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ASSESSING THE PREDICTIVE ABILITY OF
A DETERMINISTIC MODEL AND A STOCHASTIC MODEL

by

Kem Patrick Krueger

A Dissertation Submitted to the Faculty of the
DEPARTMENT OF PHARMACY PRACTICE AND SCIENCE

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1999
As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Kem Patrick Krueger entitled Assessing the Predictive Ability of a Deterministic Model and a Stochastic Model and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

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ABSTRACT

Formulary decision-makers must make choices based upon the safety, efficacy, and projected budgetary impact of medications. Models used to predict cost impacts are rarely assessed to determine how accurately they predict treatment cost changes.

The purpose of this research was to assess the ability of a decision analytic based deterministic model and a regression analytic based stochastic model to predict the average diabetes-specific costs incurred by a managed care organization during the 12 month period following the addition of metformin to an HMO formulary. The ability of the stochastic model to predict the average diabetes-related costs and total health care costs was also assessed.

The deterministic model, a decision tree, was constructed within an equilibrium framework using literature-based probabilities and internal costs to predict the expected diabetes-specific costs. The estimate of the total diabetes-specific cost impact came within 5% of the actual costs. The model underestimated the diabetes-specific medical costs (predicted was 73% of actual) and overestimated the diabetes-specific pharmacy costs (predicted was 258% of actual).

A regression model was constructed using medical and pharmacy claims data to predict the expected diabetes-specific, diabetes-related and total health care costs. The average total cost estimates produced by the total health care cost model were within 7% of the actual average costs incurred. The diabetes-related and diabetes-specific cost models produced estimates that were within 12% and 18% of the actual costs incurred, respectively. The total, diabetes-related, and diabetes-specific average medical costs produced by the regression models were within 6%, 50%, and 46% of the actual costs.
respectively. The total, diabetes-related, and diabetes-specific average pharmacy costs were within 20%, 45%, and 49% of the actual costs respectively.

Further research is needed to determine the best way to construct a model to estimate the economic impact of adding a medication to the formulary. A decision tree constructed with internal data should be used to predict the disease-specific economic impact of adding a medication to the formulary when only medical and pharmacy claims data from the previous year are available. A regression model should be used to predict the total health care cost impact.
CHAPTER 1
INTRODUCTION

Pharmacoeconomics has been described as an emerging discipline that systematically describes and analyzes the costs and consequences of pharmaceuticals and pharmaceutical services (Bootman, Townsend, & McGhan, 1991, p. 4). Pharmacoeconomic analyses assist in decisions about the selection and use of medications and pharmacy services. Such decisions may be made at a patient level by physicians, pharmacists, or case managers, or at a population level by pharmacy and therapeutic (P&T) committees, benefits managers, or other policy makers (Kozma, Reeder, & Schulz, 1993).

Pharmacoeconomics is related to the broader discipline of health economics, which describes and analyzes distribution of inputs and consequences of any health care intervention or service (Feldstein, 1993, p. 5). The importance and popularity of these disciplines has grown exponentially over the last 30 years as evidenced by the increased number of published health care economic studies (Bradley et al., 1995). Elixhauser, Luce, Taylor, and Reblando (1993) reported that the number of published studies that evaluated both the costs and consequences of an intervention grew from five in 1966 to 251 in 1990. These studies involved numerous medical procedures and treatments including drug therapy.

The use of health economic data as an aid to medical decision making, and more specifically, the use of pharmacoeconomic data as an aid to formulary decision making, has been prompted by three inter-related factors. These factors include escalating health
care costs, increased third party payments for health care, and a changing health care delivery system. The annual health care expenditures in the United States have risen steadily from $27.1 billion in 1960 to $666.2 billion in 1990 product (Levit, Lazenby, Cowan, & Letsch, 1991). While the overall growth of the economy is responsible for some of this increase, it cannot account for all the growth in health care expenditures because the average annual percentage growth in national health expenditures has consistently outpaced the gross national product.

During this same 30-year time period, there has been a steady rise in the proportion of personal health care expenditures that are paid by third party payers. In 1960, fifty-six percent of personal health care expenditures were paid directly by the patient. By 1990 only twenty-three percent of the personal health care expenditures were paid directly by the patient, while seventy-seven percent were paid by third party payers which include private insurers, self-insured groups, and state and federal health care programs including Medicaid and Medicare (Levit et al., 1991). The rise of third party health care payments created a market in which the final consumer of health care, the patient, was no longer directly responsible for paying for health care services. Furthermore, the health care provider, acting as the agent of the patient, was free to order any test or treatment that he or she deemed necessary. As the number of available treatments and diagnostic tests grew, so did national health care expenditures.

The rise in third party coverage in both the public and private sectors and the corresponding changes in federal legislation has created dramatic changes in the health care delivery system over the past thirty-five years. To better understand the relationship
between these changes and the growing importance of pharmacoeconomic evaluations, the evolution of the public and private health care delivery systems will be discussed briefly.

Medicare and Medicaid were enacted in the mid-sixties. Although annual expenditures for these programs were projected to be $2 billion, the federal government actually spent $3.5 billion the first year and $140 billion in 1990 (Feldstein, 1993, p. 300). The initial programs allowed patients to choose any provider. Providers were paid the usual and customary fees and hospitals were reimbursed cost plus two percent. Taxes were increased in the late sixties to cover the escalating costs of the programs, and the two percent bonus was removed from the hospital reimbursement scheme. In the early seventies, the government froze wages and prohibited price increases, but costs continued to escalate. By the mid-seventies, utilization review programs were initiated to ensure proper use of medical resources; the Medicare Fee Index limited physician fees; and hospital capital expenditures were limited by federal legislation (Feldstein, 1993, p. 301).

Congress passed several pieces of legislation to stimulate competition in the health care market. The first was the Health Professions Education Act of 1963, which increased funding for health education (Feldstein, 1993, p.302). Several new health professional schools were built and funding for scholarships and grants was increased.

The second piece of legislation was the HMO Act, passed in 1973. This legislation freed federally qualified Health Maintenance Organizations (HMOs) from restrictive state medical practice acts. This act also mandated that any company with more than 25 employees must offer HMO coverage for its employees, provided that a
federally qualified HMO served the area. Unfortunately the benefits package HMOs had to offer to be federally qualified was usually more expensive than traditional indemnity plans, so managed care did not spread too rapidly. In 1979, some of the restrictive parts of the HMO Act were removed and HMOs were granted permission to expand their hospital services.

In 1981, another piece of legislation aimed at stimulating competition in the health care market was passed. The Medicaid Act was amended to allow states to negotiate contracts with physician groups thus ending freedom of choice of providers. Diagnostic Related Groupings (DRGs) were introduced in 1983 to further limit Medicare Expenditures. Under the DRG program, hospital treatments were divided into 476 diagnostic groups and hospitals were reimbursed a fixed amount to treat a patient based on the diagnosis. Hospitals were put at risk to cover the costs of treatment if they exceeded the allowed amount. By the early eighties, managed care was starting to take hold.

The increased influence of managed care was also fueled by events that transpired in the private sector during this time period. Private companies were faced with increasing health care expenditures because unions had bargained for an increase in non-taxable health insurance benefits (Feldstein, 1993, 304). The recession in the early eighties forced companies to cut costs, so they applied pressure to the insurance companies to reduce health care costs. Some companies became self-insured, other cost-cutting measures were introduced such as patient co-payments, larger deductibles, prior
authorization for certain medical procedures, and authorization for more outpatient procedures that were previously restricted to the inpatient setting.

In response to the changing market forces created by both private and public sector initiatives, the health care industry went through numerous changes. In response to government regulations of the early seventies (e.g., caps on capital expenditures and certificate-of-need laws) hospitals diversified to provide services such as home health care, outpatient pharmacies, and physician office building management to maintain profits (Sahney, 1996). Within five years, hospitals were experiencing a surplus of hospital beds, so they developed joint ventures with physicians to secure and increase admissions (Sahney, 1996). The next change in health care delivery, horizontal integration, followed the introduction of DRGs in 1983. Hospitals formed networks in an attempt to achieve economies of scale and secure regional and or national insurance contracts.

The growth of managed care and increased competition during the nineteen eighties led health care corporations to vertically integrate. This was done to align physician groups and other providers with health care organizations in an attempt to exert more control over medical resource utilization (Sahney, 1996). The health care delivery system is currently undergoing virtual integration. This puts large health care organizations, including insurers, in the business of assembling care. Providers and specialists are contracted to provide care and are electronically linked to the network.

One of the consequences of moving from a provider-based fee-for-service system to a vertically integrated health care delivery system is that the decision making authority
for drug product selection has shifted from the individual physician to a purchasing agent for the health system or a committee such as a Pharmacy and Therapeutics (P&T) committee (Wardell, 1998).

In an attempt to control costs and stay competitive, the P&T Committees of many managed care organizations rely on a variety of sources of information to aid in the management of the formulary. Lyles, Luce, and Rentz (1997) conducted a nationally representative telephone survey of 51 large managed care organizations in the United States. All of the group/staff model HMOs reported that they maintain formularies to decrease costs, provide information and a list of medications, and to provide appropriate therapy. The next most commonly reported reasons for maintaining a formulary, in descending order, were: decreased duplication of products, to control drug use, to promote inventory control, and to meet accreditation standards.

All of the group/staff model HMOs reported that they use safety and efficacy information when making formulary decisions, and 93% reported using information on the cost and/or the cost-effectiveness of the medications. Fifty-seven percent reported to use information on the quality of life of the patients to aid in the formulary decision-making process. One hundred percent of the respondents reported using peer-reviewed literature as a source of drug assessment information followed by evaluations performed by the industry (79%), government reports (71%), reports from other HMOs (71%), articles in non-peer-reviewed journals (29%), and pharmacy benefits managers (PBMs) reports (21%) (Lyles et al., 1997).
Ninety-three percent of the staff/group model HMOs that responded indicated that a person within the organization was responsible for drug assessments. Of these, 62% reported that drug assessments were the primary job responsibility of that individual (Lyles et al., 1997).

When asked about the anticipated usefulness of various types of assessments to future formulary decisions, the most useful type of assessment to group/staff model HMO decision makers was clinical effectiveness, followed by safety, cost-effectiveness, quality of life, and cost of treatment (Lyles et al., 1997).

The public sector is also using pharmacoeconomic data to help manage formularies. The U.S. Department of Defense (DOD) established a Pharmacoeconomic Center (PEC) to conduct and use applied pharmacoeconomic data to "evaluate drug therapy and formulary choice to control costs within one of the largest, vertically integrated, staff-model health maintenance organizations in the country" (Finder, 1997).

Pharmaceutical manufacturers have responded to the change in decision making authority by marketing to managed care decision makers who have become increasingly interested in economic as well as the clinical outcomes of medical therapy (Langley and Martin, 1997). Many pharmaceutical manufacturers developed a hybrid sales force that combined science and marketing. The intent behind this sales force is to have clinically trained scientist sharing information with other clinically trained scientists. By sharing information about clinical trials and other studies, they are able to circumvent some of the advertising restrictions imposed by the United States Food and Drug Administration and the Federal Trade Commission.
Although this hybrid sales force is not specifically oriented toward pharmacoeconomics, they often use pharmacoeconomic analyses because a pharmacoeconomic study can demonstrate both the clinical and economic benefits of a medication. Pharmaceutical manufacturers have a vested interest in providing favorable clinical and economic data about their products to ensure their products are on as many formularies as possible. Evidence that pharmaceutical companies are increasingly using pharmacoeconomic studies to support their products was reported by Neumann, Zinner, and Palteil (1996) who found that pharmaceutical companies sponsored an average of two pharmacoeconomic studies in 1988 compared to an average of 24 studies per company in 1994.

