairment (WPAI-AS).

Research Question 3.1: Are the following variables significant explanatory variables of overall allergy work impairment: in vitro allergy test status, age, gender, race, medication use, severity of symptoms?

Null Hypothesis 3.1: Overall allergy work impairment is not associated with the following variables:

a) in vitro test status
b) age
c) gender
d) race
e) medication use
f) severity of symptoms
Analysis: For hypothesis 3.1, an allergy work impairment model will be estimated with overall allergy work impairment as the dependent variable and with in vitro allergy test status, age, gender, race, medication use, severity of symptoms considered as independent variables.

3.5.6 Objective 4:

To evaluate the quality of life of patients who received in vitro testing for allergic rhinitis using generic and allergy specific quality of life instruments.

Research Question 4.1: Are the following characteristics significant explanatory variables of overall Mini-RQLQ scores: in vitro allergy test status, age, gender, race, medication use, severity of symptoms?

Null Hypothesis 4.1: Overall Mini-RQLQ scores is not associated with the following variables:

a) in vitro test status
b) age
c) gender
d) race
e) medication use
f) severity of symptoms.
Analysis: For hypothesis 4.1, an allergy-specific quality of life model will be estimated with overall Mini-RQLQ scores as the dependent variable and with in vitro allergy test status, age, gender, race, medication use, severity of symptoms considered as independent variables.

Research Question 4.2: What are the differences in SF-8 quality of life scores among patients who have had in vitro testing and the general United States population?

Null Hypothesis 4.2.1: Compared to U.S. norms, patients who had in vitro allergy testing have the same overall physical composite SF-8 scores.

Null Hypothesis 4.2.2: Compared to U.S. norms, patients who had in vitro allergy testing have the same overall mental composite SF-8 scores.

Analysis: For hypothesis 4.2.1 and 4.2.2, survey physical and mental mean composite scores will be compared to U.S. population physical and mental mean composite scores. All SF-8 scores will be adjusted for age and gender differences.

3.6 Conclusion

A cross-sectional observational study design was used to study outcomes of patients in a Midwestern managed care organization who had in vitro testing for inhalant allergies. Study outcomes of interest included: 1) prevalence of allergy to specific allergens, 2) sensitivity and specificity of specific allergens, 3) allergy-specific medical charges, 4) allergy-specific
prescription charges, 5) allergy-specific work impairment, 6) allergy-specific
quality of life, and 7) generic quality of life. In order to measure the outcomes of
interest, data were collect through the linking of medical claims, prescription
claims, and a mailed survey. Data variables, research questions, hypotheses,
and data analysis plans were provided and defined within this chapter. The
next chapter contains information concerning the study population and data
analysis results.
REFERENCES FOR CHAPTER 3


17. Bagenstose SE, Bernstein JA. Treatment of Chronic Rhinitis by an Allergy Specialist Improves Quality of Life Outcomes. Annals of Allergy, Asthma, & Immunology 1999; 83:524-528.


20. Juniper EF, Thompson AK, Ferrie PJ, Roberts J. Development and Validation of the Mini Rhino-Conjunctivitis Quality of Life Questionnaire (Mini-RQLQ). Journal of Allergy and Clinical Immunology 1999; 103:653


CHAPTER 4

RESULTS

This chapter is divided into two main sections. The first section describes the study sample and the survey respondents. The second section provides the results of the research questions. A brief discussion of the results follows each statistical analysis. Data analyses were performed using Statistical Package for the Social Sciences Version 10.1 (SPSS), Version 10, R (a free version of S-Plus), and STATA Version 7.0.
4.1 Sample Description

Patients medical and prescription charge records were obtained from the Health Alliance Plan (HAP) databases if 1) they had an \textit{in vitro} inhalant test battery between January 1, 1998 and December, 2000 and, 2) were continuously enrolled in HAP in the year 2000. Of the total of 338 patients who met the inclusion criteria, eight potential subjects were excluded because they were pregnant during the 2000 calendar year. Returned surveys were collected for five weeks, dating from August 10\textsuperscript{th} to September 14\textsuperscript{th}, 2001. A total of 232 subjects returned surveys, yielding a 70\% response rate. More specifically, the first mailing of the survey packet resulted in 186 returned questionnaires (56\%) and a total of 46 surveys (14\%) were returned from the second survey mailing (Appendix I). Overall, 72 out of the 232 (31\%) returned surveys were received after the telephone call reminders were placed. However, because the second survey was mailed one or two days prior to the telephone call reminder, it is not possible to differentiate the response rate effect between the telephone call reminders and the second survey. Of the 232 subjects, 170 returned useable surveys (51\% response rate of total subjects). Thus, a total of 160 subjects either did not return the survey (n = 98) or did not return usable questionnaires (n = 62). Reasons for unusable surveys included refusal to participate and partial completion of the questionnaire.

The majority of enrolled subjects and survey respondents were female (Table 4.1). Additionally, most subjects were Caucasian. The average age of the enrolled study subject was forty-six, with an age range between eighteen and eighty-four. The mean age of survey respondents who returned useable responses
was forty-five, with an age range of eighteen to eighty-four. Other subjects, defined as non-respondents and study subjects who returned unusable surveys, had a mean age of forty-seven, with an age range between nineteen and eighty-four. Hereafter, survey respondents who returned useable surveys will be referred to as simply ‘respondents’, and those who did not respond or who return unusable surveys will be referred to as ‘other subjects’.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Demographics</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled subjects</td>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 330)</td>
<td>Male</td>
<td>93</td>
<td>28.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>237</td>
<td>71.2</td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>206</td>
<td>62.4</td>
</tr>
<tr>
<td></td>
<td>Non-Caucasian</td>
<td>124</td>
<td>37.6</td>
</tr>
<tr>
<td>Respondents of Usable Surveys</td>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 170)</td>
<td>Male</td>
<td>47</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>123</td>
<td>72.4</td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>111</td>
<td>65.3</td>
</tr>
<tr>
<td></td>
<td>Non-Caucasian</td>
<td>59</td>
<td>34.7</td>
</tr>
<tr>
<td>Other Subjects</td>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 160)</td>
<td>Male</td>
<td>46</td>
<td>28.7</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>114</td>
<td>71.3</td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>95</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>Non-Caucasian</td>
<td>65</td>
<td>40.6</td>
</tr>
</tbody>
</table>

Table 4.1: Subjects gender and race.
A comparison of usable survey respondents versus other study subjects found no significant difference in age, gender, and race between the study subjects who returned useable surveys and those who did not (Tables 4.2 to Table 4.4). An independent samples t-test was used for the continuous variable age, and chi-square tests were used to compare the two groups on dichotomous variables. The majority (43%) of respondents had some college or technical school training and had a managerial or professional occupation (Table 4.5). At the time of the survey, 75% of the patients indicated they were currently experiencing allergies, with the average patient having experienced allergies for 18.6 years (SD = 14.9 years, median = 15 years) (Table 4.6). Although all the patients had in vitro testing for allergies only 58% of the respondents recalled having had a blood test for allergies. Moreover, 75% of the study subjects report having had skin testing for allergies, with 72% of the group stating that they had immunotherapy treatment. Of those who reported having had immunotherapy treatment, 28% stated that they were currently be treated for their allergies by immunotherapy.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Demographic</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usable Surveys Respondents</td>
<td>Age</td>
<td>45</td>
<td>11.6</td>
<td>0.10</td>
</tr>
<tr>
<td>Other Subjects</td>
<td></td>
<td>47</td>
<td>13.7</td>
<td></td>
</tr>
</tbody>
</table>

Independent Samples T-test, df = 328, n = 330

Table 4.2: Mean age of subjects.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Female (Percent)</th>
<th>Male (Percent)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usable Surveys Respondents</td>
<td>114 (48.1%)</td>
<td>46 (49.5%)</td>
<td>160</td>
</tr>
<tr>
<td>Other Subjects</td>
<td>123 (51.9%)</td>
<td>47 (50.5%)</td>
<td>170</td>
</tr>
<tr>
<td>Total</td>
<td>237</td>
<td>93</td>
<td>330</td>
</tr>
</tbody>
</table>

Chi-square = 0.050, df = 1, p-value = 0.824, n = 330

Table 4.3 Subjects by gender.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Caucasian (Percent)</th>
<th>Other (Percent)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usable Surveys Respondents</td>
<td>111 (53.9%)</td>
<td>59 (47.6%)</td>
<td>170</td>
</tr>
<tr>
<td>Other Subjects</td>
<td>95 (46.1%)</td>
<td>65 (52.4%)</td>
<td>160</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td>124</td>
<td>330</td>
</tr>
</tbody>
</table>

Chi-square = 1.231, df = 1, p-value = 0.267, n = 330

Table 4.4 Subjects by race.
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Some high school</td>
<td>7</td>
<td>4.1</td>
</tr>
<tr>
<td>High school graduate</td>
<td>32</td>
<td>18.8</td>
</tr>
<tr>
<td>Some college or technical school</td>
<td>73</td>
<td>42.9</td>
</tr>
<tr>
<td>College graduate</td>
<td>58</td>
<td>34.1</td>
</tr>
<tr>
<td><strong>Occupation</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managerial, professional</td>
<td>56</td>
<td>36.6</td>
</tr>
<tr>
<td>Technical, sales, and administrative support</td>
<td>26</td>
<td>16.9</td>
</tr>
<tr>
<td>Service occupations</td>
<td>17</td>
<td>11.1</td>
</tr>
<tr>
<td>Precision production, craft, and repair</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Operators, fabricators, labors</td>
<td>9</td>
<td>5.9</td>
</tr>
<tr>
<td>Farming, forestry, and fishing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Student</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Other</td>
<td>36</td>
<td>23.5</td>
</tr>
</tbody>
</table>

*Occupation frequency and percent based on the 153 out of 170 survey respondents who answered the occupation question.

Table 4.5 Respondents by education and occupation.
<table>
<thead>
<tr>
<th>Allergy-related experience</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently experiencing allergies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>127</td>
<td>74.7</td>
</tr>
<tr>
<td>No</td>
<td>39</td>
<td>22.9</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>2.4</td>
</tr>
<tr>
<td>Primarily manages allergies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family doctor</td>
<td>55</td>
<td>32.4</td>
</tr>
<tr>
<td>Allergist</td>
<td>40</td>
<td>23.5</td>
</tr>
<tr>
<td>Myself</td>
<td>49</td>
<td>28.8</td>
</tr>
<tr>
<td>A friend or family member</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other doctor or health care professional</td>
<td>8</td>
<td>4.7</td>
</tr>
<tr>
<td>Missing</td>
<td>18</td>
<td>10.6</td>
</tr>
<tr>
<td>Ever had skin tests for allergies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>127</td>
<td>74.7</td>
</tr>
<tr>
<td>No</td>
<td>39</td>
<td>22.9</td>
</tr>
<tr>
<td>Don’t know</td>
<td>4</td>
<td>2.4</td>
</tr>
<tr>
<td>Ever had blood test for allergies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98</td>
<td>57.6</td>
</tr>
<tr>
<td>No</td>
<td>54</td>
<td>31.8</td>
</tr>
<tr>
<td>Don’t know</td>
<td>18</td>
<td>10.6</td>
</tr>
<tr>
<td>Ever had immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>123</td>
<td>72.4</td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>25.3</td>
</tr>
<tr>
<td>Don’t know</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Currently being treated by immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>27.9</td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>69.8</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Table 4.6 Respondents allergy-related experience.

4.2 Research Questions and Analyses

4.2.1 Objective 1

The first study objective was to estimate the disease prevalence and the parameters of \textit{in vitro} allergy tests in the absence of a gold standard. More specifically, the two research questions were presented to address this first objective.
Research Question 1.1: What is the prevalence of allergy to specific allergies (i.e., cat, short ragweed) in this managed care population?

Research Question 1.2: What are the sensitivity and specificity estimates of specific allergens (i.e., cat, short ragweed)?

Using data the Bayesian data analysis framework described by Joseph et. al. to analyze diagnostic tests in the absence of a gold standard, a review of the published allergy literature provided prior information concerning the sensitivity and specificity of cat and common ragweed diagnostic tests.1 These particular allergy tests were chosen because a range of values for sensitivity and specificity of other tested allergens in the study population were not found in the literature. In vitro cat allergy sensitivity compared to skin testing has been reported to range from 0.63 to 0.82, while specificity ranges from 0.91 to 0.96.2,3 In vitro common allergy sensitivity compared to skin testing has been reported to range from 0.29 to 0.69, while specificity ranges from 0.97 to 1.00.2,4 Using the available published data, prior information in the form of a beta density was calculated for the sensitivity and specificity of each diagnostic test (Table 4.7). Because all of the study subjects (n = 330) had in vitro allergy testing, all study subjects were included in this analysis. The in vitro CAP allergy laboratory results for the study population had sixty-six and sixty-five patients testing positive for cat and short ragweed allergies, respectively (Table 4.8).
<table>
<thead>
<tr>
<th>Allergen</th>
<th>Range (%)</th>
<th>Mean (%) (SD)*</th>
<th>Beta Coefficients (α, β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat Sensitivity</td>
<td>63-82</td>
<td>72.5 (3.17)</td>
<td>(143.12, 54.29)</td>
</tr>
<tr>
<td>Cat Specificity</td>
<td>91-96</td>
<td>93.5 (0.83)</td>
<td>(823.93, 57.28)</td>
</tr>
<tr>
<td>Short Ragweed</td>
<td>29-69</td>
<td>49.0 (6.67)</td>
<td>(27.03, 28.14)</td>
</tr>
<tr>
<td>Short Ragweed</td>
<td>97-100</td>
<td>98.5 (0.50)</td>
<td>(581.15, 8.85)</td>
</tr>
</tbody>
</table>

* Using the equation: Standard deviation x 6 = Range
† A uniform density over the range [0,1] (α = 1, β = 1) was used for the prior distribution for the prevalence of cat and short ragweed allergies in the managed care population.

Table 4.7: Probability ranges and coefficients of the beta prior densities for the test parameters.

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Positive Test Results</th>
<th>Negative Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>66</td>
<td>264</td>
</tr>
<tr>
<td>Short Ragweed</td>
<td>65</td>
<td>265</td>
</tr>
</tbody>
</table>

Table 4.8: Results of *in vitro* testing in a managed care population.

Given the prior information and the current data concerning *in vitro* allergy testing for cat and common ragweed, estimations for the prior distributions was possible. By Bayes theorem, the posterior distribution is proportional to the product of the likelihood function and the prior distribution. Joseph et al. programming codes were used to estimate the parameters of interest (Appendix J). Data analysis required knowledge of the following: 1) the total number of positive and negative outcomes in the population tested by 136.
the \textit{in vitro} allergy test, 2) a starting value for the unobserved number of true positives which is arbitrary but has to be an integer less than the total number of positive outcomes in the population tested, 3) a starting value for the unobserved number of false negatives which is arbitrary but has to be an integer less than the total number of negative outcome in the tested population, 4) starting values for the sensitivity, specificity, and prevalence of the test which need to be between the value of 0 and 1, 5) the first and second coefficient of the Beta prior distribution for the prevalence, 6) the first and second coefficient of the Beta prior distribution for the sensitivity, 7) the first and second coefficient of the Beta prior distribution for the specificity, 8) the number of Gibbs iterations, and 9) the number of Gibbs iterations to throw away.

Posterior parameter estimates for cat and common ragweed prevalence in this population were calculated to be 20.7% and 39.5%, respectively. In this case, the final 95 percent posterior credible interval for the prevalence of cat allergies was 13.9% to 28.3%, where credible interval is defined as being 95% certain that the true values lie inside the stated limits. The final 95 percent posterior credible interval for the prevalence of short ragweed allergies was 27.6% to 59.3% (Table 4.9). The sensitivity and specificity of \textit{in vitro} allergy testing for cat is 72.4% and 93.5%. The sensitivity and specificity of \textit{in vitro} allergy testing for short ragweed was estimated to be 47.9% and 98.5%, respectively.
<table>
<thead>
<tr>
<th>Allergen</th>
<th>Parameter</th>
<th>Median</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>Prevalence</td>
<td>0.207</td>
<td>0.139 - 0.283</td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>0.724</td>
<td>0.660 - 0.783</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>0.935</td>
<td>0.918 - 0.950</td>
</tr>
<tr>
<td>Short Ragweed</td>
<td>Prevalence</td>
<td>0.395</td>
<td>0.276 - 0.593</td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>0.479</td>
<td>0.348 - 0.610</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>0.985</td>
<td>0.973 - 0.993</td>
</tr>
</tbody>
</table>

Table 4.9: Posterior medians and lower and upper limits of the posterior 95% credible intervals for the prevalence, sensitivities, specificities for cat and short ragweed in vitro diagnostic tests.

Additional analyses concerning the positive predictive value of cat diagnostic testing indicate 74.6% of individuals screened positive with the test actually have an allergic reaction to cat (Table 4.10). Similarly, 95.7% of the individuals screen positive with the diagnostic test actually have short ragweed allergy. The negative predictive value of cat allergen indicates 92.9% of the individuals diagnosed as not allergic do not have the disease. Likewise, 74.4% of the individuals who were diagnosed as not allergic to short ragweed do not have allergies to this weed.
<table>
<thead>
<tr>
<th>Allergen</th>
<th>Parameter</th>
<th>Median</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>Positive Predictive Value</td>
<td>0.746</td>
<td>0.616 – 0.831</td>
</tr>
<tr>
<td></td>
<td>Negative Predictive Value</td>
<td>0.929</td>
<td>0.886 – 0.958</td>
</tr>
<tr>
<td>Short Ragweed</td>
<td>Positive Predictive Value</td>
<td>0.957</td>
<td>0.908 – 0.983</td>
</tr>
<tr>
<td></td>
<td>Negative Predictive Value</td>
<td>0.744</td>
<td>0.517 – 0.862</td>
</tr>
</tbody>
</table>

Table 4.10: Posterior medians and lower and upper limits of the posterior 95% credible intervals for the positive and negative predictive value for cat and short ragweed *in vitro* diagnostic tests.

4.2.2 Objective 2:

The second study objective was to examine variables associated with allergic rhinitis-linked prescription and non-prescription medical charges. Two research questions were proposed to answer this second objective.

Research Question 2.1: Are the following characteristics significant explanatory variables of allergy specific non-prescription medical charges: *in vitro* allergy test status, age, gender, race, and severity of symptoms?
Null Hypothesis 2.1: Allergy specific medical charges are not associated with the following variables:

a) *in vitro* allergy test status
b) age
c) gender
d) race
e) severity of symptoms.

Allergy specific non-prescription medical charges were assessed by calculating an allergy-specific average monthly charge amount for the months of June, July, and August of the year 2000. Because independent variables (i.e., medication use, severity of symptoms) included in the regression equation required information obtained from the survey, those subjects who returned usable surveys were included in the analysis. Moreover, only patients who were *in vitro* tested before May 31, 2000 were included in this analysis—to capture the effect of *in vitro* allergy testing. Thus, the final sample size for the allergy-specific non-prescription medical charge analysis included 139 individuals.

Original data analysis plans for this research question consisted of analyzing the data by simple linear regression. However, upon review of the non-prescription medical charge data, a number of subjects where found to have accumulated no non-prescription medical charges during the specified time period (Table 4.11). Reassessment of the data analysis plan was required
because of the large number of zero charge values and necessitated the use of logistic (comparing subjects with no non-prescription medical charges versus those with some non-prescription medical charges) instead of linear regression. Non-prescription medical charges ranged from $0 to $117.33.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Variable</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n = 139)</td>
<td>Allergy specific non-prescription medical charges</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Charge Amount</td>
<td>122</td>
<td>87.8</td>
</tr>
<tr>
<td></td>
<td>Some Charge Amount</td>
<td>17</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Table 4.11: Characteristics of non-prescription medical charges.

The first step in model building entailed entering each independent variable into the model separately. After examining each of the individual explanatory variables, none of the explanatory variables were found to be significant (p > 0.15). Because none of the explanatory variables was independently significant, no further model building was performed. Forward selection and backward elimination logistic regression model estimations was also performed to verify the model building process and resulted in no significant independent variables. None of the independent variables were significantly associated with non-prescription medical charges, therefore, the null hypothesis failed to be rejected.
Research Question 2.2: Are the following characteristics significant explanatory variables of allergy specific prescription charges: *in vitro* allergy test status, age, gender, race, and severity of symptoms?

Null Hypothesis 2.2: Allergy prescription charges are not associated with the following variables:

a) *in vitro* allergy test status

b) age

c) gender

d) race

e) severity of symptoms.

Allergy specific prescription medical charges were assessed by obtaining August 2000 prescription charge amount based upon prescription claims for the month of August. Because some patients may receive greater than a thirty day supply at one time, prescription drug claims for June and July were examined and any charges which could be attributed to taking prescription medications during the month of August were also included in the final charge amount. Independent variables (i.e., medication use, severity of symptoms) included in the regression equation required information obtained from the survey, therefore, those subjects who returned usable surveys were included in the analysis. Moreover, only patients who were *in vitro* tested before May 31, 2000 were included in this analysis—to capture the effect of *in vitro* allergy testing. Thus, the final sample size for the allergy-specific non-prescription medical charge analysis included 139 individuals.
Original data analysis plans for this research question consisted of analyzing the data by simple linear regression. However, upon review of the prescription medication charge data, a number of subjects where found to have incurred no prescription medical charges during the specified time period (Table 4.12). Prescription medical charges ranged from $0 to $176.86. Reassessment of the data analysis plan was required because of the large number of zero charge values, and thus polychotomous logistic regression was used instead of linear regression.

<table>
<thead>
<tr>
<th>Subjects Variable</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Allergy specific prescription charges</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 139)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Charge Amount</td>
<td>79</td>
<td>56.8</td>
</tr>
<tr>
<td>Some Charge Amount</td>
<td>60</td>
<td>43.2</td>
</tr>
</tbody>
</table>

Table 4.12: Characteristics of allergy specific prescription charges.

Polychotomous logistic regression is used when there are more than two outcome variables. To estimate a polychotomous logistic regression, prescription medical charges were divided into three groups: $0 group, $1-$63 group, and $63-$177 group. The $0 group was created as the comparator, while the other two groups were created by evenly dividing the remaining individuals into two groups containing thirty subjects each.
The first step in the polychotomous model building entailed entering each independent variable into the model separately. After examining each of the individual explanatory variables, none of the explanatory variables were found to be significant ($p > 0.05$) in either of the two reported logits. Because none of the explanatory variables were independently significant, no further polychotomous model building was performed. Thus, logistic regression was used with prescription charge data was divided into variables, no charge amount and some charge amount.