The need for pharmaceutical manufacturers to show their medications in a positive light combined with the lack of standard pharmacoeconomic methods has led some to interpret the findings of pharmacoeconomic analyses with great caution. This distrust was summed up by Cahill (1995) who stated that pharmacoeconomic methods are "almost infinitely malleable and thus can be manipulated to support a preordained conclusion." The fear of predetermined results has led the New England Journal of Medicine to issue guidelines for the acceptance and publication of pharmacoeconomic studies. Concerns about the lack of scientific rigor, non-standardized methodologies, and confusion among the consumers of pharmacoeconomic research has also prompted the U.S. Food and Drug Administration (FDA) to issue draft pharmacoeconomic guidelines in 1995 through its Division of Drug Marketing, Advertising, and Communications (Neumann, Zinner, & Paltiel, 1996).
Much of the distrust in pharmacoeconomic analyses comes from the fact that modeling is often used in place of controlled experiments because it is too costly to conduct randomized controlled trials to answer every pharmacoeconomic issue that arises in day to day clinical practice (Sheldon, 1996). Assumptions about the data or underlying population of interest must be made when using any model to answer a research question. The models most commonly used in the pharmacoeconomic literature fall into two groups, deterministic and stochastic models.

Deterministic models are the more common of the two types of models and usually take the form of a decision tree or a Markov model. They are based on estimates of the costs and effects associated with the given interventions under study.

Linear or logistic regression models are the most common form of stochastic models. Stochastic models are based upon patient-level or primary data (Sacristan, Day, Navarro, Ramos, & Hernandex, 1995; Coyle, 1996). Patient-based data may be obtained from numerous sources including questionnaires, medical records, administrative claims databases, or clinical trials.

The United States DOD PEC prefers to use stochastic models based on statistical techniques because they allow multiple interventions to be assessed simultaneously more readily than decision analytic deterministic models (Finder, 1997).

Problem Statement

It is clear that the number and types of pharmacoeconomic analyses will only increase because the U.S. Food and Drug Administration in recent years has approved a record number of new drugs. One hundred-ten new drugs were approved in the 18-
month period ending June 1998, which is a 37% increase from similar periods in the past (USAToday, July 10, 1998).

Managed care pharmacy costs have increased anywhere from 8-20%, and costs within certain medication classes has risen even more, due in part to the introduction of new agents and direct-to-consumer advertising (McCarthy, 1998). Managed care organizations have implemented several strategies to combat this trend such as adjustable co-pays that are higher for drugs of questionable medical necessity, exclusion of drugs from the formulary, restrictions on medication, and information hotlines to provide information to patients on the proper use of certain medications (McCarthy 1998).

With more new drugs on the market, formulary managers are faced with more formulary requests from providers and patients, and pharmaceutical companies are applying more pressure on decision makers to increase the market share of their products. Because health care budgets are limited, formulary decision-makers are forced to make choices as to which medications will be included on the formulary. In addition to answering questions of safety and efficacy, formulary decision-makers need to estimate the budgetary impact of formulary additions.

Thus, it is more important than ever for managed care organizations to have a way to predict the budgetary impact of adding a medication to their formulary. Applied pharmacoeconomics offers a variety of techniques to predict such impacts. Unfortunately, these techniques and models have not been assessed and/or compared to determine how accurately they predict changes in treatment costs.
Although there are discussions in the pharmacoeconomic literature about how to build models to conduct cost and cost-effectiveness analyses, little attention is given to the validity of the use of models (Sheldon, 1996). Thus models are being used to set clinical policy, funding priorities, and product development strategies without knowledge of the accuracy of the model results (or predictions). As Sheldon stated: “The question being asked is not whether economic evaluation is of fundamental importance, but whether, in its current stage of development it is methodologically mature enough and carried out with enough rigor to play this decisive role.”

Statement of Purpose

The purpose of this research was to assess the ability of a decision analytic based deterministic model and a regression analytic based stochastic model to predict the average diabetes-specific costs incurred by a managed care organization during the 12 month period following the addition of metformin to the formulary of a managed care organization. The ability of the stochastic model to predict the average diabetes-related costs and total health care costs was also assessed. In addition this research also assessed each model to determine if the assumptions used to construct each model were consistent with what actually occurred in year 2.
Research Objectives

1. To compare the predicted average diabetes-specific costs obtained from the deterministic and stochastic models to the actual average diabetes-specific costs incurred during the 12 month period following the addition of metformin to the formulary of the managed care organization (year 2).

Hypothesis 1a: $\mu_{DSC-DM} = \mu_{DSC-SM} = \mu_{DSC-Actual}$

Hypothesis 1b: $\mu_{DSMC-DM} = \mu_{DSMC-SM} = \mu_{DSMC-Actual}$

Hypothesis 1c: $\mu_{DSPC-DM} = \mu_{DSPC-SM} = \mu_{DSPC-Actual}$

Where:

$\mu_{DSTC-DM}$ is the average diabetes-specific total cost predicted by the deterministic model;

$\mu_{DSTC-SM}$ is the average diabetes-specific total cost predicted by the stochastic model;

$\mu_{DSTC-Actual}$ is the average diabetes-specific total cost actually incurred in year 2;

$\mu_{DSMC-DM}$ is the average diabetes-specific medical cost predicted by the deterministic model;

$\mu_{DSMC-SM}$ is the average diabetes-specific medical cost predicted by the stochastic model;

$\mu_{DSMC-Actual}$ is the average diabetes-specific medical cost actually incurred in year 2;

$\mu_{DSPC-DM}$ is the average diabetes-specific pharmacy cost predicted by the deterministic model;

$\mu_{DSPC-SM}$ is the average diabetes-specific pharmacy cost predicted by the stochastic model;

$\mu_{DSPC-Actual}$ is the average diabetes-specific pharmacy cost actually incurred in year 2;
2. To compare the predicted average diabetes-related costs obtained from the stochastic model to the actual average diabetes-related costs incurred during year 2.

   Hypothesis 2a: $\mu_{\text{DRTC-SM}} = \mu_{\text{DRTC-Actual}}$

   Hypothesis 2b: $\mu_{\text{DRMC-SM}} = \mu_{\text{DRMC-Actual}}$

   Hypothesis 2c: $\mu_{\text{DRPC-SM}} = \mu_{\text{DRPC-Actual}}$

Where:

- $\mu_{\text{DRTC-SM}}$ is the average diabetes-related total cost predicted by the stochastic model;
- $\mu_{\text{DRTC-Actual}}$ is the average diabetes-related total cost actually incurred in year 2;
- $\mu_{\text{DRMC-SM}}$ is the average diabetes-related medical cost predicted by the stochastic model;
- $\mu_{\text{DRMC-Actual}}$ is the average diabetes-related medical cost actually incurred in year 2;
- $\mu_{\text{DRPC-SM}}$ is the average diabetes-related pharmacy cost predicted by the stochastic model;
- $\mu_{\text{DRPC-Actual}}$ is the average diabetes-related pharmacy cost actually incurred in year 2;

3. To compare the predicted average total costs obtained from the stochastic model to the actual average total costs incurred during year 2.

   Hypothesis 3a: $\mu_{\text{TC-SM}} = \mu_{\text{TC-Actual}}$

   Hypothesis 3b: $\mu_{\text{TMC-SM}} = \mu_{\text{TMC-Actual}}$

   Hypothesis 3c: $\mu_{\text{TPC-SM}} = \mu_{\text{TPC-Actual}}$
Where:

\( \mu_{TC-SM} \) is the average health care total cost predicted by the stochastic model;

\( \mu_{TC-Actual} \) is the average health care total cost actually incurred in year 2;

\( \mu_{TMC-SM} \) is the average health care total medical cost predicted by the stochastic model;

\( \mu_{TMC-Actual} \) is the average health care total medical cost actually incurred in year 2;

\( \mu_{TPC-SM} \) is the average health care total pharmacy cost predicted by the stochastic model;

\( \mu_{TPC-Actual} \) is the average health care total pharmacy cost actually incurred in year 2;

4. To assess the assumptions associated with the deterministic model. Specifically, to determine if the assumed distribution of patients among the various treatments is similar to the actual distribution in year 2. The actual and predicted number of diabetes-specific physician visits and hemoglobin-A1C tests will also be compared.

5. To assess the assumptions associated with the stochastic model. Specifically, the model was assessed to determine if the data meet the assumptions of the Gauss-Markov Theorem and are appropriate for use in the general linear model. The stability of the parameter estimates will also be assessed as will the actual and predicted distribution of patients among the therapy regimens.
Significance of the Problem

Pharmacoeconomics is an evolving discipline and people do not trust models because they fear that the study sponsors or the interests of the analyst may affect the outcomes of pharmacoeconomic analyses. One of the steps required to alleviate these fears is to assess the predictive capabilities of models to ensure that information obtained from the models is consistent with clinical practice.

Williams (1974) is credited with developing the first guidelines for conducting economic evaluations in health care. Since 1974 many others have published similar guidelines (Shepard & Thompson, 1979; Eisenberg, 1989; Bootman, Townsend, & McGhan, 1991; Drummond, Stoddart, & Torrance, 1987; Jolicoeur, Jones-Grizzle, & Boyer, 1992; McGhan & Lewis, 1992). The basic steps outlined in these guidelines include: define the program and study perspective; calculate the net cost; calculate the net health effects; perform a sensitivity analysis; and apply decision rules.

Following the prescribed steps in conducting a pharmacoeconomic analysis does not ensure that the cost or outcome estimates obtained from the analysis coincide with what actually occurs in daily practice. Part of this potential discrepancy between estimated and actual outcomes stems from the fact that there are so many patient-specific and provider-specific factors that cannot be accounted for in the models.

Because no gold standard exists, the validity of pharmacoeconomic models has not been assessed. When conducting an analysis from the perspective of a health system, the closest thing to a comparative gold standard is to compare the costs predicted by the model to the cost actually incurred by the health system. However, estimates obtained
from pharmacoeconomic models are rarely if ever assessed against the costs actually incurred in a clinical setting.

Decisions based on faulty models may lead to inappropriate clinical policies/decisions that may result in poor economic, clinical, and humanistic outcomes. Sophisticated computer models will become easier to develop as more clinical and financial data are available from linked computerized databases. However, there is a need to assess these models to determine if such models improve the predictive capabilities over decision analytic models such as decision trees.
Definitions

**Allocative Efficiency:** An allocation of resources such that no change in the allocation could be made that would improve the welfare of one person without reducing the welfare of another. This is also known as Pareto efficiency or Pareto optimality.

**Average Cost-Effectiveness Ratio:** The ratio of the total cost of an intervention or service divided by the effect or outcome of the intervention or service. This is also known simply as the cost-effectiveness ratio.

**Average costs:** The total costs of an intervention or service divided by the total quantity of treatment units provided.

**Cap:** The maximum level of expenditure reimbursable by a plan in a specified time period.

**Capitation:** A prospective payment to a healthcare provider based on an actuarial projection of expected drug or medical service utilization rates for a predetermined patient population.

**Deterministic:** Accounting for all the variance, containing no disturbance term.

**Drug Formulary:** A listing of prescription medications preferred for use by a health system which can be prescribed by participating providers and dispensed through participating pharmacies to covered persons. An open formulary allows coverage for medications on the preferred list and for those not on the list, while a closed formulary limits coverage to those drugs on the preferred list (Taken from: Ito, S.M. and Blackburn, S. (eds) (1995) A Pharmacist's Guide to Principles and
Practices of Managed Care Pharmacy. Foundation for Managed Care Pharmacy, Alexandria, VA as cited in Lyles, Luce, & Rentz, 1997).

**Formulary Decision Maker:** An individual, such as the chief purchasing officer for a health system, or group of individuals, such as the Pharmacy and Therapeutics committee members, that can influence which medications are added to the formulary or considered for formulary addition.

**Health Maintenance Organization:** A managed care plan that offers prepaid comprehensive healthcare coverage, minimal co-pay and co-insurance, and usually case management to those enrolled in the plan.

**Incremental Cost-Effectiveness Ratio:** The ratio of the difference in costs to the difference in effect of one intervention or service and the next most effective intervention or service. This ratio provides an estimate of cost of producing one more successful outcome when using the intervention or service in question rather than the next most effective one.

**Managed Care:** An organized system of healthcare delivery designed to control costs and quality, by such means as mandatory drug formulary lists, pre-admission screening, case management, etc. Participating providers generally agree to accept discounted payment and to abide by the plan's cost and quality control measures.

**Marginal costs:** The cost of one additional unit of product or service delivered.

**Metformin:** Metformin an oral medication used to treat Type 2 diabetes. It is a member of the biguanide class. Although the exact mechanisms of action of this
class are unknown, a reduction in hepatic glucose production; increase in peripheral insulin sensitivity; and a decrease in glucose absorption from the intestine appear to play a role (American Diabetes Association, 1995). Biguanides do not cause weight gain and improve the lipid profile of diabetic patients. Self-limiting GI side effects are common when therapy is initiated.

**Opportunity cost:** The cost of using financial or physical resources for some purpose. It is measured by determining the value of those resources when put to the next best alternative use.

**Stochastic:** Containing a disturbance term to account for variance in individual observations that is not accounted for by the model.

**Technical Efficiency:** The point of producing the optimum output given the current input constraints.

Unless otherwise noted, the definitions presented above were taken from or are based upon the Glossary of Terms Used in Health Economics, and Pharmacoeconomic and Quality-of-Life Analyses found in: *PharmacoEconomics* 11(1):111-114, January 1997.
CHAPTER 2
REVIEW OF RELATED LITERATURE

Introduction

Pharmacoeconomics addresses the needs of clinical practitioners and clinical
decision-makers by combining techniques from the fields of medical decision making,
epidemiology, statistics, and economics. The incorporation of economic variables into
clinical trials and the availability of clinical and administrative databases have created
opportunities to use new techniques to evaluate the costs and effects of medical
interventions. The purpose of this research was to determine how well two types of
models could predict changes in the average costs of treating patients with diabetes
following the addition of an oral hypoglycemic medication to the formulary of a managed
care organization. A decision tree and a linear regression model were used in this
research representing a deterministic model and a stochastic model respectively. Each of
these analyses was conducted within an equilibrium framework.

Because researchers from multiple disciplines contribute to the
pharmacoeconomic literature, different terms are sometimes used to describe similar
techniques and methods. To avoid confusion of terms and to put this research into
context, a hierarchy of pharmacoeconomic research is presented in Table 1. This table
also provides the framework for the review of the literature.

The first section will discuss the difference between the traditional and
equilibrium approaches to pharmacoeconomic research, followed by a discussion of the
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CBA = cost-benefit analysis, CEA = cost-effectiveness analysis, CMA = cost-minimization analysis, CUA = cost-utility analysis, ANOVA = analysis of variance, ANCOVA = analysis of covariance

* Decision analytic models are generally deterministic models
** Models based on statistical analysis/techniques are stochastic models because they include a random error term
* Regression Models include linear models, logistic regression models, and simultaneous equations
** ANOVA Models include one- multi-way models and ANCOVA models
different types of pharmacoeconomic analyses that are found in the literature. Issues surrounding the use of models in pharmacoeconomic research are discussed next followed by a review of the use of deterministic and stochastic models in pharmacoeconomic research. The next section will address issues involved with claims database research, and the final section will describe the diabetes disease process, recommended standards of care, and therapies available during the time of this study.

Throughout this chapter, models will be discussed in terms of comparing medications. However, these models can be used to assess any medical intervention or service.

Framework for Conducting Pharmacoeconomic Research

The Traditional Approach to Pharmacoeconomic Analysis

The traditional approach to applying economic analyses to health care has centered around the use of decision analytic models to conduct cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-minimization analysis (CMA), and cost-utility analysis (CUA) (Weinstein & Stason, 1977; Drummond et al., 1987; Bootman et al., 1991). However, the type of analysis is not what distinguishes the traditional from the equilibrium approach to pharmacoeconomic research; rather the use of specific assumptions when conducting pharmacoeconomic analyses is what distinguishes the traditional from the equilibrium framework. The traditional approach generally focuses on comparing two or more medications under the assumptions that the medications are substitutes for one another, that complete substitution will occur and that marginal costs
equal average costs (the constant cost assumption) (Langley & Martin, 1997). Because a new medication is usually compared to one or two other agents, the traditional approach has a drug focus rather than a disease-state focus. In addition, the traditional approach may include only pharmacy costs or it may include system-wide costs.

The notion that two drugs are substitutes for one another assumes that they have equal therapeutic effects, identical side effect profiles, and that patient preference for the two agents is the same. This assumption is valid when comparing agents within the same generic class such as DiaBeta® or Micronase®, which are two name brands for glyburide. This assumption also holds when comparing agents within the same pharmacological class that have similar efficacy and side effect profiles, such as glyburide and glipizide which are both second generation sulfonylurea agents. The validity of this assumption is questionable when comparing medications from different pharmacological classes that are used to treat the same disease because the therapeutic effects and side effects may differ from one patient group to another.

Complete substitution of one drug for another implies that one therapy will no longer be available so patients treated with that agent will be switched to a different one. This assumption is made implicitly through the use of incremental cost effectiveness ratios. An incremental cost-effectiveness ratio is calculated to determine the additional costs required to achieve an additional unit of effect when patients are switched from one agent to the next most effective one (Karlsson & Johannesson, 1996). Partial switching of patients from one agent to another is not considered under the traditional approach. Assuming complete substitution is valid if one agent is being removed from the
formulary and replaced with another as often occurs for agents within the same pharmacological class. This assumption is not valid if an agent is being added to the formulary rather than replacing a current formulary agent because patients who achieve their clinical goals on one medication will not likely be switched to a new agent.

The constant cost assumption implies that the marginal costs of treating a group of patients with a given disease are constant and equal to the average cost of treating these patients, regardless of the proportion of patients treated (Langley & Martin, 1997). This assumption is consistent with clinical practice when the patients being treated have the same co-morbid conditions, severity of disease, and compliance patterns. Unfortunately, few patient groups are this homogenous. In practice, patients that are not responding to their current therapy and who are expected to respond to the new entity have treatment initiated. As the proportion of patients treated with the new therapy increases, then the likelihood of starting patients on the drug who are not perfect candidates for the therapy increases. More treatment failures and therefore more medical resources will likely be consumed by these patients. Thus the marginal cost of treating these patients will be higher than the marginal costs of treating the initial patients, violating the assumption of constant cost.

The constant cost assumption must be made when using any deterministic model because costs are aggregated over patient groups. Although this is also a problem when using deterministic models in an equilibrium framework, it is presented in this section because the traditional approach places more emphasis on the use of deterministic models.
The Equilibrium Approach to Pharmacoeconomic Analysis

The equilibrium approach to pharmacoeconomic research is based on a system-wide budget perspective rather than a pharmacy-specific budget perspective and takes a disease-focus rather than a drug-focus.

In order to understand the concepts of equilibrium examine Figure 1. The quantity of medical supplies and quantity of clinical services are given on the x- and y-axes respectively. For the purposes of this discussion, it is assumed that each “unit” of clinical service costs the same as every other unit of clinical service, and that the cost of each “unit” of medical supplies is equal to every other “unit” of medical supplies. The budget line is line AB, which runs perpendicular to the origin in Figure 1. It reflects the objective market data regarding product prices and income within the health system and shows the various combinations of the supplies and services that can be purchased with a set income (McConnell, 1987, p.513). The slope of this line is the price of clinical services divided by the price of medical supplies. If a unit of clinical service costs $200 and a medical supply unit costs $300 then the slope of the budget line is 2/3. Since the slope of the line equals the change on the y-axis divided by the change on the x-axis, this means that 2 units of medical supplies at $300 must be given up to obtain 3 units of clinical services at $200.
The location of the budget line varies with income. If income increases then the line is shifted to the right to line CD, for example. Likewise a decrease in income will shift the budget line to the left. A change in any of the unit prices will alter the location of the budget line. If the unit costs of both clinical services and medical supplies increase, then the budget line is shifted toward the left because this is equivalent to a decrease in income. The opposite is true if there is a decrease in the unit costs of both. If the unit cost of either services or supplies changes while the unit cost of the other remains constant or changes to a different degree or direction, then the slope of the budget line will change. Lines CD and EF demonstrate this.

The indifference, I, curve is the downward sloping line, which is convex to the origin. It represents all combinations of services and supplies, which will yield the same level of satisfaction or utility to the consumer. The consumer is indifferent toward the
choice between any point on a given indifference curve because every point on the same curve yields the same utility. The perspective of the analysis will determine the consumer. In this example, the consumer is a health care system.

The indifference curve has several identifying characteristics. The slope of the indifference curve is always negative (downward sloping) because there is an inverse relationship between the quantity of services and supplies. The indifference curve is convex to the origin — the slope decreases as we move from point J to K (McConnel, 1987, p. 515). The indifference curve measures the marginal rate of substitution, in this example, it shows the rate, at the margin, at which the health system is prepared to substitute medical supplies for medical services so as to remain equally satisfied. The diminishing slope of the indifference curve means the willingness to substitute services for supplies diminishes as one moves down the curve (McConnel, 1987, p. 514).

It is possible to have a series of indifference curves each with a downward slope and convex to the origin such as curves $I_2$ and $I_3$. Each successive curve (i.e., the one to the right of the previous one) represents a higher level of utility derived from a combination of medical supplies and clinical services. This series of indifference curves is known as an indifference map (McConnel, 1987, p. 515). By combining the budget line and the indifference map, the equilibrium position is obtained. The utility maximizing position/combination will be the point on the budget line that is tangent to the highest attainable indifference curve (McConnel, 1987, p. 516).

Any changes that affect the health systems budget or treatment patterns (e.g., a change in acquisition costs, formulary additions, availability of new diagnostic
technology) has the potential to shift the health system to a new budget line or indifference curve and a new point of equilibrium. Thus, within the equilibrium framework, it makes no sense to compare one drug being added to the formulary to one already on the formulary in isolation because they are both part of the overall equilibrium which encompasses all medical and non-medical interventions for a given disease.

Just as there are assumptions associated with the traditional approach, the use of the equilibrium approach to pharmacoeconomic analysis also requires several assumptions. The first is that the distribution of patients among treatment options is at equilibrium prior to the addition of a new therapy. A new equilibrium is established after an agent is added to the treatment armamentarium within a given disease area. The impact of this new equilibrium on the costs and outcomes of treating patients in that disease area is then assessed.

This approach also assumes that providers will switch patients between alternative therapies until the last dollar spent on each patient to achieve a particular outcome is equal. Patients will be switched to new therapies as long as the cost of producing a given outcome can be reduced or the maximum outcome is obtained at a given cost. The benefits from introducing a new therapy can only be evaluated by comparing the system impact in contrasting the total costs before and after the new therapy has been introduced and patients have been reallocated between therapy options.

Another assumption of the equilibrium approach to pharmacoeconomic analysis is that treatment costs per unit of outcome increases as the proportion of patients treated in a given population increases (Langley, 1996). Thus the average cost per unit of outcome is
a function of the distribution of patients among competing therapies, and therefore competing therapies should not be compared before this distribution of patients is known (Langley & Martin, 1997).

Types of Pharmacoeconomic Analyses

The analyses used in pharmacoeconomic research can be categorized as partial or complete analyses. Cost analyses and outcomes analyses are considered partial analysis because they only consider either the costs or the outcomes of an intervention. Another type of partial analysis is the program description that describes the costs and outcomes of a single program or intervention without comparing it to another. CBA, CEA, CMA, and CUA are considered full economic analyses, because at least two alternatives are compared and both the costs and benefits are included in the analysis (Drummond et al., 1987).

The question being asked, available data sources, and available financial and time resources will dictate whether a full or partial analysis is conducted. Partial analyses are sufficient to answer certain questions such as the cost impact of adding a new drug to the formulary, but a full economic analysis is required to answer questions of allocative efficiency (Drummond et al., 1987).

Cost Analysis

As stated previously, this type of analysis is a partial economic analysis because the costs of an intervention are included in the analysis while the outcomes are excluded. A cost analysis deals only with the costs incurred by an intervention with no regard to the
benefits or outcomes of the intervention. Therefore it does not address issues of technical or allocative efficiency.

The clinical trial is another partial analysis (an outcomes analysis) which answers questions of safety and efficacy. P&T committees use information obtained from clinical trials to make formulary decisions. Similarly, cost analyses can be used by P&T committees to determine the economic impact of a new formulary decision or for other budget-planning activities.