The first step in model building entailed entering each independent variable into the model separately. After examining each of the individual explanatory variables, none of the explanatory variables were found to be significant ($p > 0.15$). Because none of the explanatory variables was independently significant, no further model building was performed. Forward selection and backward elimination logistic regression model estimations were also performed to verify the model building process and resulted no significant independent variables. None of the independent variables were significantly associated with prescription medical charges, therefore, the null hypothesis failed to be rejected.
4.2.3 Objective 3:

To examine the variables associated with overall work impairment as defined by the Allergy Specific Work Productivity and Activity Impairment (WPAI-AS). One research question was investigated to answer this objective.

Research Question 3.1: Are the following characteristics significant explanatory variables of overall allergy work impairment: in vitro allergy test status, age, gender, race, medication use, severity of symptoms?

Null Hypothesis 3.1: Overall allergy work impairment is not associated with the following variables:

a) in vitro test status
b) age
c) gender
d) race
e) medication use
f) severity of symptoms

Productivity of the study sample was assessed using the Work Productivity and Activity Impairment Questionnaire: Allergy Specific (WPAI-AS). Because independent variables (i.e., medication use, severity of symptoms) included in the regression equation required information obtained from the survey, those subjects who completed usable surveys were included in the analysis. In order to assure that patients were in vitro tested before
completing the survey, only patients who were *in vitro* tested before May 31, 2000 were included in this analysis. The sample was further limited to include those patients who were currently working for pay (n = 101).

Percent overall work impairment—higher values indicating greater impairment and less productivity due to allergies—was calculated from the study sample. Percent overall work impairment ranged from 0 to 100% with a mean of 15 and a standard deviation of 24.4. Domains measured in overall work impairment in the workplace include percent time missed due to allergies and percent impairment while working due to allergies. Percent overall allergy work impairment was transformed into a dichotomous variable—no allergy work impairment or some allergy work impairment—because of the large number of subjects who experienced no allergy-related work impairment (Table 4.13).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Variable</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working subjects</td>
<td>Overall work impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 101)</td>
<td>None</td>
<td>56</td>
<td>55.4</td>
</tr>
<tr>
<td></td>
<td>Some</td>
<td>45</td>
<td>44.6</td>
</tr>
</tbody>
</table>

Table 4.13: Characteristics of overall allergy work impairment.

The first step in model building was to enter each independent variable into the model separately. Thereafter, forward and backward selection logistic regression model estimations were performed. Both forward and backward
selection models eliminated the same variables from the model (i.e., in vitro test status, age, race, and medication use). Gender and symptom severity remained in the model (Table 4.14). The presence of an effect modifier (gender x symptom severity) was examined, but not found to be significant (p > 0.10). Moreover, symptom severity was found to be linear in the logit. Thus, the odds of males experiencing overall allergy work impairment is 0.33 as likely or 67% less likely than the odds of females experiencing overall allergy work impairment. For every one point increase in symptom severity, productivity impairment increased by a factor of 1.16. A Hosmer-Lemeshow goodness-of-fit test was performed because this analysis was a predictive modeling procedure. The Hosmer-Lemeshow goodness-of-fit statistic using 9 groups was not significant in the final model (df(7), p = 0.55) — indicating the model fits.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Value</th>
<th>Standard Error of Beta</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI for Adjusted Odds Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (reference = female)</td>
<td>-1.124</td>
<td>0.508</td>
<td>0.325</td>
<td>(0.120, 0.881)</td>
<td>0.03</td>
</tr>
<tr>
<td>Symptom Severity</td>
<td>0.150</td>
<td>0.058</td>
<td>1.161</td>
<td>(1.036, 1.302)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 4.14: Final model of overall allergy work impairment.
In summary, the null hypothesis of no association between the dependent variable allergy work impairment and the independent variables gender and symptom severity was rejected. Furthermore, the null hypothesis of no association between the dependent variable allergy work impairment and the independent variables *in vitro* test status, age, and race failed to be rejected.

4.2.4 Objective 4: The last objective of the study was to examine the generic and allergy specific quality of life of patients who received *in vitro* allergy testing. Allergy specific quality of life was assessed through the use of the Mini-RQLQ, while generic quality of life was assessed using the SF-8. More specifically, two research questions were presented to address this last study objective.

Research Question 4.1: Are the following characteristics significant explanatory variables of overall Mini-RQLQ scores: *in vitro* allergy test status, age, gender, race, medication use, and severity of symptoms?

Null Hypothesis 4.1: Overall Mini-RQLQ scores is not associated with the following variables:

   a) *in vitro* test status
   b) age
   c) gender
   d) race
   e) medication use
   f) severity of symptoms.
Overall Mini-RQLQ score was calculated for each of the study subjects who returned usable survey responses. Overall Mini-RQLQ ranged from 0 to 5.6, with a mean of 1.78 and a standard deviation of 1.18. Only patients who returned usable surveys and were *in vitro* tested before May 31, 2000 were included in this analysis—to capture the effect of *in vitro* allergy testing. Thus, the final sample size for the overall mini-RQLQ analysis included 139 individuals.

Simple linear regression analysis was used to assess the association between the overall Mini-RQLQ scores and the independent variables. As a first step in model building, each of the independent variables were independently added to a regression model. Two of the explanatory variables, *in vitro* test status and age, were not significant predictors (p > 0.20) of overall Mini-RQLQ scores and were not considered in further model building. All four of the remaining variables were added into a regression model. Subsequently, each of the variables was removed from the model and tested to see if the variable significantly added to the overall model. Gender, race, *in vitro* test status, and medication use, alone and in combination, did not significantly add to the model. Hence, the final regression model contained only the variable symptom severity (adjusted $R^2 = 0.470$) (Table 4.15). Thus with every one unit increase in symptom severity, overall Mini-RQLQ increases by 0.201. Stated differently, as symptom severity increases, allergy specific quality of life decreases.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Value</th>
<th>Standard Error of Beta</th>
<th>95% CI for Beta</th>
<th>T-value</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Severity</td>
<td>0.201</td>
<td>0.018</td>
<td>(0.165, 0.236)</td>
<td>11.099</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 4.15: Final model of overall Mini-RQLQ scores.

In summary, the null hypothesis of no association between the dependent variable overall allergy work impairment and the independent variable symptom severity was rejected. Furthermore, the null hypothesis of no association between the dependent variable allergy work impairment and the independent variables *in vitro* test status, age, gender, race, and medication use failed to be rejected.

**Research Question 4.2:** What are the differences in SF-8 quality of life scores among patients who have had *in vitro* allergy testing and the general United States population?

**Null Hypothesis 4.2.1:** Compared to US norms, patients who had *in vitro* allergy testing have the same overall physical composite SF-8 scores.

**Null Hypothesis 4.2.2:** Compared to US norms, patients who had *in vitro* allergy testing have the same overall mental composite SF-8 scores.

SF-8 item and summary scores were calculated for all subjects who returned useable surveys (n = 170) (Table 4.16). After adjusting for age and gender, the allergy sample had lower scores on all SF-8 scales except the role physical item (Figure 4.1).
<table>
<thead>
<tr>
<th>Subject</th>
<th>SF-8 Items</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondents</td>
<td>General Health (GH)</td>
<td>47.5</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Physical Functioning (PF)</td>
<td>46.2</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Role Physical (RP)</td>
<td>50.0</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>Bodily Pain (BP)</td>
<td>48.4</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Vitality (VT)</td>
<td>47.7</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>Social Functioning (SF)</td>
<td>46.6</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Mental Health (MH)</td>
<td>45.7</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Role Emotion (RE)</td>
<td>45.5</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Physical Composite Score (PCS)</td>
<td>47.6</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>Mental Composite Score (MCS)</td>
<td>45.8</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Table 4.16: SF-8 scores for *in vitro* allergy tested sample.

![Graph showing SF-8 scores](image)

**Figure 4.1:** *In vitro* allergy tested sample versus U.S. population on individual SF-8 items.
Physical and mental composite scores in the \textit{in vitro} allergy tested group were lower than published U.S. population norms (Figure 4.2). Difference scores between the age and gender adjusted \textit{in vitro} allergy group composite scores and the U.S. population norms were calculated and tested for statistical significance. The null hypothesis of equal overall physical composite SF-8 scores between the study sample and the US population failed to be rejected (Table 4.17). However, there was a statistically significant difference in the mental composite measure. Thus, the null hypothesis of equal overall mental composite SF-8 scores between the study sample and the US population was rejected.

Figure 4.2: \textit{In vitro} allergy tested sample versus U.S. population on composite SF-8 items.
<table>
<thead>
<tr>
<th>Subject</th>
<th>SF-8 Items</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent</td>
<td>Physical Summary Difference Score</td>
<td>-1.04</td>
<td>10.1</td>
<td>0.182</td>
</tr>
<tr>
<td></td>
<td>Mental Summary Difference Score</td>
<td>-2.66</td>
<td>11.3</td>
<td>0.003</td>
</tr>
</tbody>
</table>

One Sample T-test, df = 169, n = 170

Table 4.17: SF-8 summary difference scores adjusted for gender and age.
REFERENCES FOR CHAPTER 4


CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

The purpose of this final chapter is to discuss and summarize the results of the study and to provide recommendations for future research. First, the chapter begins with a general overview of the study. Then, the results of the research questions are answered and discussed. In the third section, the limitations of the study are discussed. Lastly, recommendations for further research are presented.
5.1 Study Overview

5.1.1 Background

Although allergic rhinitis and associated co-morbid conditions are seldom life threatening, their impact on patient quality of life and the economy is substantial. In 1987, an estimated 39 million persons suffered from allergic rhinitis in the United States. Researchers estimate the direct costs of allergic rhinitis in the United States to be over $1 billion annually. Moreover, associated time loss from work or school may significantly and adversely affect productivity. Therefore, considerable direct medical and indirect costs of allergic rhinitis represent enormous personal and social economic burdens.

Studies have suggested as few as half of the estimated 40 million suffers in the United States have a true immuno-modulated condition. Notwithstanding current practice guidelines stressing the importance of adequate patient assessment including medical history and physical exam, one of the goals of this research is to investigate the sensitivity and specificity of certain in vitro tested allergens. Additionally, this research explored the medical charges, quality of life, productivity, of an in vitro tested population in a managed care environment.

5.1.2 Study Methods

A cross-sectional observational design was used in this study. The population for this study included enrollees in a Midwestern managed care organization who had in vitro testing for inhalant allergies. Patients over
eighteen years of age who had in vitro inhalant test battery between January 1, 1998 and December 31, 2000 and were continuously enrolled in the managed care health plan during the year 2000 were enrolled in the study. Pregnant patients were excluded because of the following reasons: 1) the safety of taking prescription allergy medication during pregnancy has not been established by the Food and Drug Administration (FDA), and 2) general medical practice standards do not recommend beginning immunotherapy in a pregnant patient. Study subjects included all individuals who met the study enrollment criteria.