Cost-Benefit Analysis

A cost-benefit analysis is a procedure that measures individuals' gains and losses in dollars, then aggregates the gains and losses and expresses them as net social gains or losses (Pearce, 1983). It is grounded in the welfare economic notion of Pareto efficiency (Drummond et al., 1987). Pareto efficiency, also known as allocative efficiency, is an allocation of resources such that no redistribution of resources would improve the welfare of one person without reducing the welfare of another.

Because a single unit of measure, such as the dollar, is used for both the benefits and costs in a cost-benefit analysis, several outcomes can be included in the same analysis and they do not have to be of the same type (Kitz, 1991). The benefits include any savings that are realized by the intervention as a result of ending or preventing morbidity. By translating the net benefits into a dollar amount, the analysis not only accounts for more than one outcome, but also includes opportunity costs of implementing the intervention or service. The opportunity costs associated with any intervention are
the (financial) benefits forgone for investing money into the intervention under study rather than investing money elsewhere.

To conduct a cost-benefit analysis, first define the population that will incur the costs and benefits of the interventions or services included in the analysis. The actual costs and benefits should also be identified and converted into equivalent dollars in the year in which they occur, then converted to present value using the selected discount rate. Finally, the costs are subtracted from the benefits and the intervention or service with the largest net benefit is selected (Bootman, McGhan, & Schondelmeyer, 1982).

Although cost-benefit analysis appears to be consistent with welfare economic theory, several problems prevent its widespread use in health care. First is the difficulty of identifying all benefits of a program and converting them to a dollar figure. Second, it is difficult and sometimes unsavory to place a dollar value on human life and third, there is debate in the economic literature over the best method to use: willingness to pay or the human capital approach. Another problem inherent to all economic analyses is determining the appropriate discount rate (Bootman et al., 1982; Kitz, 1991; Drummond et al., 1987).

Cost-Effectiveness Analysis

Cost-effectiveness analysis is tool to help decision makers choose between a variety of therapy interventions or clinical services by summarizing the benefits obtained from and resources consumed by each (Shepard & Thompson, 1979). The purpose of cost effectiveness analysis has been stated three ways. The first is that cost-effectiveness analysis allows decision-makers to maximize aggregate health effectiveness given a
limited budget, regardless of the distribution of treatments among patients (Karelsson & Johannesson, 1996; Weinstein & Stason, 1977; Wagstaff, 1991). The second stated purpose is that cost-effectiveness analysis allows decision-makers to achieve a given rate of output at the least cost (Birch & Gafni, 1992). The third statement of purpose is that cost-effectiveness analysis provides a way of assessing technical efficiency, which relates the value of inputs to the quantity of outputs.

A cost-effectiveness analysis entails the calculation of a cost to benefit ratio. The denominator of the ratio is a single outcome measure of the intervention and it is measured in natural units (Drummond et al., 1987; Birch & Gafni, 1992). Sometimes intermediate outcome measures must be used because final outcomes data are not available. Examples of intermediate outcomes include: mmHg decrease in systolic blood pressure, proportion of patients responding to a therapy, or change in mmol total cholesterol, whereas examples of final outcomes include: increased number of life years or number of deaths. Since only one outcome can be used in a cost-effectiveness analysis, the outcomes of the interventions being compared must be singular and common to all comparators in the analysis (Birch & Gafni, 1992). This limits the comparisons to programs or interventions with the same outcome.

The numerator of the cost-effectiveness ratio is cost, measured in monetary units. This is the total cost required to provide the therapy intervention under consideration, and is calculated by summing acquisition costs, the cost associated with treating side effects of the therapy, and the treatment costs associated with the extended life provided by the
therapy intervention. The savings associated with alleviating morbidity are then subtracted from this sum to yield the total costs (Weinstein & Stason, 1977).

While some studies report only the average cost-effectiveness ratios, that is the expected cost divided by the expected outcome, Karlsson & Johannesson (1996) claim that this is inappropriate because it does not aid in selecting the most cost-effective therapy. By simulating a study of numerous treatments in three different homogenous populations, Karlsson and Johannesson demonstrate that just because two separate therapies have equal average cost-effectiveness ratios, it is impossible to conclude that they are equally cost-effective. The incremental cost-effectiveness ratio must be used to determine the most cost-effective therapy.

To estimate the incremental cost-effectiveness ratio, the therapies are ranked in increasing order of effectiveness. Then the incremental cost-effectiveness ratio is calculated by dividing the incremental costs by the incremental effect for each successively more effective treatment alternative. This ratio shows how much the cost is increased when the next marginally effective treatment option is chosen. It should only be calculated for mutually exclusive treatment option within a homogenous patient group and not across groups (Karlsson & Johannesson, 1996).

Once the incremental cost-effectiveness ratio is calculated, two different decision rules can be used to select the most cost-effective therapy. The first relies on the budget. The treatment with the lowest incremental cost-effectiveness ratio is implemented, then add independent treatment in other homogenous groups or replace mutually exclusive treatments with more cost-effective ones until the budget is exhausted. Using the budget
as the decision rule may result in different treatments within a homogenous patient group. This raises ethical issues about the distributive justice and equality (Karlsson & Johannesson, 1996).

The second decision rule is to set a maximum willingness to pay for a unit of effectiveness. Using this approach, a cut off is set and all patients within a homogenous treatment group receive the treatment that has an incremental cost-effectiveness ratio at or below the cut-off point. This approach always leads to the adoption of the same treatment within a patient group (Karlsson & Johannesson, 1996).

**Cost-Minimization Analysis**

A variation of the CEA is the cost-minimization analysis. The costs included in this analysis are calculated just as they are in the CEA. Similarly, the benefits of the interventions included in the CMA are represented by a single outcome measured in natural units (Bootman et al., 1991, p.4). In addition to having a common outcome for the interventions included in the CMA, the magnitude of the outcome must also be the same. Thus the CEA is reduced to a CMA because the “effectiveness” of both interventions is equal.

**Cost-Utility Analysis**

Another variation of the CEA is the cost-utility analysis. The numerator of the cost-utility ratio is the cost of the intervention or service as measured in the cost-effectiveness ratio above. In theory, the denominator of the cost-utility ratio is a measure of utility, which is patient preference (Birch & Gafni, 1992; Bootman et al., 1991). The
The most common utility measure is the quality adjusted life year (QALY) or healthy year equivalent (HYE). One advantage of the CUA over the CEA is that the analyst is not forced to select a single outcome measure. This allows comparison of programs that do not have the same outcomes (Birch & Gafni, 1992).

There are several unresolved issues regarding CUA. First, who should provide the utility estimates, the patient, the caregivers, health care providers, or the payers? Second, there is some question as to whether a utility measure taken in one disease area is equivalent to one in another disease.

As stated above, complete pharmacoeconomic analyses compare two or more interventions or services. Furthermore, there is usually some degree of uncertainty about the final outcomes and amount of resources needed to support an intervention or service. Thus, a decision analytic framework is used to conduct most CBA, CEA, CMA, or CUA in the traditional approach to pharmacoeconomic analysis.

Analytic Methods and Types of Models Used in Pharmacoeconomic Research

Models are used extensively in pharmacoeconomic research regardless of the type of analysis or framework used in the study. The term modeling has two meanings when applied to pharmacoeconomic research. The first use is the more general one which refers to the abstraction of pertinent information from complex systems into simpler elements which allow us to understand how the system works or to predict the effects of the system (Rittenhouse, 1996; Sheldon, 1996). This use refers to the noun and is usually called “a model” or “the model”.
The second use of the word modeling deals with the use of data in a model of the first type (Rittenhouse, 1996). Certain data, which are not measured directly due to measurement difficulties (or other constraints), are estimated based on the best available data, which has been measured directly. These estimates (i.e., the modeled data) are then used in "the model" to answer some question or address some issue. This second use of the word is usually a verb or adjective.

Models are used to study phenomena when complete data are lacking. Proponents of the use of models in pharmacoeconomic research argue that they are necessary to use because randomized, controlled clinical trials, the method commonly used to prove the safety and efficacy of medications, are too costly to conduct to answer every pharmacoeconomic question that must be addressed. This is one of the reasons why the U.S. DOD PEC has adopted the use of models over clinical trials for pharmacoeconomic research (Finder, 1997). Others contend that clinical trials are not sufficiently long enough to gather information on long term outcomes and usually have strict inclusion and exclusion criteria to control for potential confounding factors (Langley & Martin, 1997; Motheral & Fairman, 1997). Thus the use of homogenous study subjects, who are compliant with the study medication and who have no co-morbidities, maintains the internal validity of the clinical study while limiting the external validity. One group of clinicians reported that 85% of their patient population would have been excluded from a clinical trial reported in the literature (Hlatky et al., 1984).
Both opponents and proponents of the use of models for pharmacoeconomic research voice concerns that policy and funding decisions are based on models that have not been validated and may be constructed to favor commercial or government interests (Cahill, 1995; Sheldon, 1996). The ease with which models can be manipulated to favor one product over another has led many to question the “science” behind pharmacoeconomics and view pharmacoeconomic analyses as nothing more than marketing exercises. In addition to being concerned about the bias of the model builder, clinicians are often suspicious of pharmacoeconomic analyses because the models used do not represent clinical practice. This observation highlights one of the primary problems facing the model builder, namely the level of detail used in the model.

To minimize bias and maximize the acceptance of a model, a few key points should be followed when constructing a model. First, models should be sufficiently detailed to include all key characteristics of the situation being modeled (Detsky, Naglie, Krahn, Naimark, & Redelmeier, 1997). The key characteristics may include the most common events or events with largest consequences. Exclusion of key characteristics could bias the results produced by the model. Second, the thoroughness of model building must be counter balanced with simplicity. If the model is too complex then calculations become cumbersome and the potential for mathematical errors increases. Furthermore, data needed to build an overly complex model may not be available. Overly complex models are more difficult to understand and interpret and may defeat the purpose of the model.
Types of Models Used in Pharmacoeconomic Research

In the book *A Guide to Econometrics*, Kennedy (1996) explains that the difference between an economist and an econometrician is that econometricians are concerned with disturbance terms. Although Kennedy was talking about how the two groups view relationships among economic variables, this comparison describes the heart of the difference between the two types of models used in pharmacoeconomic research, deterministic and stochastic models. Each type of model is based on a unique relationship between the variables used in the model.

A relationship between two variables can be described in a number of ways, depending upon the context in which the variables are examined. Within an analytical context, two specific relationships are used to describe the interaction among variables: the functional relationship and the statistical relationship. The functional relationship is a relationship between two (or more) variables that is specified by a mathematical formula. For instance, \( Y = f(X) \), where \( Y \) is a function of \( X \). This formula specifies a specific value of \( Y \) for each level of \( X \) -- a perfect relationship.

Deterministic models are based on functional relationships between variables and the model is assumed to account for 100 percent of the variation. For instance, Goldstein, Larson, Yamashita, and Boyd (1997) used a decision tree to estimate the expected cost of two approaches to treating non-steroidal anti-inflammatory drug (NSAID)-induced ulcers. One sub-tree, the NSAID sub-tree, consisted of three branches for NSAIDs taken with either misoprostol, H2-receptor antagonists, or with no ulcer medication. The expected cost of this sub-tree is given as a function of the specific treatment regimen and
the resources that are supposedly associated with successful and unsuccessful treatment with that regimen. The probabilities, costs, and outcomes used in the decision tree are based on point estimates derived from the literature, clinical and administrative databases, or expert opinion. Unique patient characteristics, measurement errors, or factors omitted from the model are not accounted for in the deterministic model. Most wholly deterministic models used in traditional pharmacoeconomic research adopt a decision analytic approach and calculate cost-effectiveness or cost-utility ratios. Generally no tests of statistical significance are conducted (Coyle, 1996).

Unlike the functional relationship, the statistical relationship is not a perfect one. Imagine two variables plotted on a scatter plot, Y vs. X. A line drawn through the points in a scatter plot suggests the statistical relationship between the two variables. The points in the scatter plot do not necessarily fall directly on the line of relationship, this “scatter” of points around the line is the variation in Y not accounted for by X. This scatter could be due to measurement error, omission of other variables that impact the relationship between X and Y, or it could be due to the unique characteristics of the subjects from which measurements of X and Y were taken.

Stochastic models are based upon statistical relationships and include an error term or disturbance term that is based on the scatter of points around the line on the scatter plot. The disturbance term accounts for the variance in Y that is not accounted for by X. The presence of the disturbance term not only acknowledges the fact that the model does not account for all the variance, it should also allow for more accurate estimates when used in pharmacoeconomic analyses. The actual distribution of costs or
effects is known in a wholly stochastic model because they are based on primary data or patient-level data (Sacristan et al., 1995; Coyle, 1996). Data used in stochastic models are obtained by collecting economic and outcome data during a randomized controlled trial or from clinical and administrative databases that contain patient-level data. Although stochastic models generally utilize statistical analysis, they do not preclude the calculation of average or incremental cost-effectiveness ratios.

Uncertainty in these two types of models arises from different causes and is handled differently. Economic analyses that use deterministic models are sensitive to the point estimates of the costs and consumption of resources used in the model. These could be affected by the populations studied, the geographic location of the populations studied, the differences between efficacy and effectiveness rates, the different outcomes considered, and the use of different discount rates. Stochastic models built from claims data are subject to sampling and measurement errors such as miscoding, typing errors, and missing claims (Coyle, 1996).

**Decision Analysis and Deterministic Models**

Decision analysis was introduced into health care in the early seventies and its use has increased over the years. Decision analysis is useful when a choice has to be made between two or more alternatives (e.g., treatment interventions or clinical services) and there is uncertainty about which option is most appropriate (Weinstein & Fineberg, 1980).

Decision analysis separates a decision into three components: alternatives, probabilities, and outcomes (Hagen, 1992). The viable alternatives will differ from one
analysis to another depending on the situation being modeled, and may include pharmacotherapy, surgery, non-pharmacological therapy, or no treatment. The probabilities used in a decision analysis are estimates of the likelihood that a given event will occur, and can come from a variety of sources such as randomized controlled trials, observational studies, or clinical databases. The outcomes can be clinical or financial in nature and represent the end-point of the decision tree.

The analyst is responsible for defining the characteristics of the decision and patients being modeled (Hagen, 1992). Exact specification is preferred to ambiguous descriptions because it helps the consumer of the research determine if the model is applicable for their clinical setting and patient population. For example, rather than saying that a model represents diabetes, it should be stated that the model represents patients with type 2 (non-insulin dependent diabetes mellitus) that are currently receiving oral anti-diabetic medications.

In addition to specifying the characteristics of the patient population, a decision model should include all key characteristics of the situation or treatment intervention being modeled. However, care should be taken to avoid making the model too complex or cumbersome. Data may not be available to complete an overly complex model and they have the potential to confuse decision-makers without providing any additional information (Detsky, Naglie, Krahn, Naimark et al., 1997; Moskowitz, Dunn, Lau, & Pauker, 1984).

Although decision analysis is a useful tool, it is not without problems. First of all, it is time consuming. Novices may underestimate the time and technical expertise
required to conduct a proper analysis. Improper model construction will limit the usefulness of the model because it is incomplete which may bias the results (Hagen, 1992). It is often difficult to develop and obtain appropriate utility measures or clinical outcomes. It is undecided how or if tests of statistical significance should be conducted on decision analysis models (Hagen, 1992).

**Techniques for Building a Decision Tree Model**

The decision tree is a common way to operationalize a decision analysis. The starting point of a decision tree is the decision node or choice node, which is represented by a square (Weinstein & Fineberg, 1980; Hagen, 1992). This point indicates where the decision-maker must choose between several alternatives that are represented as branches radiating from the decision node. All branches emanating from the same node in a decision tree represent mutually exclusive options.

The events that occur in the branches following the decision node are not under the control of the decision maker, that is, the patient may respond favorably to the therapeutic intervention, have an adverse reaction, or die. These events are represented as branches emanating from the chance nodes. Chance nodes are represented as circles and the branches arising from these nodes should represent all clinically relevant events that could occur (Weinstein & Fineberg, 1980; Hagen, 1992). The probabilities associated with the branches extending from a given chance node should sum to one. As with the branches emanating from a decision node, the branches from a chance node should represent mutually exclusive events so that a given patient may travel only one path through the decision tree (Weinstein & Fineberg, 1980; Hagen, 1992).
The time frame covered by the model will be dictated by the disease state or therapy intervention under study. The time frame should be long enough to capture key outcomes (Detsky, Naglie, Krahn, Naimark et al., 1997). For instance, a one-month time frame would be sufficient if an acute infection such as otitis media is being modeled. This would capture the initial office visit and treatment as well as a relapse if applicable. A one to three year time frame should be used when modeling most chronic conditions such as asthma, diabetes, hyperlipidemia, heart failure, etc. (Detsky, Naglie, Krahn, Naimark et al., 1997). When modeling asthma, a one-year time frame should provide sufficient time for a medication adjustment period, as well as visits to the emergency room and hospital to control acute exacerbations. When considering the time frame, one must consider the trade off between accuracy and simplicity and completeness versus data availability (Detsky, Naglie, Krahn, Naimark et al., 1997).

The appearance of a decision tree may vary slightly from one author to another, depending upon the computer programs used to construct the tree. However, there are basic recommendations that should be followed when constructing a tree. Most of the recommendations are made to ensure that consistent results are obtained from the sensitivity analysis. Detsky, Naglie, Krahn, Redelmeier, and Naimark (1997) recently offered six recommendations for building a decision tree:

1. The decision tree must have balance and accurately reflects the clinical problem.

Each tree should be designed such that no single branch carries all the risk or all the benefits. If any single branch did contain all the risks (or all the benefits), then it
either fails to represent the clinical problem or the problem did not require decision analysis in the first place.

2. Only two branches should extend from a chance node.

This is done for practical rather than logical reasons to avoid inconsistencies in the sensitivity analysis. Having only two branches extend from any chance node makes it easier to assign the compliment of a probability that is altered during the sensitivity analysis since the sum of the probabilities of all the branches arising from a chance node must sum to one.

3. The decision tree should not contain any embedded decision nodes.

This is also done to prevent illogical results during a sensitivity analysis.

4. The branches should be linked with one another.

A linkage specifies the relationship between probabilities that are related. If a decision tree contains subtrees that are repeated within the model, then the same variable name (i.e., probability code) should be given to probabilities that are equal within the tree. This allows them to be simultaneously varied during the sensitivity analysis.

5. Each decision tree must have symmetry.

This is done to ensure that all the treatment options available to patients are appropriately represented in all the branches. Progression from one level of therapy to the next is dependent upon the treatment status at the beginning of the study period and should proceed in a logical and clinically relevant manner.

6. The order of the branches does not matter.
The branches can be arranged for aesthetic or practical reasons. The order makes no difference in the calculation of the expected costs or outcomes.

The actual probabilities used in a decision tree are unknown and must be estimated. The estimate can come from a published meta-analysis, clinical studies, expert opinion, or existing databases (Naglie, Krahn, Naimark, Redelmeier, & Detsky, 1997). The steps involved in deriving the probabilities for the tree are given below.

1. Conduct a systematic review of the literature including computerized searches, file-drawer searches, and review of references.

2. If probabilities are found in an applicable meta-analysis they may be used. Otherwise, the analyst should examine the clinical studies obtained from the search to determine if they are applicable to the current model. Assess the study design, population studied, the study setting, and time frame.

3. Discard non-relevant studies and studies that are methodologically flawed.

4. If one study is methodologically superior to all the others, then the probabilities obtained in this study may be used.

If more than one relevant study exists, average the results of the studies to obtain the probability estimate for the model. A weighted average (weighted by N) may be used.

Because some degree of uncertainty surrounds these estimates, the range of probabilities or the 95% confidence interval around the average should be used in the sensitivity analysis.
Dealing with Uncertainty in Deterministic Models

Because point estimates of the probabilities, costs, and outcomes are used to conduct cost or cost-effectiveness analyses with a decision tree, uncertainty is assessed by a sensitivity analysis (O'Brien, Drummond, LaBelle, & Willan, 1994). A sensitivity analysis assesses the robustness of the results of a deterministic model over a range of alternative values for uncertain variables. One-way and two-way analyses are most frequently conducted.

A deterministic model is initially run using the base case probability and outcome estimates (outcome estimates may be economic or clinical outcomes). The base case estimates represent the analyst's best guess of the actual value of the probability or outcome being used. The estimates can come from clinical trials, actual practice patterns, expert opinion, or the subjective estimate of the analyst. The analyst's confidence in the base case estimates will be higher for some than others, depending on how the estimates were obtained. The uncertainty around the probability, cost, or outcome estimates determine which variables will be included in the sensitivity analysis. Those with greater uncertainty will be included in the sensitivity analysis to determine if the model is robust to changes in that variable.

To conduct a one-way sensitivity analysis, first determine which probability or outcome variables are to be included in the sensitivity analysis. Then conduct the analysis using the base case probability and outcome estimates. Next systematically alter each variable included in the sensitivity analysis (one at a time) using the highest and lowest value within the reasonable range of values. Finally, determine if the conclusions
of the analysis change over the range of values for each variable included in the sensitivity analysis (Weinstein & Fineburg, 1980). If the conclusions do not change then the model is not sensitive to (i.e., is robust) to changes in the estimated variable. If the conclusions change when any of the variables are altered, then the model is sensitive to that estimate and the analyst should do everything possible to ensure that the best estimate is obtained. The more robust the model, the more confidence can be placed in the results of the analysis.

The same procedure is used to conduct a two-way or three-way sensitivity analysis except that two or three variables are altered at one time. The multi-way sensitivity analyses are difficult to interpret. Furthermore, the sensitivity analysis ignores the sampling variances of the estimated probability or outcome variables (Katz & Hui, 1989).

Several alternative methods have been proposed to assess the variability of the all the variables at once. Each variable in decision analysis is assumed to be fixed at a particular level, the point estimate of that variable. Probabilistic sensitivity analysis takes into account the uncertainty of the probabilities and outcomes used in the decision tree. This type of sensitivity analysis utilizes an assumed probability density function for each variable and determines the mean and standard deviation of this distribution using algebra (Willard & Critchfield, 1986; Katz & Hui, 1989) or Monte Carlo simulations (Doubilet, Begg, Weinstein, Braun, & McNeil, 1985; Critchfield & Willard, 1986). The use of a probability density function does not indicate that the variable is randomly distributed, rather it represents the uncertainty about a fixed but unknown value. The more consistent
the data, the smaller the uncertainty about the location of the true location of this value (Critchfield & Willard, 1986).

Using Monte Carlo simulation, the robustness of the model is assessed by performing a large number of simulations to determine how many times each pathway is selected as the dominant (or best) option. If a single pathway dominates the others all the time or most of the time, then the model is robust. If no pathway is dominant, then the model is sensitive (i.e., not robust) to the assumptions made regarding the point estimates of the probability and/or outcome variables.

Another advantage of using a Monte Carlo-based probabilistic sensitivity analysis is that an average expected cost or outcome can be calculated along with a the standard deviation and standard error of the mean. Confidence limits can then be constructed around the cost or outcome estimates.

Chalfin, Holbein, Fein, & Carlon (1993) conducted a cost-effectiveness analysis of monoclonal antibodies against gram-negative endotoxin in the treatment of presumed gram-negative sepsis. The decision tree was constructed within the traditional framework and the clinical probabilities were based on the combined results of two clinical trials. Patient charges were used as a proxy for costs, and the acquisition cost of the monoclonal antibody therapy was assumed to be $2,000 and $4,000. Resource and cost data were obtained from reviewing the charts of 1,405 patients admitted to a hospital ICU with presumed gram-negative sepsis between January 1985 and December 1988.