A researcher at the managed care organization reviewed automated laboratory reports and provided a list of all patients, within the health plan, who met the study criteria. Once all patients who had in vitro allergy testing where identified, medical and prescription insurance claims were extracted from the health care databases. Laboratory information obtained included test date, test code description, numeric test results, and non-numeric test results. Medical claims included allergy-related charges such items as physician office visits, immunotherapy injections, skin testing, and in vitro allergy testing. Prescription drug claims included allergy medications such as antihistamines, decongestants, and intranasal corticosteroids. Medical and prescription charge claims were estimated from the data for the month of August 2000.

After compiling medical and prescription claims data by patient medical record numbers, the names and postal-addresses of these enrollees were linked with the claims records in order to complete the second phase of data.
collection, namely a ten page mailed questionnaire. Survey implementation began the last week of July 2001 and followed the 'Tailored Design Method' outlined by Dillman. This method emphasizes the importance of multiple mailings; a total of five contacts were made to the study subjects. The first four contacts were sent by first class mail to the study subjects, and the final contact was made to non-respondents in the form of a telephone call.

Of the total of 338 patients who met the inclusion criteria, eight potential subjects were excluded because they were pregnant during the 2000 calendar year. Surveys were returned to the researchers from early August 2001 to mid-September 2001. A total of 232 subjects returned surveys, yielding a 70% response rate. Among the 232 subjects, 170 returned useable surveys (51% of total eligible subjects) for analysis. A comparison of usable survey respondents versus those study subjects who failed to respond or returned unusable surveys found no significant difference in age, gender, and race between the two groups.

5.2 Research Questions and Discussion

5.2.1 Objective 1: Analysis Results and Discussion

The first study objective was to estimate the disease prevalence and the parameters of in vitro allergy tests in the absence of a gold standard. More specifically, the two research questions were presented to address this first objective.
Research Question 1.1: What is the prevalence of allergy to specific allergies (i.e., cat, short ragweed) in this managed care population?

Research Question 1.2: What are the sensitivity and specificity estimates of specific allergens (i.e., cat, short ragweed)?

Data collected in this managed care population, along with prior reported sensitivities and specificities of in vitro allergy testing, were used to produce updated estimates of test parameters. The parameter estimates for cat and common ragweed prevalence in this managed care tested population were calculated to be 20.7% (credible interval: 13.9% - 28.3%) and 39.5% (credible interval: 27.6% - 59.3%), respectively. The sensitivity and specificity of in vitro allergy testing for cat were calculated to be 72.4% (credible interval: 66.0% - 78.3%) and 93.5% (credible interval: 91.8% - 95.0%). The sensitivity and specificity of in vitro allergy testing for short ragweed were estimated to be 47.9% (credible interval: 34.8% - 61.0%) and 98.5% (credible interval: 34.8% - 61.0%), respectively.

Although other authors in the allergy field have published the sensitivity and specificity of in vitro allergy testing for cat and common ragweed, no known authors have used Bayesian methods to calculate in vitro allergy test parameters. Calculation of in vitro allergy testing parameters has always required a direct comparator, such as skin testing or intradermal testing. The
use of Bayesian statistics allowed for the use of prior published information concerning the sensitivity and specificity of in vitro testing for cat and common ragweed to be used in lieu of a direct comparator in this study.

Moreover, the use of the Joseph et al. Bayesian technique to calculate diagnostic testing parameters allowed for the calculation of not only point estimates, but credible intervals. The interpretation of these credible intervals is that, given the prior information and the data, we are 95% certain that the true values lie inside these limits. Prior publications concerning the sensitivity and specificity of certain in vitro allergy tests only established point estimates. Furthermore, although this study examined just two in vitro tested allergens, parameters for other in vitro tested allergens (e.g., dog, dust mite, molds) can be estimated using this same technique.

Health care providers should give consideration to test accuracy when choosing to perform in vitro allergy tests. The accuracy of test results depends on the sensitivity and specificity of the particular test. Inaccurate test results can lead to false positive or false negative results resulting in inappropriate therapy. Because allergic rhinitis has a substantial impact on patient outcomes, physicians should give careful consideration to patients who present with allergic rhinitis symptoms. According to the American Academy of Allergy, Asthma, and Immunology (AAAAI), specific allergen avoidance and treatment measures should be based on positive history and diagnostic testing. Traditional pathways emphasize the prominent role of allergist referral and skin testing, however, the use of serum specific IgE testing by family practitioners
has been acknowledged as a tool useful in identifying specific allergen sensitivities and helpful in focusing further investigation and referral. Moreover, although skin prick testing for aeroallergens could be performed by the general practitioner, it requires training in technique and more importantly, in interpretation of the results.

The availability of in vitro specific IgE measurement may provide physicians, especially family practitioners, the opportunity to have more detailed information concerning a patient's condition. This is especially important considering that approximately 50% of patients with rhinitis do not have allergic rhinitis. Multiple in vitro specific IgE measurements can be completed from a single blood sample, a great benefit when testing for allergies in all patients, especially children.

Although a test may have many characteristics which determine its performance in a clinical setting (e.g., reliability, safety, convenience), one of the most important factors in evaluating its usefulness is determining how well the test works in identifying disease. The most common way of describing a test's ability to identify a disease state is through the use of sensitivity and specificity. Thus, if in vitro allergy testing is to be used in medical practice, accurate estimates of the tests' sensitivities and specificities are vital to enable the practitioner to correctly identify the presence or absence of a specific allergy.
5.2.2 Objective 2: Analysis Results and Discussion

The second study objective was to examine variables associated with allergic rhinitis-linked prescription and non-prescription medical charges. Two research questions were proposed to answer this second objective.

Research Question 2.1: Are the following characteristics significant explanatory variables of allergy specific non-prescription medical charges: *in vitro* allergy test status, age, gender, race, and severity of symptoms?

Research Questions 2.2: Are the following characteristics significant explanatory variables of allergy specific prescription charges: *in vitro* allergy test status, age, gender, race, and severity of symptoms?

Logistic regression analysis was used to evaluate the association between medical and prescription August 2000 charges and other patients' background information who had *in vitro* allergy testing. Original data analysis plans were to use a simple multiple regression to estimate the model, however, the large number of zero charge values made logistic regression the more appropriate modeling technique. Thus, we categorized the charge amounts into two groups, those with no charge amounts and those who had charges in the insurance database. Model building for non-prescription medical and prescription charges found none of the explanatory variables (*in vitro* allergy test status, age, gender, race, and severity of symptoms) significant at a p < 0.05 level. Because this analysis was exploratory in nature, it may be argued...
that a more lenient level of significance should be examined with these models. However, even when the alpha level was \( p = 0.10 \), none of the variables were found to be significant.

Additional analysis with the total allergy-specific medical charges, defined as the sum of non-prescription medical and prescription charges, found over half of the patients did not have any allergy-related charges for the month of August 2000 (Table 5.1). Total allergy-specific medical charges ranged from $0 to $222, with approximately 90% of the individuals having charges totaling less than $100. A logistic regression model was estimated using the allergy specific total medical charges and the same independent variables described above. Once again, none of the explanatory variables was significantly associated with allergy-specific total medical charges.

<table>
<thead>
<tr>
<th>Subjects (n = 139)</th>
<th>Variable</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>Allergy-specific total medical charges</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Charge Amount</td>
<td>71</td>
<td>51.1</td>
</tr>
<tr>
<td></td>
<td>Some Charge Amount</td>
<td>68</td>
<td>48.2</td>
</tr>
</tbody>
</table>

Table 5.1: Characteristics of total allergy-specific medical charges.

Although none of the independent variables were found to be significantly associated with the charge data, an interesting finding is the non-significance of *in vitro* test status. Logically, one would believe that the presence or absence allergic rhinitis would be a predictor of allergy-related
medical or prescription charge data. Lack of significant association of the variables could be attributed to the limited number of tested in vitro allergens and thus created a misclassification error. Classification of in vitro test status was based on whether or not a patient was allergic to a fall allergen or a perennial allergen. The allergens tested were limited to a total of 12 different allergens common to the Detroit area. It is possible that subjects could have been allergic to an allergen not on the in vitro allergen panel and thereby been classified as not being allergic when they truly were.

An alternative explanation of the lack of significance between in vitro test status and medical charges is the possibility of failure to include other important factors into the model. For example, the first line of therapy for allergic rhinitis is environmental control. It is possible that some subjects who were classified as allergic made substantial changes to their environment in the hopes of alleviating their symptoms (e.g., removal of a pet, placement of air filters, removal of carpet). These environmental changes could have considerably impacted their symptoms and hereby decreased their medical and prescription charge amounts within the managed care company. Thus, future studies attempting to explain allergy-specific charge values should consider including a variable within their model which would help control for environmental conditions.

National studies have estimated the direct medical cost of allergic rhinitis to be millions of dollars each year.\textsuperscript{3,5} Yet despite all the research reported on costs associated with allergic rhinitis, no known published study has
investigated the medical or prescription charges associated with in vitro tested cases of allergic rhinitis. Hence, research was needed to ascertain the medical and prescription charges associated or not associated with an in vitro tested population.

5.2.3 Objective 3:

The third objective of the study was to examine the variables associated with overall work impairment as defined by the Allergy Specific Work Productivity and Activity Impairment (WPAI-AS). One research question was investigated to answer this objective.

Research Question 3.1: Are the following characteristics significant explanatory variables of overall allergy work impairment: in vitro allergy test status, age, gender, race, medication use, severity of symptoms?

Logistic regression analysis was used to evaluate the association between overall allergy work impairment and various descriptive variables of patients who had in vitro allergy testing. Model building for overall allergy work impairment found gender and symptom severity significantly associated with work impairment. More specifically, the odds of males experiencing overall allergy work impairment was 67% less likely than the odds of females experiencing any impairment. Additionally, for every one point increase in
symptom severity, productivity impairment increased by a factor of 1.8. The remaining explanatory variables—*in vitro* allergy test status, age, race and medication use—were not significant in the final model.

The final overall allergy impairment model results indicate a positive association between symptom severity and work impairment. This result is not unexpected because as a patient’s symptoms worsen, one would logically expect work productivity to decrease. Whereas one could expect and explain an association between symptom severity and overall allergy work impairment, the association between gender and overall allergy work impairment is not as easily explained. A review of the literature found no evidence supporting greater allergy work impairment in females when compared to males. Thus, it is important to realize that the reported association between gender and overall allergy work impairment may be spurious. Further research evaluating the relationship between gender and allergy work impairment should investigated prior to reporting the findings in this study.

Although worker productivity has no direct economic impact on health care providers, research investigating the impact health conditions have on productivity has gained the attention of those typically outside the health care realm. Employers, in their role as health care payers, have become interested in health care benefit decisions. Moreover, employees themselves are interested in how medical treatment will potentially effect not only their quality of life but productivity. Productivity may be especially important when studying allergic rhinitis because of the documented agents, namely first generation anti-
histamines, which have been reported to cause sedation. Thus, investigating the effect allergic rhinitis has on productivity is important because it has been shown to affect employees' ability to attend work or perform while at work.

5.2.4 Objective 4: Analysis Results and Discussion

The last objective of the study was to examine the generic and allergy specific quality of life of patients who received in vitro allergy testing. Allergy specific quality of life was assessed through the use of the Mini-RQLQ, while generic quality of life was assessed using the SF-8. More specifically, two research questions were presented to address this last study objective.

Research Question 4.1: Are the following characteristics significant explanatory variables of overall Mini-RQLQ scores: in vitro allergy test status, age, gender, race, medication use, and severity of symptoms?