The baseline results of the analysis were that monoclonal antibody therapy was more costly and more effective than standard antibiotic therapy. The average cost-
effectiveness ratio for monoclonal antibody therapy was lower than that of the standard antibiotic therapy and the incremental cost-effectiveness ratio was $14,125 and $39,125 for the monoclonal acquisition cost estimates of $2,000 and $4,000 respectively. The Monte Carlo simulation produced similar results. The average expected cost and standard deviation of all the simulations were reported for both therapeutic options. Both the average expected cost and survival were higher for the monoclonal antibody treatment. Standard antibiotic therapy was selected as the lowest cost treatment arm in 71.5% of the simulations and had the highest survival probability in 20.2% of the simulations (Chalfin et al., 1993).

The robustness of this model is a judgement call. Nearly 75% of the simulations were consistent with the results obtained from using the baseline estimates. Conversely, the results were inconsistent 25% of the time. It is up to the user of these results to determine if they are comfortable with the robustness of this model or if the model should be respecified with new probability and cost estimates.

Decision Analysis Used in the Literature

The three decision analytic studies discussed below compare a low-molecular-weight heparin, enoxaparin, with standard unfractionated heparin for the prevention of deep vein thrombosis following hip replacement surgery. These studies were chosen because they incorporated different assumptions into the model, were modeled in three separate practice settings, used different methods to obtain the probability estimates and costs, and obtained different results.
Hawkins, Langley, and Krueger (1997) conducted a cost-effectiveness analysis using a decision tree within a traditional framework to determine whether the enoxaparin was more cost-effective than unfractionated heparin. Probabilities from three clinical trials that compared the two agents were modeled separately. The costs were obtained from other analyses reported in the literature and the decision tree was based on current treatment DVT prophylaxis and treatment patterns in the United States. The perspective of the analysis was that of a managed care organization and only direct medical costs were included. A series of one-way sensitivity analyses were conducted to assess the robustness of the model to changes in the costs of hospitalization, length of stay, and length of DVT-prophylaxis. This study was sponsored by the manufacturer of enoxaparin.

The average or expected cost of DVT-prophylaxis with enoxaparin was $35 to $50 higher than the average cost of heparin prophylaxis. However, because enoxaparin therapy was more effective (i.e., prevented more DVTs), it was associated with a lower average cost-effectiveness ratio. The incremental cost-effectiveness of switching from heparin to enoxaparin was reported to range from $494 to $2,273 per additional DVT avoided depending on the probabilities used.

To use the results of the Hawkins et al. study, a formulary decision-maker within a managed care organization must accept the assumptions of the traditional approach to pharmacoeconomic analysis. The assumptions of the traditional approach are not necessarily inconsistent with this disease state. Given the limited number of agents indicated for the prophylaxis of DVTs following hip replacement surgery and the
mechanism of action of enoxaparin and heparin, it is clinically logical to include only these two agents in the analysis. Furthermore, chances are high that only one agent will be used in a DVT prophylaxis protocol, so they are complete (or near complete) substitutes for one another. The assumption of constant costs is not necessarily inconsistent in this clinical scenario because a recurrent DVT, pulmonary emboli, or a major hemorrhagic event will be treated the same way and use the same resources no matter what other co-morbid conditions exist.

In addition to accepting the assumptions of the traditional framework, the decision maker will also have to assume that the costs used in the model and the patients in the clinical trials (from which the decision tree probabilities are based) are similar to the costs and patients in the managed care organization. Having made these two assumptions, the results indicate that it will cost, on average, between $35 and $50 per person treated to switch from heparin to enoxaparin for DVT prophylactic therapy, and 22 to 89 additional DVTs per 1,000 patients treated will be prevented. Given the assumptions of the model, enoxaparin is more efficient than heparin based on the incremental cost-effectiveness ratios.

Given the variability in the results and the assumptions that need to be made to apply them, perhaps the biggest contribution of the analysis is that it provides a framework that a managed care organization could use to plug in its own costs and probabilities for internal use.

Using a decision tree within the traditional framework, Drummond, Aristides, Davies, and Frobes (1994) estimated the cost-effectiveness of enoxaparin and heparin for
prophylaxis against deep vein thrombosis following elective hip surgery. The perspective of this analysis was that of the United Kingdom National Health Service. Resource consumption was based on expert opinion and the costs came from other published cost analyses. The probabilities used in the decision tree came from a single study, and one-way sensitivity analyses were conducted by varying the probability of a DVT and the cost of prophylaxis.

The results reported by Drummond et al. (1994) differ from the others reported in that the expected cost of the enoxaparin prophylaxis arm is less than that of the unfractionated heparin arm (104 British pounds versus 124 British pounds, respectively). Even though the costs in the Drummond study are measured in pounds as opposed to U.S. dollars, the ratio of heparin to enoxaparin acquisition costs is much higher than that reported by Hawkins et al. (1997). Furthermore, Drummond et al. included 10 minutes of nursing time per drug injection, so 34.10 pounds was added to the cost of heparin prophylaxis and 8.40 pounds to the cost of enoxaparin prophylaxis. The administration costs for heparin appear disproportionately high even though heparin was administered every eight hours and enoxaparin was administered every twelve hours.

The higher administration costs for heparin and lower acquisition costs for enoxaparin reported by Drummond et al. (1994) might reflect pricing differences between the British and U.S. health care markets. The differences may also reflect a poor assumption or a mathematical error. Since the cost of prophylaxis with enoxaparin costs less and prevents more deaths, there was no need to conduct an incremental cost-effectiveness analysis.
Another cost-effectiveness analysis was conducted by Anderson et al. (1993) comparing enoxaparin with unfractionated heparin for the prevention of deep vein thrombosis following hip replacement surgery. A decision analytic approach within the traditional framework was adopted. The costs used in the analysis were actual hospital expenditures from a Canadian hospital that were adjusted to 1992 dollar figures and converted to U.S. dollars using the exchange rate for that period. The enoxaparin acquisition costs were estimated because the medication was not available in Canada at the time of the study. Resources used in the analysis were based upon chart reviews of patients that underwent hip replacement surgery and develop a deep vein thrombosis, pulmonary embolism, or had a hemorrhagic event at the hospital.

The probability estimates used in the Anderson analysis were derived from published clinical trials that compared a low-molecular-weight heparin to standard unfractionated heparin for the prevention of deep vein thrombosis following hip replacement surgery. A meta-analytic technique proposed by Mantel and Haenszel was used to combine the studies to obtain an odds ratio for each outcome (proximal DVT, distal DVT, pulmonary embolism, major bleed, and minor bleed). The odds ratio provides an estimate of the probability of an event occurring among patients treated with a low-molecular-weight heparin compared to patients treated with unfractionated heparin — it is a measure of relative effectiveness. The Mantel-Haenszel method is a fixed-effect model and requires that the combined studies have a homogenous effect size, and the studies combined by Anderson et al. (1993) met this requirement. In order to use the odds ratios in the cost analysis, they had to be converted back into rates. This was done
by first calculating the weighted average event rates in the heparin group, then
multiplying this figure by the respective odds ratio to obtain best estimate of the event
rate in the low-molecular-weight heparin group.

Based on local resource consumption and costs and combined probability
estimates, Anderson et al. (1993) estimated that the average cost to prophylactically treat
everyone with enoxaparin was $340 (1992 U.S. dollars) compared to $388 (1992 U.S.
dollars) for heparin prophylaxis. Thus, on average, $44 (1992 dollars) per person would
be saved by using enoxaparin rather than heparin. The ratio of heparin to enoxaparin
acquisition costs in the Anderson study is consistent with the Drummond et al. (1994)
study and higher than the Hawkins et al. (1997) study. Anderson et al. estimated the
acquisition costs by multiplying the cost of heparin by 2.6, which was the ratio of
enoxaparin to heparin acquisition costs in France where enoxaparin was already on the
market. Conducting a one-way sensitivity analysis on this ratio revealed that even if
enoxaparin cost more than four times the amount of heparin then the expected cost of
heparin therapy would be less than the expected cost of enoxaparin. In the Hawkins et al.
study, enoxaparin is over six times the price of heparin.

Discussion of these three studies demonstrates how the assumptions used in a
model can affect the results of an analysis. Each of the cost and resource utilization
assumptions used in each of the three studies may have been appropriate for the treating
environment in which it was modeled. From the two studies that reported an incremental
cost-effectiveness ratio, a formulary decision-maker can determine the additional expense
per additional deep vein thrombosis avoided by using the most effective therapy (i.e.,
enoxaparin). But this does not provide any estimate of the budgetary impact of switching all patients from heparin to enoxaparin for the prophylaxis of deep vein thrombosis following hip replacement surgery. Examining the difference in expected costs of each treatment and multiplying that figure by the number of hip replacement surgeries can provide an estimate of the budgetary impact. However, the three studies produced different expected cost differences and one was reported in a currency other than the U.S. dollar. Because none of the models were validated in an actual practice setting to see if the cost estimates predicted by the models were realized, which study can the decision maker believe? Once again it is imperative that the consumer of pharmacoeconomic research look at the practice setting upon which the model is based and the underlying assumptions and characteristics of the model before determining if it provides useful information to his or her practice.

Menzin, Colditz, Regan, Richner, and Oster (1995) also conducted a cost-effectiveness analysis of two therapies for the prevention of deep-vein thrombosis following hip replacement surgery. Enoxaparin was compared to low-dose warfarin using a decision tree within a traditional framework. The probabilities used in the decision tree were the weighted average probabilities obtained from combined clinical trials. The trials included in the analysis were not head-to-head comparisons of enoxaparin and warfarin. The drug acquisition costs were based on average hospital purchase prices. The costs of diagnostic and laboratory tests were estimated using national relative value scales. The cost of physician time was estimated from payment rates under Medicare's Resource-Based Relative Value Scale. The perspective of this
analysis is not specifically stated, however, only direct medical costs were included in this analysis. This study was also sponsored by the manufacturer of enoxaparin.

The average cost to provide DVT prophylaxis and treatment to patients undergoing hip replacement surgery using enoxaparin was $379 compared to $326 using low-dose warfarin. Enoxaparin prophylaxis prevented three additional thromboembolic deaths per 1,000 patients treated compared to warfarin therapy and prevented an additional 17 DVTs per 1,000 patients treated. The average cost-effectiveness ratio for enoxaparin is lower than that of warfarin because enoxaparin prevented more deaths, however, the incremental cost-effectiveness ratio for enoxaparin is higher than warfarin, indicating that warfarin is the preferred therapy. This finding was consistent over a number of one-way sensitivity analyses.

The results of the Menzin et al. (1995) study could aid in a formulary decision if the decision-maker accepts the assumptions of the traditional approach to pharmacoeconomic analysis (all patients will be switched from warfarin to enoxaparin, the costs of treating all patients in a given arm is constant regardless of the proportion of patients treated) Furthermore, the assumption that the costs used in the model and the patients in the clinical trials (from which the decision tree probabilities are based) are similar to the costs and patients in the managed care organization.

Goldstein et al. (1997) conducted a cost analysis to compare the expected cost of five different strategies for managing NSAID induced gastropathy. A decision tree modeled within a traditional framework was used to assess the expected cost of various therapy combinations. The costs were obtained from other published studies and the
probabilities were obtained from the literature or from expert opinion. Most of the probabilities were obtained from a single source, however, it is not stated how the probabilities obtained from multiple sources were combined. A series of one-way sensitivity analyses were done on several key variables. The base case estimate was listed for each variable included in the sensitivity analysis along with the range over which the sensitivity analysis was conducted. To further test the model, they ran a Monte Carlo simulation of 10,000 patients. Although the details are not provided it appears that the probabilities and costs included in the sensitivity analysis were randomly selected from a distribution with a mean equal to the base case estimate and a range equal to that used in the sensitivity analysis.

The decision tree was constructed with two primary branches, one contained the three NSAID regimen subtrees and the other contained the two diclofenac/misoprostol combinations. The expected average cost estimated for the two primary arms using the Monte Carlo simulations was similar to the expected costs estimated with the base case estimates.

The purpose of the Goldstein et al. (1997) analysis was to "apply decision-analysis modeling to compare and contrast various approaches to the treatment of patients who are at risk for developing NSAID-induced gastropathy and also to evaluate a newer approach to the management of these patients." Although the perspective of the analysis is not stated, it is most likely that of a third party payer. This is assumed because the model included only direct medical costs that would be covered by a third party payer,
such as drug acquisition costs, physician visits, hospitalizations, and lab tests. So what information does the analysis provide a third party payer?

The expected costs of the two primary branches of the decision tree are presented. This indicates that, on average, patients treated with the NSAID regimens will cost $1,153 over a six-month period, while patients on the diclofenac/misoprostol (Arthrotec®) regimens will cost, on average, $939 over a six-month period. The authors also give the expected cost of each of the five sub-trees, NSAID alone, NSAID with a histamine-2 receptor antagonist, NSAID with misoprostol, diclofenac/misoprostol 50mg/200μg BID/TID, and diclofenac/misoprostol 75mg/200μg BID. In order to use this information, the decision-maker will have to assume that his or her patient population is similar to those in the clinical trials from which the decision-tree probabilities were taken. This is an example of a decision analytic model used in a traditional framework requiring the assumption of perfect and complete substitution -- perfect substitution in that each arm is compared to the other arm as if you could treat a patient with any of the regimens. In reality, the regimen for arthritic patients on other chronic NSAID therapy is very patient specific and as is the treatment or prevention of NSAID-induced ulcers. Although the authors did assume a distribution of patients across the five sub-trees, they did not compare this distribution before and after the addition of the diclofenac/misoprostol regimens. The authors did acknowledge this by stating that the model does not take into account the age or co-morbid conditions of the patient and that the ability to stratify patients by risk would may make it possible to maximize therapy.
Statistical Analysis and Stochastic Models

Stochastic models traditionally have not been used in pharmacoeconomic analyses because patient level data have not been widely available. However, the use of stochastic models should increase as the use of clinical and administrative databases for outcomes research increases and more pharmacoeconomic data are collected during clinical trials. Stochastic models may offer an advantage over deterministic models because they allow patient characteristics to be considered in the analysis.

Stochastic models are based on patient level data rather than aggregated data. Statistical techniques are used to partition the observed variance into two portions, that due to error (or within-group variance) and that due to the model (or between-group variance). Because the data are at the patient level, stochastic models contain a disturbance term that accounts for individual differences that are not accounted for by the regression model.

Statistical analysis is based upon the statistical relationship between variables as opposed to functional relationships. As stated previously, the scatter of points along an imaginary line within a statistical relationship forms the basis of the regression analytical techniques described below.

Often, the way in which the data were generated and the nature of the relationship between two variables is unknown. This in turn affects the way in which population estimates are generated from sample data. Because we cannot pull an infinite number of samples to determine the distribution of the parameter estimates, we must make some assumptions as to how the data were generated to determine how to calculate the
parameter estimates. The general linear model (GLM) encompasses a number of assumptions and provides the most common framework within which analyses may be conducted.

The GLM provides a framework within which certain techniques can be used to estimate population parameters. To fit the data into the GLM framework, assumptions are made that simplify the calculations or make them possible. The formula, or estimator, by which the data are used to develop the parameter estimates within the GLM is known as the ordinary least squares (OLS) estimator. According to the Gauss-Markov theorem, the OLS parameter estimates are BLUE, the best linear unbiased estimates, provided that the assumptions of the GLM are met. The assumptions listed below are compiled from Neter, Wasserman, and Kutner (1990) and Kennedy (1996), and are as follows:

1. Dependent variable is a linear function of a specific set of independent variables plus a disturbance term;
2. Expected value of disturbance term is zero;
3. Disturbances have uniform variance, are uncorrelated, and are normally distributed;
4. Observations on independent variables can be considered fixed in repeated samples;
5. No exact linear relationships between independent variables and more observations than independent variables.
Regression analysis is an inferential technique, which means that inferences are made about the variables within the population from which the sample data were drawn. It is used to determine the relationship between independent variables and dependent variables, so predictions can be made about changes in mean response of the dependent variable following changes in the mean response of an independent variable. However, this technique is not used to infer a cause and effect relationship because this is done through research design and experimental methods rather than data analysis.

The general form of a regression equation is:

\[ \mathbf{Y} = \mathbf{a} + \mathbf{p} \mathbf{X} + \mathbf{e} \]

where \( \mathbf{Y} \) is a column vector of dependent variable observations, \( \mathbf{a} \) is the intercept term (a column vector of constants); \( \mathbf{p} \) is an \( N \times k \) matrix of parameters (\( N \) is the number of observations and \( k \) is the number of independent variables); \( \mathbf{X} \) is an \( N \times k \) matrix of independent variable observations; and \( \mathbf{e} \) is a column vector of error terms.

In regression analysis the total variation in the dependent variable is divided into two portions, that explained by the model and that due to random error:

\[ SS_{\text{total}} = SS_{\text{regression}} + SS_{\text{within}} \]

\[ \sum (y_i - \bar{y}) = \sum (\hat{y}_i - \bar{y}) + \sum (y_i - \hat{y}_i) \]

where \( y_i \) is the \( i \)th observation; \( \bar{y} \) is dependent variable mean; \( \hat{y}_i \) is the predicted \( Y \) value for the \( i \)th observation (Neter et al., 1990).
**Consequences of Violating the Assumptions of the General Linear Model**

The assumption that the dependent variable is a linear combination of a set of independent variables can be violated if key independent variables are excluded from the model, a non-linear relationship exists, or the parameters are not constant over time. Excluding key variables makes the variance-covariance matrix of the $\beta$'s smaller and may bias the estimates. However, if the omitted variables are uncorrelated with the variables in the model, then only the intercept term is biased. If the omitted variables are uncorrelated with the included variables and the mean value of the omitted variable is zero then no parameter (including the intercept term) is biased (Kennedy, 1996).

If a non-linear model is estimated within the GLM framework, then the parameter estimates are biased and uninterpretable because the model only explains the linear variation in the dependent variable. The problems associated with changing parameters are primarily associated with time series data. Because the parameters (and parameter estimates) are assumed to be constant, their constancy over time should be checked when using time series data (Kennedy, 1996).

Another assumption of the GLM is that the expected value of the error terms is zero. If this assumption is violated, the intercept term is biased. The bias in the intercept is equal to the amount that the average of the error terms differs from zero. If the intercept term is excluded from the model then the other parameter estimates (the slope estimates) are biased (Kennedy, 1996).

The general linear model also assumes that the variance of the error terms is constant, the errors are uncorrelated, and that they are normally distributed. Violation of
this assumption leads to heteroscedasticity and autocorrelation of the error terms. Heteroscedasticity leads to a biased variance-covariance matrix, which is the foundation of the test of the parameter estimates, therefore, the t test, with the null hypothesis, \( \beta = 0 \), is no longer valid. If heteroscedasticity is present in a regression model, the parameter estimates are not biased, but they are no longer the most efficient linear estimates (the generalized least squares estimates are BLUE). Autocorrelation of the error terms is most commonly seen with time series data (Kennedy, 1996).

The fourth assumption is that observations on independent variables can be considered fixed in repeated samples, i.e., the X's are drawn independently. This assumption of fixed independent variables basically means that the X's are distributed independently of the error terms. Measurement errors associated with the independent variables make them random rather than fixed. If the independent variables are random (or stochastic) but distributed independently of the error terms, then the OLS parameter estimates are still BLUE. If the regressors are contemporaneously uncorrelated, then the parameter estimates are biased but retain the asymptotic properties (consistent and efficient estimates in large samples). A regressor is considered contemporaneously uncorrelated if the nth observation of that regressor is not correlated with the nth error term, and this holds for all observations. Observations may be correlated with the error terms of other observations, and still be considered contemporaneously uncorrelated. If the regressors are contemporaneously correlated, then the estimates are biased and do not retain the desirable asymptotic properties (Kennedy, 1996).
The fourth assumption can also be violated if a lagged value of the dependent variable is included in the model as an independent variable. For instance, if the dependent variable is the concentration of a medication in the blood after the nth dose and the concentration after the (n-1)th dose is included in the model as an independent variable, it is stochastic not fixed (Kennedy, 1996).

The fifth assumption is that no exact linear relationship exists between the independent variables. Violation of this assumption leads to multicollinearity. Correlation among the independent variables does not affect the prediction of the model, but it does affect the interpretation of the individual parameter estimates. The reason for this is based on the fact that the estimates are calculated from the unique variance explained by each variable, when two independent variables are correlated with one another, the variance explained by both variable increases, while the unique variance explained by each variable decreases. Because less information (uniquely explained variance) is used to estimate the parameters, the variance of the parameter estimates increases which increases the standard error of the estimate. This in turn decreases the value of the t statistic and increases the likelihood of a type II error (Kennedy, 1996).

**Interpreting the Parameter Estimates**

If none of the data have been transformed then the interpretation of the parameter estimates is straightforward. The parameter estimate is the change in the dependent variable per unit change in the independent variable. Cost data are often skewed, and must be transformed by taking the natural logarithm of the costs. The distribution of the
transformed variable is usually normally distributed which means that the error terms should also be normally distributed.

In a lognormal regression model, a parameter estimate associated with a continuous explanatory variable (multiplied by 100) equals the percentage change in the unit value of the dependent variable per unit change in the explanatory variable. For example, if the natural log of diabetes-specific cost is regressed on age, then the parameter estimate associated with age gives the percent change in diabetes-specific costs (not the natural log of diabetes-specific costs) for every one-year increase in age.

However, the interpretation of a parameter estimate associated with a binary variable is interpreted differently. Halvorsen and Palmquist (1980) point out that if an estimate of the percentage impact is required then the parameter estimate, b, needs to be transformed by the following expression: $100\times\{e^b - 1\}$. This adjusted parameter estimate can be interpreted as the percentage increase in average diabetes-specific (or diabetes-related) cost when a particular characteristic is present.

A deterministic model utilizes sensitivity analyses to assess the robustness of the results of a model over a range of alternative values for uncertain variables. This is in contrast to stochastic analysis such as the analysis of data from a clinical trial where inferential statistics are used to estimate the magnitude of a treatment effect and construct formal tests of hypotheses (O'Brien et al., 1994).

**Stochastic Models Used in the Literature**

Using medical and pharmacy claims data from a Northern California-based managed care organization, Selby, Zhang, Ray, and Colby (1997) compared the cost
incurred to provide care to 85,209 diabetic patients with that of 85,209 age and gender-matched controls over a twelve month period ending December 31, 1994. Patients were identified from a diabetic registry maintained by the managed care organization and consisted of patients who filled prescriptions for diabetic medications or supplies, had abnormal hemoglobin-A1C values, had any primary or secondary hospital discharge diagnosis of diabetes, or had medical claim containing the ICD-9-CM diagnostic code for diabetes. Ninety percent of the diabetic patients treated in the HMO were contained in the registry, but two and a half percent of the patients in the registry did not have diabetes. Internal costs obtained from the organization's cost management information system were used in the study.

The total excess medical and pharmacy expenditures for the diabetic group were $282.7 million for the twelve-month study period. The cost to provide care to the diabetic patients was 2.4 times greater than the amount spent to treat the matched controls. Hospitalizations and outside referrals accounted for 38.5% and 33.7% of the excess costs respectively. Over 40% of the total excess costs were attributable to the short term and long term complications of diabetes. The short-term complications included visits to the emergency department or hospitalization for hypoglycemia, uncontrolled hyperglycemia, hyperosmolar coma, or ketoacidosis. Long-term complications include amputation, eye disease, heart disease, stroke, end-stage renal disease, and other vascular disease (Selby, Zhang, Thomas et al., 1997).

Using regression analysis to control for maternal and infant characteristics, Scheffler, Feuchtbaum, and Phibbs (1982) conducted a cost analysis of a preventive
program designed to improve pregnancy outcomes through intensive diabetes management prior to conception and throughout the pregnancy. Although it was called a cost-effectiveness analysis, it was actually a cost-analysis because the costs of the program were subtracted from the savings to yield the results.

The dependent variables used in the two regression models were the natural logarithm of length of stay and the natural logarithm of total hospital charges aggregated across baby and mother. Because the program costs could be incurred over an eighteen-month period, they were discounted at an eight per cent rate from the hospital component of the consumer price index. The independent variables included maternal age, race, diabetes classification, birth weight, mother's source of payment, and program participation. The variables race, diabetes classification, source of payment and program participation were all binary variables. Because the models included in the Scheffler analysis were semi-log models (i.e., the dependent variables are in logarithms), the interpretation of the parameter estimates associated with continuous variables is the percentage change in the un-transformed dependent variable per unit change in the independent variable. The program savings were calculated by the estimating the percent change in hospital charges between program participants and non-participants.