Research Question 4.2: What are the differences in SF-8 quality of life scores among patients who have had in vitro allergy testing and the general United States population?

Results of the regression model indicate that five variables—in vitro allergy test status, age, gender, race, and medication use—were found to be completely independent from overall Mini-RQLQ scores. In other words, an insignificant amount of the variance in overall Mini-RQLQ scores was explained
by *in vitro* allergy test status, age, gender, race, and medication use. However, predicted overall Mini-RQLQ scores increased by 0.201, with each one-point increase in symptom severity score. Because a higher overall Mini-RQLQ score indicates a decrease in quality of life, the model estimates indicate that an increase in allergy symptoms significantly decreases an individual's allergy-specific quality of life. The model with symptom severity alone explained about 47% of the variance in overall Mini-RQLQ scores.

Although a number of the variables in the model did not significantly explain overall Mini-RQLQ scores, most unexpected was the non-significance of medication use. The variable medication use was an indicator of overall medication use, with higher values indicating little or no medication use. Researchers have found higher quality of life when allergic patients are placed on medication, hence, no significant association between quality of life and medication use in this population was a surprising finding.\(^{28,29}\) One reason there may have been no association between the two variables is because patients may have used allergen avoidance therapy instead of drug therapy. Alternatively, perhaps only patients who have severe allergy symptoms are significantly impacted by medication use. Inclusion of allergen avoidance therapy and investigating patients with severe allergic rhinitis symptoms in future studies may result in different findings concerning the association of quality of life and medication usage.
Quality of life measurements assessed by the SF-8 survey found a higher reported value for the role physical item in the sample when compared to the U.S. population but found lower values for the remaining individual SF-8 domains—general health, physical functioning, bodily pain, vitality, social functioning, mental health, and role emotion. After adjusting for age and gender, no difference was found between the physical composite score in the \textit{in vitro} study population and the U.S. published norms. However, a significant difference was found between the two groups on the mental composite scores.

Although a review of the literature found no publications evaluating quality of life of allergic rhinitis suffers using the SF-8, the SF-36 has been used to study these patients.\textsuperscript{30-34} Similar to the results presented here, other researchers have found decreased mental health quality of life scores when compared to control groups.\textsuperscript{31,33} However, whereas no significant difference was found in the \textit{in vitro} test population compared to the U.S. published norms, other investigators have found significant differences in physical health of patients who had allergic rhinitis compared to their control groups.\textsuperscript{31,33}

The utilization of two different quality of life instruments allowed for the investigation of different quality of life characteristics. The Mini-RQLQ focused on the quality of life of five different allergy-specific domains: activity limitations, practical problems, nose symptoms, eye symptoms, & other symptoms. Additionally, the Mini-RQLQ's format questioned subjects concerning their allergy symptoms over the past seven days. Use of the SF-8 in the study population focused on eight broader quality of life areas (general health, vitality, social functioning, mental health, and role emotional).
physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role emotion) and asked subjects to respond to the questions considering the past four weeks. Thus, the Mini-RQLQ focused on allergy-specific symptoms in the past week, while the SF-8 concentrated on a wide range of issues and asked for a longer recall time-frame. Both surveys were useful in providing different quality of life information concerning the study population.

5.3 Study Limitations

This study had several limitations. First, there are many problems which might have occurred in the managed care insurance claims database. Although the claims database provided an inexpensive and complete way to integrate information from all components of health care through linkages between medical service use and prescription drug use, it is not comprehensive and may contain incomplete or inaccurate data. Claims data does not reflect any costs unrelated to insurance reimbursement and therefore contains no records of non-formulary drugs, over-the-counter medications, or drug samples handed out by the physician. The lack of information concerning over-the-counter medication usage for allergic rhinitis may have significantly impacted the total amount spent on prescription allergy drugs. Patient information concerning environmental changes made by individuals also would not have been recorded in the insurance database. Furthermore, we assumed the database provided accurate coding of medical visits and procedures. Inaccurate coding may be a
result of imprecision and constant changing of the coding system, typographical errors, and can be based upon attempting to maximize reimbursement incentives. Additionally, the insurance claims database provided values in terms of charge and payment amounts rather than in the preferred cost data form.

A second study limitation which could have impacted the assessment of quality of life differences between the in vitro tested population and the general U.S. population was the inclusion of all individuals into the survey—regardless of their symptom severity score. As mentioned earlier, researchers have found significant general quality of life differences between patients who have allergic rhinitis compared to controls. However when investigating quality of life differences between groups, researchers may often include only those patients who have moderately severe or severe allergic rhinitis symptoms. Restricting subjects who have only moderately severe or severe allergic rhinitis enables researchers to more readily find a significant difference between the two groups, if a difference truly exists. Although this study used symptom severity scales found commonly in the allergic rhinitis literature, no restrictions on symptom severity were placed on the subjects in order to be included in the study. As a result of the decision rule to include all individuals who returned usable surveys in the SF-8 quality of life analysis, the overall mean symptom severity of the group at the time of survey was low with a mean of only 6.9
(SD = 4.3) out of a possible 20. Thus, symptom severity of the in vitro tested group at the time of survey administration could have impacted allergic rhinitis quality of life estimations.

The use of the SF-8 instead of the SF-36 to evaluate generic quality of life in this patient population could be viewed as a study limitation. Although no known published literature had estimated general quality of life in an in vitro tested population using the SF-8, future studies should consider using the SF-36. Even though the SF-8 covers the same domains and is validated as the SF-36, the single item domain distributions did not allow for statistical comparisons to the eight single item U.S. published norms. Consequently, only summary mental and physical composite scores could be statistically compared to the U.S. norms. Using the SF-36 instead of the SF-8 may have provided a more normally distributed domain score and thus enable statistical testing on each of the eight domains.

Another study limitation was the limited number of in vitro allergy tested allergens. A total of twelve allergens — Alternaria Alternaria, Aspergillus fumigatus, cat, dog, cocklebur, dust mite (Dermatophagoide Farinae), plantain, common ragweed (also known as short ragweed), birch, maple, oak, and bluegrass — were tested in the entire study population. In vitro allergy test status, an independent variable in all the modeling equations, was based upon whether or not patients tested positive on any perennial or fall allergens. It is possible that study subjects could have been misclassified as not allergic in the fall because of the limited number of in vitro tested allergens. For example,
only one type of dust mite (*Dermatophagoide Farinae*) was tested, yet another common dust mite is *Dermatophagoides Pteronyssinus.* Alternatively, although two mold were tested, *Alternaria Alternaria* and *Aspergillus fumigatus,* *Cladosporium herbarum* is also considered one of the most common causes of mold allergies, but was not included in the aeroallergen panel. In sum, based upon the limited data available concerning specific allergens, subjects could have been misclassified when placed into the allergic versus not allergic groups.

One last limitation was the timing difference between the allergy-specific insurance database and survey administration. There were three different timing components in this study: the charge data were from the year 2000, the *in vitro* allergy laboratory tests were performed between 1998 and 2000, and the allergy surveys were administered in the fall of 2001. Investigating associations between the insurance claims database and the allergy survey required several assumptions. First, it was assumed that patients remained consistent in their allergic state from the time of *in vitro* allergy testing until the time of survey administration. For example, a patient who tested negative to a dust mite allergy in 1998 was assumed to have not developed a dust mite allergy by the year 2001. Alternatively, a patient who was diagnosed positive with a mold allergy was assumed not to be non-atopic to mold prior to survey administration. If this assumption was violated, misclassification of *in vitro* test status may have occurred. A second assumption was that a patient’s degree of allergy severity did not significantly change from the time of data collection of the charge database (2000) and the time period of survey administration.
Large changes in a patient’s allergy symptoms between the autumn seasons of 2000 and 2001 could have impacted the outcome of the non-prescription charge and prescription charge models.

5.4 Recommendations for Future Research

Given the current lack of research investigating the economic and quality of life research reported on in vitro allergy testing, the potential for future investigation into this area is great. One future research plan could revolve around further estimation of the sensitivity and specificity of in vitro tested allergens. This study investigated only two allergen, cat and common ragweed, using a Bayesian approach. Obtaining information from other researchers or publications concerning the currently available data regarding the sensitivity and specificity of other available in vitro tested allergens would allow for new estimations of these parameters. Moreover, if study subjects were able to have two different types of diagnostic non-gold standard allergy tests performed (ie., mRAST and ImmunoCAP), then a Bayesian approach could be used to estimate the sensitivity and specificity of each of the tests, along with the sensitivity and specificity for the combination of the tests. The combination of information provided by both tests would allow for more precise inferences to be drawn concerning the patients’ allergic state.

This study had patients who were in vitro allergy tested respond to three different quality of life instruments, the Mini-RQLQ, the SF-8, and the AOS. While the RQLQ and SF-36 have been used to evaluate the quality of life in many allergic rhinitis patients, no studies have used the Mini-RQLQ, SF-8, and
the AOS in one study population. Basic information concerning the quality of life scores for each of the instruments would provide background information concerning the use of these questionnaires for future researchers. Comparisons and a summary of the findings between the three different quality of life instruments used in this study may help future researchers evaluate whether or not these instruments would provide useful and meaningful results in their allergic rhinitis study sample.

Of particular interest would be a comparison between the SF-8 and the AOS. The AOS is a recently developed allergy-specific quality of life instrument which to date has little published information concerning its use. The creators of the AOS used the SF-36 and RQLQ to evaluate its convergent validity. A similar analysis evaluating the AOS with the SF-8 and Mini-RQLQ would provide further knowledge and insight concerning this relatively new allergy-specific quality of life instrument. For example, how well does the AOS total score correlate with overall Mini-RQLQ scores?

Future research investigating in vitro aeroallergen testing could repeat this study with some modifications. If this study would be considered to be repeated, researchers should consider a clinical trial type format where study subjects are obtained from multiple centers across the United States. Study subjects who present with moderate to severe allergy symptoms would be enrolled and randomized into either a control group or a second group which receives in vitro allergy testing. Prior to any type of intervention or testing, both groups would complete a survey which would include questions concerning
quality of life, productivity, severity of symptoms, and environmental conditions. Ideally, cost for treating their symptoms prior to intervention would be collected over a particular allergy season (e.g., spring, autumn). Subsequently, both groups would receive physical exams and have a detailed history taken by family practice physicians. The family practice physicians would then treat the patients as they believe is medically appropriate, with the only difference between the two groups involving the additional diagnostic information provided for the in vitro tested aeroallergen group. Thereafter, both groups would be asked to complete the same survey containing quality of life, productivity, severity of symptoms, and environmental conditions every three months for the next year. Additionally, any allergy-related cost incurred over this time frame would also be collected. Such a longitudinal control would provide greater and more accurate information concerning the impact of in vitro allergy testing.

In conclusion, further research is needed to investigate the association between in vitro allergy testing and quality of life, productivity, and medical cost outcomes. Research performed in various locations across the United States would help increase generalizability of the any findings and help control for regional allergy differences. The utilization of control groups and a prospective study design would strengthen the study design and allow for further conclusions concerning the impact of in vitro allergy testing.
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177


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July 31, 2001

Dear NAME

Henry Ford Hospital and investigators at The Ohio State University are researching how to improve the medical care of allergy patients. Because health system records show you may have been tested or treated for allergies or allergy-related conditions, we are interested in understanding how allergies affect the quality of your life. We will be mailing you a survey to complete concerning allergies and allergy-related quality-of-life. In addition to the survey, we will use Henry Ford data to obtain allergy-related office visits and medication information. Included in the study will be over 1000 allergy patients such as yourself.

Next week you will receive in the mail a request to fill out our study questionnaire. Even if you are not currently experiencing problems with allergies, we still value and need your participation. The data gathered are extremely useful as the medical profession and your health system seek to determine the most effective way to treat patients with allergies.

We are writing in advance because we have found many people like to know ahead of time that they will be asked to participate in a survey. If you do not wish to participate, please return the survey unanswered. This will indicate your wish not to be involved in the study.

We appreciate the time and effort to complete the survey. As a small token of our appreciation, we will send you a $2.00 bill along with the survey.

Thank you for your time and consideration. It is with the help of individuals like you that progress will be made in treating patients who suffer from allergies.

If you have any questions about this study, please contact Suzan Kucukarslan at (313) 916-8718 or Sheryl Szeinbach at (614) 292-1363.

Sincerely,

Suzan Kucukarslan, PhD
Program Evaluation and Outcomes Researcher
Henry Ford Hospital
University

Sheryl Szeinbach, PhD
Professor
The Ohio State
APPENDIX B

First Survey Cover Letter
August 6, 2001

Dear NAME ID#

Henry Ford Hospital and health care researchers at The Ohio State University are investigating ways to improve the medical care of allergy patients. Because health system records show you may have been tested or treated for allergies or allergy-related conditions, we are interested in understanding how allergies affect the quality of your life.

Enclosed is the survey we are asking you to complete concerning allergies and allergy-related quality-of-life. Additionally, we will use Henry Ford data to obtain allergy-related office visit and medication information. Included in the study will be over 1000 allergy patients such as yourself.

Your help is needed. Please take about 5-10 minutes to complete and return the enclosed survey questionnaire. Your responses are completely confidential and we will not report any of your information that we collect.

If you do not wish to participate, please return the survey unanswered. This will indicate your wish not to be involved in the study. The completion of the enclosed survey implies your consent to participate in the research study.

We appreciate the time and effort you will have spent completing the survey. As a token of our appreciation, please accept the enclosed $2 bill.

Thank you for participating in this important research. It is with the help of individuals like you that progress will be made in treating patients who suffer from allergies.

If you have any questions about this study, please contact Suzan Kucukarslan at (313) 916-8718 or Sheryl Szeinbach at (614) 292-1363.

Sincerely,

Suzan Kucukarslan, PhD
Program Evaluation and Outcomes Researcher
Henry Ford Hospital
University

Sheryl Szeinbach, PhD
Professor
The Ohio State
APPENDIX C

Postcard Reminder
Last week a survey seeking your help to describe the affect 
allergies have on your daily life was mailed to you. Your 
name was selected from a list of who have seen a Henry 
Ford physician for allergies.

If you have already completed and returned the 
questionnaire to us please accept our sincere thanks. If not, 
please do so today. We are especially grateful for your help 
because it is only by asking people like you to share your 
experiences that we can know how allergies are affecting 
your every day life.

If by some chance you did not receive the questionnaire, or 
it was misplaced, please call us at (313) 916-8718 or (614) 
292-1363 and we will get another one in the mail to you 
today.

Sincerely,

Suzan Kucukarslan, PhD  Sheryl Szeinbach, PhD
Outcomes Researcher  Professor
Henry Ford Hospital  The Ohio State University
APPENDIX D

Second Survey Cover Letter
August 21, 2001

Dear NAME,

Recently we sent you mail requesting your input concerning your personal experiences with allergies. Because our records show we have not received your survey and because we need your responses to successfully complete this important research, we are sending you a copy of the survey that we would like you to complete and return. Please disregard this packet if you have already completed and mailed the survey.

This research, conducted by Henry Ford Hospital and health care researchers at The Ohio State University, involves investigating ways to improve the medical care of allergy patients. Because health system records show you may have been tested or treated for allergies or allergy-related conditions, we are interested in understanding how allergies affect the quality of your life.

Your help is needed. Please take about 5-10 minutes to complete and return the enclosed survey questionnaire. Although we will use Henry Ford data to obtain allergy-related office visit and medication information, your responses and information are completely confidential and we will not report any of your information that we collect.

If you do not wish to participate, please return the survey unanswered. This will indicate your wish not to be involved in the study. The completion of the enclosed survey implies your consent to participate in the research study.

Thank you for participating in this research. It is with the help of individuals like you that progress will be made in treating patients who suffer from allergies.

If you have any questions about this study, please contact Suzan Kucukarslan at (313) 916-8718 or Sheryl Szeinbach at (614) 292-1363 or E-Mail us at allergysurvey@hotmail.com.

Sincerely,

Suzan Kucukarslan, PhD
Program Evaluation and Outcomes Researcher
Henry Ford Hospital
University

Sheryl Szeinbach, PhD
Professor
The Ohio State
APPENDIX E

Telephone Script
Telephone script:

Hello. May I please speak to __patient name__. My name is Kristina I am calling from Henry Ford Hospitals. I am a research associate and am calling to remind you about a survey we recently sent you. I am not selling anything.

Recently we sent you mail requesting your input concerning your personal experiences with allergies. This research, conducted by Henry Ford Hospital and health care researchers at The Ohio State University, involves investigating ways to improve the medical care of allergy patients. All information will be kept confidential. At this time, our records show we have not received your survey and we were calling to remind you to please return the survey in the postage paid envelope provided. Thank you for taking the time to speak to me. Have a good evening.

Answering machine:

Hello. May I please speak to __patient name__. I am calling on behalf of Henry Ford Hospitals and the Ohio State University.

Recently you received an allergy survey by mail. I am just calling to remind you about the survey and ask that you return it. If you have already done so, please disregard this call. Thank you for your help with this allergy research. Have a good evening.

Message left with another household member:

Recently __patient name__ received an allergy survey by mail. I am just calling to remind him/her about the survey and ask that he/she return it. If they have already done so, please disregard this call. Thank you for your time. Have a good evening.

If patient does not want to return the survey:

Thank you for taking the time to speak me. If you do not wish to participate, please return the survey unanswered in the postage paid envelope provided. Have a good evening.

If the patient has any question:

Try to answer them or provide them the information below.

If you have any questions about this study, please contact Dr. Kucukarslan at (313) 916-8718 or Dr. Szeinbach at (614) 292-1363 or E-Mail us at allergysurvey@hotmail.com.
APPENDIX F

Mailed Questionnaire
Allergy Survey

Please return your completed questionnaire in the provided prepaid envelope addressed to:

The Ohio State University
2500 Kenny Road
Columbus, Ohio 43210-9975

Questions and comments can be directed to Suzan Kucukarslan, PhD (313)916-6718
Or E-mail allergiesurvey@hotmail.com
Please answer every question by either circling the appropriate letter or by placing your answer in the space provided. Do not consider any food or drug allergies when answering this survey.

1. Has a doctor ever told you that you have allergies?
   a. No
   b. Yes
   c. Don’t know/can’t remember

2. Do you think you have allergies?
   a. No \(\rightarrow\) (Skip to question 51 on page 8)
   b. Yes
   c. Maybe, I am not sure

3. Are you currently experiencing allergies?
   a. No
   b. Yes

4. Approximately how many years have you had allergies?
   \(\boxempty\) Year(s)

5. At this time, who primarily manages your allergies?
   a. Family doctor
   b. Allergist
   c. Myself (I manage my allergies)
   d. A friend or family member who is not a health care professional
   e. Other doctor or health care professional (Please specify) \(\text{______________}\)

Please complete all questions by circling the number that best describes how severe your allergies have been during the last week.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Absent (Not present)</th>
<th>Mild (Symptom present but not annoying or troublesome)</th>
<th>Moderate (Symptom frequently troublesome but not interfering with normal daily activity or sleep)</th>
<th>Severe (Symptom sufficiently troublesome to interfere with normal daily activity or sleep)</th>
<th>Very Severe (Symptom severe enough to warrant immediate visit to physician)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. SNEEZING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. RUNNY NOSE</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. ITCHY NOSE, PALATE (ROOF OF MOUTH) AND/OR THROAT</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. ITCHY, WATERY AND/OR RED EYES</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. NASAL CONGESTION</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
For each question, please mark the appropriate circle.

11. Overall, how would you rate your health during the past 4 weeks?
   - Excellent
   - Very good
   - Good
   - Fair
   - Poor
   - Very Poor

12. During the past 4 weeks, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?
   - Could not do physical activities
   - Not at all
   - Very little
   - Somewhat
   - Quite a lot

13. During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?
   - Could not do daily work
   - Not at all
   - A little bit
   - Some
   - Quite a lot

14. How much bodily pain have you had during the past 4 weeks?
   - None
   - Very mild
   - Mild
   - Moderate
   - Severe
   - Very Severe

15. During the past 4 weeks, how much energy did you have?
   - Very much
   - Quite a lot
   - Some
   - A little
   - None

16. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?
   - Could not do social activities
   - Not at all
   - Very little
   - Somewhat
   - Quite a lot

17. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?
   - Not at all
   - Slightly
   - Moderately
   - Quite a lot
   - Extremely

18. During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?
   - Could not do daily activities
   - Not at all
   - Very little
   - Somewhat
   - Quite a lot
Please complete all questions by circling the number that best describes how troubled you have been during the last week as a result of your nose/eye symptoms.

<table>
<thead>
<tr>
<th>ACTIVITIES</th>
<th>Not troubled</th>
<th>Hardly troubled</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quite a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. REGULAR ACTIVITIES AT HOME AND AT WORK (your occupation or tasks that you have to do regularly around your home and/or garden)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>20. RECREATIONAL ACTIVITIES (indoor and outdoor activities with friends and family, sports, social activities, hobbies)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>21. SLEEP (difficulties getting a good night's sleep and/or getting to sleep at night)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>PRACTICAL PROBLEMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. NEED TO RUB NOSE/ EYES</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>23. NEED TO BLOW NOSE REPEATEDLY</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
How troubled have you been during the last week as a result of these symptoms?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Not troubled</th>
<th>Hardly troubled at all</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quite a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NOSE SYMPTOMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. SNEEZING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>25. STUFFY/ BLOCKED NOSE</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>26. RUNNY NOSE</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td><strong>EYE SYMPTOMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. ITCHY EYES</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>28. SORE EYES</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>29. WATERY EYES</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td><strong>OTHER SYMPTOMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. TIREDNESS AND/OR FATIGUE</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>31. THIRST</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>32. FEELING IRRITABLE</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

197
Please answer every question by circling the appropriate number or letter. If you are unsure about how to answer a question, give the best answer you can.

33. In the past 4 weeks, how often have you been bothered by your allergy symptoms?
   a. None of the time
   b. A little of the time
   c. Some of the time
   d. Most of the time
   e. All of the time

34. Overall, how would you now rate your allergy symptoms?
   a. None
   b. Very Mild
   c. Mild
   d. Moderate
   e. Severe
   f. Very Severe

35. Compared to one year ago, how would you now rate your allergy symptoms in general?
   a. Much better
   b. Somewhat better
   c. About the same
   d. Somewhat worse
   e. Much worse

36. During the past 4 weeks, on average how many days per week did you need to use allergy medications (any)?
   a. Not at all
   b. 1 or 2 days
   c. 3 or 4 days
   d. 5 or 6 days
   e. Every day

37. During the past 4 weeks, how many weeks have you taken:

   Allergy medications (pill form) purchased "over the counter" : (without a prescription)
   a. 0 weeks
   b. 1 week
   c. 2 weeks
   d. 3 weeks
   e. 4 weeks
38. During the past 4 weeks, how many weeks have you taken:

Allergy medications (pill form) prescribed by your doctor:

a. 0 weeks  
b. 1 week  
c. 2 weeks  
d. 3 weeks  
e. 4 weeks

39. During the past 8 weeks, how many weeks have you taken:

Nasal sprays prescribed by your doctor:

a. 0 weeks  
b. 1-2 weeks  
c. 3-4 weeks  
d. 5-6 weeks  
e. 7-8 weeks

40. Please place a check next to all of the seasons during which you experience seasonal/outdoor allergies in the past year. (If you know what you are allergic to during that season (for example, tree pollen, ragweed, grass), please list it in the space provided.)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter</td>
<td>To what are you allergic in winter</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>To what are you allergic in spring</td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>To what are you allergic in summer</td>
<td></td>
</tr>
<tr>
<td>Autumn</td>
<td>To what are you allergic in autumn</td>
<td></td>
</tr>
<tr>
<td>I do not have seasonal/outdoor allergies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I do not know if I have seasonal/outdoor allergies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

41. Please place a check next to all of the seasons during which you experience indoor allergies in the past year. (If you know what you are allergic to during that season (for example, cat, dust, mold), please list it in the space provided.)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter</td>
<td>To what are you allergic in winter</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>To what are you allergic in spring</td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>To what are you allergic in summer</td>
<td></td>
</tr>
<tr>
<td>Autumn</td>
<td>To what are you allergic in autumn</td>
<td></td>
</tr>
<tr>
<td>I do not have indoor allergies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I do not know if I have indoor allergies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The following questions ask about the effect of your allergies on your ability to work, attend classes, and perform regular daily activities. When you think about the past seven days, do not include today. Please check the line or fill in the blank as indicated.

42. Are you currently employed (working for pay)?
   NO  YES
   (If NO, check "NO" and skip to question 48.)

43. In general, how many hours per week do you usually work?  _____ HOURS

44. During the past seven days, how many hours did you miss from work because of problems associated with your allergies? Include hours you missed because you were sick, times you went in late, left early, etc. because you were experiencing problems with your allergies.  _____ HOURS

45. During the past seven days, how much did allergies affect your productivity while you were working? Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If allergies affected your work only a little, choose a low number. Choose a high number if allergies affected you work a great deal. (Circle a number.)

<table>
<thead>
<tr>
<th>Allergies had no effect on my work</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergies completely prevented me from working</td>
<td>CIRCLE A NUMBER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

46. Do you currently attend classes in an academic setting (middle school, high school, college, graduate school, additional course work, etc.)?  (If "NO", check "NO" and skip to question 50.)
   NO  YES

47. In general, how many hours per week do you usually attend classes?  _____ HOURS

48. During the past seven days, how many hours did you miss from class or school because of problems associated with your allergies?  _____ HOURS

200
49. During the past seven days, how much did allergies affect your productivity while in school or attending classes in an academic setting? Think about days your attention span was limited, you had trouble with comprehension or days in which you could not take test as effectively as usual. If allergies affected your productivity at school or in classes only a little, choose a low number. Choose a high number if allergies affected your productivity a great deal. (Circle a number.)

Allergies had no effect on my class work

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

CIRCLE A NUMBER.

50. During the past seven days, how much did your allergies affect your ability to do your regular daily activities, other than work at a job or attend classes? By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If allergies affected your activities only a little, choose a low number. Choose a high number if allergies affected your activities a great deal. (Circle a number.)

Allergies had no effect on my daily activities

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

CIRCLE A NUMBER.

51. What is your current primary employment status? (Please only circle one.)

a. Employed full time
b. Employed part time
c. Homemaker
d. Looking for work
e. Retired
f. Student
g. Unable to work for health reasons
h. Other (please specify) ____________________________________

52. Which one of the following best describes your occupation? (Please circle only one.)

a. Managerial, professional
b. Technical, sales and administrative support
c. Service occupations
d. Precision production, craft and repair
e. Operations, fabrications, laborers
f. Farming, forestry, and fishing
g. Student
h. Other (please specify) ____________________________________
Please provide the following information about yourself. The following information about you will help us categorize and analyze the results. Answer every question by circling the appropriate letter or by placing your answer in the space provided.

53. Have you ever had skin tests (for example, scratch tests) for allergies?
   a. No  → (Skip to question 55)
   b. Yes
   c. Don’t know  → (Skip to question 55)

54. When thinking about your skin tests, please mark all that apply:
   ○ The skin tests were valuable.
   ○ The skin tests were not valuable.
   ○ I changed my habits or activities based on the skin test results.
   ○ My doctor changed my allergy medications based on my skin test results.

55. Have you ever had a blood test for allergies?
   a. No  → (Skip to question 57)
   b. Yes
   c. Don’t know  → (Skip to question 57)

56. When thinking about your blood test for allergies, please mark all that apply:
   ○ The blood test was valuable.
   ○ The blood test was not valuable.
   ○ I changed my habits or activities based on the blood test results.
   ○ My doctor changed my allergy medications based on my blood test results.

57. Have you ever had allergy immunotherapy (for example, allergy shots)?
   a. No  →(Skip to question 59)
   b. Yes
   c. Don’t know  →(Skip to question 59)

58. Are you currently being treated for your allergies by immunotherapy?
   a. No
   b. Yes

59. What is your smoking history?
   a. Former smoker
      How long ago did you quit smoking? _________
   b. Current smoker
      Approximately, how many cigarettes do you smoke per day? ___ Number of years? ___
   c. Non-smoker

60. What is the highest grade or year of school you completed?
   a. Grades 1 through 8  (Elementary)
   b. Grades 9 through 11  (Some high school)
   c. Grade 12 or GED  (High school graduate)
   d. College 1 or 3 years  (Some college or technical school)
   e. College 4 years or more  (College graduate)
61. How many of the following do you have: (Please include those living and deceased.)

- Step-brothers or step-sisters
- Half-brothers or half-sisters
- Full brothers or full sisters
- Step-children or adopted children

What are their ages? (Please list all their ages.)

Children

What are their ages? (Please list all their ages.)

I have none of the above.

62. Who in your family has or has had a history of allergies? (Please circle all that apply. Do not include any food or drug allergies when answering this question.)

a. Step-mother
   Don’t know

b. Mother
   Don’t know

c. Step-father
   Don’t know

d. Father
   Don’t know

e. Step-brothers or step-sisters
   How many of your step-brothers or step-sisters have or have had allergies? Don’t know

f. Half-brothers or half-sisters
   How many of your half-brothers or half-sisters have or have had allergies? Don’t know

g. Full brothers or full sisters
   How many of your full brothers or full sisters have or have had allergies? Don’t know

h. Step-children or adopted children
   How many of your step-children or adopted children have or have had allergies? Don’t know

i. Children
   How many of your children have or have had allergies? Don’t know

j. Nobody in my family has a history of allergies.

Thank you for taking the time to complete this survey. Your assistance in providing this information is very much appreciated. We welcome anything else you would like to tell us about your allergies or your experience with allergy testing.

Please return the survey in the pre-paid envelope provided.
APPENDIX G

Institutional Review Board Exemption
BEHAVIORAL AND SOCIAL SCIENCES
HUMAN SUBJECTS INSTITUTIONAL REVIEW BOARD (IRB) 2001
THE OHIO STATE UNIVERSITY, Columbus, OH 43210
Research Involving Human Subjects

ACTIONS OF THE INSTITUTIONAL REVIEW BOARD

With regard to the employment of human subjects in the proposed research protocol

Research Involving Human Subjects

ACTION OF THE INSTITUTIONAL REVIEW BOARD

With regard to the employment of human subjects in the proposed research protocol

The behavioral and social sciences human subjects have taken the following action:

APPROVED

Disapproved

APPROVED WITH CONDITIONS

WAVES OF WRITTEN CONSENT GRANTED

It is the responsibility of the principal investigator to obtain a copy of this signed consent form and to keep them (2) years beyond the completion of the subject's participation in the proposed protocol. Should the principal investigator have the subject sign this consent form, the subject's signature is to be transmitted to the Human Subjects Office for the Responsible Review Board to be reviewed and documented. The subject's signature is to be transmitted to the Human Subjects Office for the Responsible Review Board to be reviewed and documented.

Date: January 23, 2001

SIGNED

205
APPENDIX H

Bayesian Programming for Estimation of

Disease Prevalence and the Parameters of a Diagnostic Test

in the Absence of a Gold Standard
## Instructions

### COPYRIGHT

(c) Copyright Lawrence Joseph, 1994 - 1997.

tt1, tt2, and tt3 are programs written by Lawrence Joseph, at the Division of Clinical Epidemiology, Department of Medicine, Montreal General Hospital. These programs are an implementation of the manuscripts Bayesian Estimation of Disease Prevalence and the parameters of Diagnostic Tests in the Absence of a Gold Standard, by L. Joseph, T. Gyorkos, and L. Coupal, American Journal of Epidemiology, 1995;141:263-72.

You are free to use these programs, for non-commercial purposes only, under two conditions:

(1) This note is not to be removed;
(2) Publications using tt1, tt2, or tt3 results should reference the manuscript mentioned above.

The manuscript mentioned above should be read carefully prior to using the program.

This file contains the program tt1.gibbs and all required subroutines to calculate Bayesian posterior distributions via Gibbs sampling for the prevalence of a disease, and sensitivity, specificity, positive and negative predictive values of a test for that disease, in the absence of a gold standard. The program is written in S-PLUS version 3.1. In order to run the program, type from the Splus prompt:

```
# tt1.gibbs(tp, tn, astart, cstart, sensstart, specstart, prevstart,
```
The output is summarized using quantities for each variable, although by changing line number 229, the full gibbs output is available.

The parameters are defined as follows:

- \( tp \) — the total number of positive outcomes in the population tested by the (non-gold standard) test
- \( tn \) — the total number of negative outcomes in the population tested by the (non-gold standard) test
- \( a_{\text{start}} \) — starting value for \( a \), the unobserved number of true positives
- \( c_{\text{start}} \) — starting value for \( c \), the unobserved number of false negatives
- \( s_{\text{sensstart}} \) — starting value for the sensitivity of the test
- \( s_{\text{specstart}} \) — starting value for the specificity of the test
- \( p_{\text{prevstart}} \) — starting value for the prevalence in the population
- \( b_{\text{alphaprev}} \) — first coefficient of the Beta prior distribution for the prevalence
- \( b_{\text{betaprev}} \) — second coefficient of the Beta prior distribution for the prevalence
- \( a_{\text{alphasens}} \) — first coefficient of the Beta prior distribution for the sensitivity
- \( b_{\text{betasens}} \) — second coefficient of the Beta prior distribution for the sensitivity
# alphaspec == first coefficient of the Beta prior distribution for the specificity
#
# betaspec == second coefficient of the Beta prior distribution for the specificity
#
# size == total number of Gibbs iterations
#
# throwaway == number of Gibbs iterations used for assessing convergence
#
# skip == step size for Gibbs iterates. skip==1 means use all iterations, skip==2 means use every second iterate, etc.
#
#------------------------------------------------------------

# The general setup is:
#
# Truth (Unknown)
#
# | + | - |     
# T ---------------
# e + | a | b | (a+b)
# s ---------------
# t - | c | d | (c+d)
# |(a+c)|(b+d)| N
#
# Note that only (a+b)=tp and (c+d)=tn are observed in the experiment.
#
# After running the program, the output variables are:
#
# prev == the posterior prevalence
# sens == the posterior sensitivity
# spec == the posterior specificity
# ppv== the posterior positive predictive value
# npv == the posterior negative value
# lrp == the posterior likelihood ratio of a positive test
# lrm == the posterior likelihood ratio of a negative test
# last.values == the vector of last values of the Gibbs sampler,
# in case more iterations are needed.
#
# A "q" in front of each variable indicates that the quantiles
# are given. For example, qprev indicates the posterior quantiles
# for the prevalence.
#
# Please let me know if you experience any problems while using   #
# these functions: Lawrence Joseph, joseph@binky.ri.mgh.mcgill.ca  #
#*****************************************************************************#
#
#tt1.a <-
#function(tp, sens, spec, prev)
#
{  
  if(p == 0) {  
      return(0)  
  }  
  p1 <- prev * sens  
  p2 <- (1 - prev) * (1 - spec) .  
  p <- p1/(p1 + p2)  
  nexta <- rbinom(1, tp, p)  
  if(p == 0) {  
      return(0)  
  }  
  if(p == 1) {  
      return(tp)  
  }  
  return(nexta)  
}  

tt1.c <-
function(tn, sens, spec, prev)
{
  if(tn == 0) {
    return(0)
  }
  p1 <- prev * (1 - sens)
  p2 <- (1 - prev) * spec
  p <- p1/(p1 + p2)
  nextc <- rbinom(1, tn, p)
  if(p == 0) {
    return(0)
  }
  if(p == 1) {
    return(tn)
  }
  return(nextc)
}

tt1.sens <-
function(a, c, alphasens, betasens)
{
  return(rbeta(1, a + alphasens, c + betasens))
}

tt1.spec <-
function(tp, tn, a, c, alphaspec, betaspec)
{
  return(rbeta(1, tn - c + alphaspec, tp - a + betaspec))
}

tt1.prev <- function(tp, tn, sens, spec, a, c, alphaprev, betaprev)
{
  nextprev <- rbeta(1, a + c + alphaprev, tp - a + tn - c + betaprev)
  return(nextprev)
}

211
function(tp, tn, astart, cstart, sensstart, specstart, prevstart, alphaprev, betaprev, alphasens, betasens, alphaspec, betaspec, size, throwaway, skip)
{
    throw <- throwaway + 1
    a.samp <- rep(-1, size)
    c.samp <- rep(-1, size)
    prev.samp <- rep(-1, size)
    sens.samp <- rep(-1, size)
    spec.samp <- rep(-1, size)
    ppv.samp <- rep(-1, size)
    npv.samp <- rep(-1, size)
    prev.samp[1] <- prevstart
    a.samp[1] <- astart
    c.samp[1] <- cstart
    sens.samp[1] <- sensstart
    spec.samp[1] <- specstart
    ppv.samp[1] <- a.samp[1]/tp
    npv.samp[1] <- (tn - c.samp[1])/tn
    for(i in 2:size) {
        a.samp[i] <- tt1.a(tp, sens.samp[i - 1], spec.samp[i - 1], prev.samp[i - 1])
        c.samp[i] <- tt1.c(tn, sens.samp[i - 1], spec.samp[i - 1], prev.samp[i - 1])
        sens.samp[i] <- tt1.sens(a.samp[i], c.samp[i], alphasens, betasens)
        spec.samp[i] <- tt1.spec(tp, tn, a.samp[i], c.samp[i], alphaspec, betaspec)
        prev.samp[i] <- tt1.prev(tp, tn, sens.samp[i], spec.samp[i], a.samp[i], c.samp[i], alphaprev, betaprev)
    }
    ppv.samp <- sens.samp*prev.samp/(sens.samp*prev.samp + (1-spec.samp)*(1-prev.samp))
    npv.samp <- spec.samp*(1-prev.samp)/(spec.samp*(1-prev.samp) + prev.samp*(1-sens.samp))
}

212
lrp.samp <- sens.samp/(1 - spec.samp)
lm.samp <- (1 - sens.samp)/(spec.samp)

# Add lines below for automatic graphics of Gibbs sampler output
#
# openlook()
# par(mfrow = c(3, 3))
# plot(1:throwaway, prev.samp[1:throwaway], type = "l")
# plot(throw:size, prev.samp[throw:size], type = "l")
# hist(a.samp[seq(throw, size, by = skip)])
# hist(c.samp[seq(throw, size, by = skip)])
# hist(sens.samp[seq(throw, size, by = skip)])
# hist(spec.samp[seq(throw, size, by = skip)])
# hist(ppv.samp[seq(throw, size, by = skip)])
# hist(npv.samp[seq(throw, size, by = skip)])
# hist(prev.samp[seq(throw, size, by = skip)])
#
# Add line below to return Gibbs output vectors, rather than summaries.
#
# return(a.samp, c.samp, sens.samp, spec.samp, prev.samp)
#
# qprev <- quantile(prev.samp[seq(throw, size, by = skip)], c(0.025, 0.05, 0.25, 0.5, 0.75, 0.95, 0.975))
qsens <- quantile(sens.samp[seq(throw, size, by = skip)], c(0.025, 0.05, 0.25, 0.5, 0.75, 0.95, 0.975))
qspec <- quantile(spec.samp[seq(throw, size, by = skip)], c(0.025, 0.05, 0.25, 0.5, 0.75, 0.95, 0.975))
nppv <- quantile(ppv.samp[seq(throw, size, by = skip)], c(0.025, 0.05, 0.25, 0.5, 0.75, 0.95, 0.975))
nnpv <- quantile(npv.samp[seq(throw, size, by = skip)], c(0.025, 0.05, 0.25, 0.5, 0.75, 0.95, 0.975))
qlrp <- quantile(lrp.samp[seq(throw, size, by = skip)], c(0.025, 0.05,
\[ 0.25, 0.5, 0.75, 0.95, 0.975) \]

\[ \text{qlm <- quantile(seq(throw, size, by = skip)), c(0.025, 0.05,} \]
\[ 0.25, 0.5, 0.75, 0.95, 0.975)) \]

\[ \text{last.values <- c(a.samp[size], c.samp[size], sens.samp[size], spec.samp[} \]
\[ \text{size], prev.samp[size])} \]

\[ \text{return(qprev, qsens, qspec, qppv, qnpv, qlrp, qlm, last.values)} \]

\} \]

\[ \text{mu.to.beta <-} \]

\[ \text{function(mu, sd)} \]

\[ \{ \]
\[ \text{var <- sd^2} \]
\[ \text{alpha <- - (mu * (var + mu^2 - mu))/var} \]
\[ \text{beta <- ((mu - 1) * (var + mu^2 - mu))/var} \]

\[ \text{return(alpha, beta)} \]

\} \]

\[ \text{beta.to.mu <-} \]

\[ \text{function(alpha, beta)} \]

\[ \{ \]
\[ \text{mean <- alpha/(alpha + beta)} \]
\[ \text{sd <- sqrt((alpha * beta)/((alpha + beta)^2 * (alpha + beta + 1)))} \]

\[ \text{return(mean, sd)} \]

\}
Appendix I

Survey Response Rate
Thank you/Reminder Postcard
- Announcement Letter
- Survey Packet #1
- Survey Packet #2
- Phone call to tested patients
- ...
Appendix J

Program Input and Output

for Parameter Estimation of

In Vitro Diagnostic Allergy Testing
> mu.to.beta(.725, .0317)
$alpha
[1] 143.1185

$beta
[1] 54.28632

> mu.to.beta(.935, .0083)
$alpha
[1] 823.9253

$beta
[1] 57.27823

ttl.gibbs(66, 264, 50, 150, .5, .5, .5, 1, 1, 143.12, 54.29, 823.93, 57.28, 20500, 500, 1)

$qprev
 2.5%    5%   25%   50%   75%   95%  97.5%
0.1385685 0.1499159 0.1829091 0.2071613 0.2320582 0.2695848 0.2826712

$qsens
 2.5%    5%   25%   50%   75%   95%  97.5%
0.6602451 0.6700046 0.7030134 0.7244236 0.7456507 0.7740845 0.7827892

$qspec
 2.5%    5%   25%   50%   75%   95%  97.5%
0.9177472 0.9206724 0.9296201 0.9354112 0.9408028 0.9480832 0.9504179

$qppv
 2.5%    5%   25%   50%   75%   95%  97.5%
0.6165051 0.6410559 0.7081123 0.7458067 0.7790248 0.8194035 0.8312349

$qnppv
 2.5%    5%   25%   50%   75%   95%  97.5%
0.8855223 0.8936676 0.9158401 0.9290039 0.9406201 0.9544268 0.9584682

$qlrp
 2.5%    5%   25%   50%   75%   95%  97.5%

$qlrm
 2.5%    5%   25%   50%   75%   95%  97.5%
0.2321722 0.2415565 0.2720580 0.2947654 0.3178105 0.3532411 0.3638582

$last.values
[1] 57.0000000 34.0000000 0.6752920 0.9386473 0.2584616
Short Ragweed: R Programming

```r
> mu.to.beta(.49, .0667)
$alpha
[1] 27.03394
$beta
[1] 28.13737

> mu.to.beta(.985, .0050)
$alpha
[1] 581.15
$beta
[1] 8.85

> ttt.gibbs(65, 265, 50, 150, .5, .5, .5, 1, 1, 27.03, 28.14, 581.15, 8.85, 20500, 500, 1)

$qprev
         2.5%   5%   25%   50%  75%   95%  97.5%
0.2759700 0.2919386 0.3485221 0.3949342 0.4498142 0.5519376 0.5934395

$qens
         2.5%   5%   25%   50%  75%   95%  97.5%
0.3476419 0.3687981 0.4334966 0.4793254 0.5255628 0.5902750 0.6104295

$qspec
         2.5%   5%   25%   50%  75%   95%  97.5%
0.9736491 0.9758762 0.9818534 0.9854602 0.9885090 0.9921747 0.9931833

$qppv
         2.5%   5%   25%   50%  75%   95%  97.5%
0.9081524 0.9182202 0.9431274 0.9566082 0.9674085 0.9797216 0.9828792

$qnpv
         2.5%   5%   25%   50%  75%   95%  97.5%
0.5169032 0.5660809 0.6845894 0.7443439 0.7930100 0.8470199 0.8618242

$qrlp
         2.5%   5%   25%   50%  75%   95%  97.5%
16.78784 18.54199 25.75372 32.77773 42.32995 62.88875 72.82629

$qrlm
         2.5%   5%   25%   50%  75%   95%  97.5%
0.3949300 0.4160954 0.4815840 0.5287517 0.5752108 0.6404924 0.6627172

$last.values
[1] 61.0000000 40.0000000 0.5686274 0.9838480 0.2828148
```

219
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