The authors were concerned that including birth weight as an independent variable in the models may induce simultaneity bias since some of the factors contributing to hospital charges and length of stay may also be related to birth weight. To test this, Scheffler and colleagues excluded birth weight from the models and compared the parameter estimates associated with the other independent variables. As
mentioned previously, the dependent variables were transformed by taking the natural logarithm of each. This was done to make the distribution of the transformed variables more normal, which also results in the normal distribution of the residuals.

A study conducted by Collins and Anderson (1995) provides an example of a stochastic study that does not involve modeling. They recruited forty subjects between the ages of 40 and 70 years who had type 2 diabetes for at least one year. Thirty-two of the forty subjects were taking diabetes and anti-hypertension medications and were included in the analysis. The subjects were placed on a 12-week weight loss program, and measures of the dependent variables, weight and monthly prescription costs, were taken at baseline, week 12, and one year after program completion. The cost of each medication regimen was estimated by surveying 16 retail pharmacies across Lexington, Kentucky.

The average weight of the study participants decreased nearly 34 pounds at twelve weeks and was 19.8 pounds lower one year after completion of the program. The average monthly out-of-pocket prescription costs decreased from $63 at baseline to $20 at week twelve, and $32 at the one-year follow-up. Six of eight people taking insulin at baseline were able to control their diabetes with oral agents alone and seventeen of the twenty-four patients who were taking oral hypoglycemic agents at baseline were able to control their diabetes with diet alone. The limitations of the pretest-posttest design make it difficult to ascribe all of the results to the intervention, however, the study does demonstrate that it is possible to conduct a cost analysis using traditional research design methods.
Claims Database Analysis

Although administrative claims databases have traditionally been used for accounting and actuarial purposes, their use has changed over the past five to ten years due to cost-constraints, accreditation requirements, and government regulation. Current uses of claims databases include epidemiology studies, health system cost analyses, treatment effectiveness studies, disease specific descriptive studies, health care resource utilization patterns, compliance studies, planning and monitoring of disease management programs (Armstrong & Manuchehri, 1997; Motheral & Fairman, 1997). The items commonly found on claims in medical and pharmacy claims databases are presented in Table 2.

<table>
<thead>
<tr>
<th>Table 2. Contents of Medical and Pharmacy Claims</th>
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<tr>
<td><strong>Medical Claims</strong></td>
</tr>
<tr>
<td>member identifier</td>
</tr>
<tr>
<td>provider identifier</td>
</tr>
<tr>
<td>place of service</td>
</tr>
<tr>
<td>date of service</td>
</tr>
<tr>
<td>procedure code</td>
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<td>financial information</td>
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Depending on the location where the service was provided, the procedure codes appearing on the claim may include Current Procedural Terminology (CPT) codes, hospital revenue codes, International Classification of Diseases, 9th edition, with Clinical Modification (ICD-9-CM) procedure codes, or codes from the Health Care Financing Administration common procedure coding system (Armstrong & Manuchehri, 1997). A claim contains a separate line for each procedure and related financial information. While a claim is specific to a patient encounter with the health system, a single encounter may have multiple claims. For instance, a visit to a physician office may involve a claim with two claim lines, one for a physical assessment and one for a visual acuity test. A second claim may be filed which contains only one line for a glycosylated hemoglobin test.

Because the medical claims and pharmacy claims are maintained in separate files and are actually two separate encounters with the health care system, it is nearly impossible to link a specific prescription to a specific medical claim or encounter. The date of service is the best link, but these two dates are usually different due to the use of prescription samples, delay in filling the prescription due to practical constraints, or delay in filling secondary to non-compliance (Armstrong & Manuchehri, 1997).

In addition to medical and pharmacy claims databases, managed care organizations usually maintain files containing patient demographic and eligibility information. Similar files are maintained for providers as well (Armstrong & Manuchehri, 1997).
Armstrong and Manuchehri (1997) outline steps involved in the extraction of data from a claims database. These steps include:

1. Define the time window for building cost and resource profiles.
2. Design algorithms to extract appropriate subsets of claims to study.
3. Search medical claims for specific diagnostic codes and or pharmacy claims for specific medications.
4. Define the unit of analysis (the patient, provider, or clinic).
5. Refine definition of patient population for specific research question.
6. Extract diagnosis driven data
   a. Medical claims carry three to eight diagnostic fields
   b. Pharmacy claims used to identify patients only for diseases with specific medications. Use NDC number to group medications into therapeutic groups.
7. Extract all claims for defined population.
   a. Obtain list of unique member numbers from medical and pharmacy claims search.
   b. Pull all medical and pharmacy claims for unique member list.
8. Assess integrity of the data
   a. Check ages and eligibility data to ensure all values are within a reasonable range.
   b. Check gender specificity if applicable. For example, ensure that no females carry a diagnosis of prostate cancer
c. Remove denied, reversed, and duplicate claims to avoid double counting of resource utilization.

9. Identify disease-related costs
   a. Classify each claim line into the proper resource-unit category using procedure codes.
   b. Classify drugs into primary therapy, secondary therapy, complications or co-morbidity treatment, and those not related to the disease.

10. Determine resource costs. The financial fields contain amount paid by the managed care organization for fee-for-service claims. For claims from capitated providers, some managed care organizations include a “market value” for actuarial purposes. This amount may be used or the average paid amount for fee-for-service claims could be used.

11. Perform analysis
   a. Descriptive cost and resource use profiles
   b. Inferential or predictive analysis (e.g., linear or logistic regression).

Benefits of Using Claims Database Analysis
Claims databases allow assessment of effectiveness rather than efficacy. They are useful for descriptive analyses of resources used to treat particular diseases. In addition to descriptive analysis, claims databases are convenient sources of data for regression analyses used to predict future costs, plan and monitor disease management programs, and help decision makers develop clinical and economic targets (Armstrong & Manuchehri, 1997).
Using a unique patient identifier, medical and pharmacy claims data bases can be combined to build resource utilization profiles for patients (Armstrong & Manuchehri, 1997). Claims databases provide a relatively low cost source of data (Motheral & Fairman, 1997). Claims databases contain information on large number of patients and do not rely on patients to remember which medications or services they received. Thus claims databases are free from this source of recall bias (Armstrong & Manuchehri, 1997). As with any research on human subjects, issues of privacy and blinded data need to be addressed, however, claims database research is less intrusive than other forms of outcomes data because patients and providers do not need to be surveyed to obtain utilization information (Armstrong & Manuchehri, 1997; Motheral & Fairman, 1997).

Claims database studies are retrospective observational studies that avoid the ethical issues of randomizing patients to treatment and control groups (Motheral & Fairman, 1997). Another advantage to claims database research is that data collection and process and sensitivity analysis are relatively easy to change if absolutely necessary and are easier to conduct compared with clinical study designs (Motheral & Fairman, 1997).
**Problems Associated with the Use of Claims Database Analysis**

Claims databases only contain information of products and services covered by the plan. Even prescriptions for medications that are covered by the plan may be excluded from the database if the patient's co-payment was greater than the cost of the medication (Armstrong & Manuchehri, 1997). Medical claims databases may lack claims from physicians that are under a capitation agreement with the managed care organization. These providers may not be required to file claims for each patient encounter since they do not get reimbursed for individual services provided.

Another source of missing or incomplete data in ambulatory claims databases comes from the bundling of inpatient claims. Most ambulatory claims databases lack detailed claims from hospitalizations, making it difficult to determine what medications or specific tests the patient received during their hospital stay (Armstrong & Manuchehri, 1997).

Claims database research is heavily dependent upon the accuracy of ICD-9-CM diagnostic codes. A number of errors are commonly associated with ICD-9-CM diagnostic codes including keystroke errors, improper documentation by the provider, improper selection of code by coder (Lloyd & Rissing, 1985; Armstrong & Manuchehri, 1997). Especially problematic for longitudinal studies is that the coding scheme can also change over time. In addition to these errors associated with the use of ICD-9-CM diagnostic codes, the possibility of upcoding or undercoding also exists. Upcoding is more commonly associated with the outpatient setting where providers try to increase
their reimbursement while undercoding is more commonly associated with the inpatient setting (Lloyd & Rising, 1985; Armstrong & Manuchehri, 1997).

Despite the potential for coding errors, using both medical and pharmacy claims data to identify specific patient groups has shown to greatly increase the accuracy of the claims databases. Quam et al. (1993) used medical and pharmacy claims databases from an insurance company to identify patients with hypertension. A patient survey and review of the medical record then confirmed a diagnosis of hypertension in the 2,079 study participants. Identifying patients using medical claims alone yielded a 74% and 64% agreement with the medical record and patient survey respectively. Using only pharmacy claims data, patient identification was in 67% agreement with the medical record and 75% agreement with the patient survey results. However, patient identification using both pharmacy and medical claims produced a 96% agreement rate with both the medical record and patient survey.

**Diabetes Mellitus**

Diabetes is an appropriate disease to model because it is a chronic disease with a finite number of treatments, it progresses in a predictable manner, and there are specific therapeutic steps that should be followed. Furthermore, organizations such as the American Diabetes Association and the World Health Organization have developed explicit treatment and monitoring guidelines that are widely disseminated.
Classification and Epidemiology

The prevalence of diabetes mellitus in the United States is nearly 7.8 million according to the 1993 National Health Interview Survey estimates, and it is estimated that up to 7 million cases have gone undiagnosed (National Center for Health Statistics, 1994). Ninety per cent of those people diagnosed with diabetes have non-insulin dependent diabetes mellitus, 7% have insulin dependent diabetes mellitus, and the remainder have diabetes secondary to some other disease process.

Diabetes mellitus is a heterogeneous group of metabolic disorders that is characterized by elevated blood glucose levels resulting from deficits of insulin secretion, action, or both (The Expert Committee, 1997). The diagnosis is made by the presence of an elevated random plasma glucose concentration accompanied by one or more diabetic symptoms such as polydipsia, polyuria, ketonuria, or rapid weight loss (National Institutes of Health, 1995; Francisco & Brooks, 1992). The diagnosis can also be made from a fasting glucose concentration greater than 140mg/dl from venous plasma, or 120mg/dl from venous or capillary whole blood (National Institutes of Health, 1995). Any elevated glucose concentration should be followed-up with a fasting glucose blood test to confirm the diabetes diagnosis (National Institutes of Health, 1995). The symptoms of elevated blood glucose include polyuria, polydipsia, polyphagia, potential weight loss (type 1), and blurred vision. Patients with diabetes are more susceptible to certain infections (The Expert Committee, 1997).

Once a diagnosis is made, diabetes may be classified into one of four types: type 1 diabetes (formerly known as insulin dependent diabetes mellitus), type 2 diabetes
(formerly known as non-insulin dependent diabetes mellitus), gestational diabetes, and diabetes secondary to another disease (The Expert Committee, 1997).

The onset of type 1 diabetes usually occurs before the age of thirty and is characterized by little to no insulin secretion from the pancreas (National Institutes of Health, 1995). The etiology of this type of diabetes is not clear, but it is thought to be environmental and genetic (Francisco and Brooks, 1992). Type 2 diabetes is characterized by low, normal, or high levels of insulin secretion (the latter is associated with insulin resistance). Patients with type 2 diabetes are not ketosis-prone and are not dependent on insulin, however, they may use insulin for glycemic control. Unlike patients with type 1 diabetes, 50% of the male and 75% of the female patients with type 2 diabetes are obese. There is a strong genetic link with type 2 diabetes, and the progression of this type of diabetes is slow (Francisco and Brooks, 1992).

**Progression and Complications of Type 2 Diabetes**

The eyes, kidneys, nerves, and heart are especially susceptible to damage after long term exposure to hyperglycemia. This damage is most likely caused by the glycation of tissue proteins and other macromolecules in combination with the excess production of polyol compounds from glucose, and fall into three categories, macrovascular, microvascular, and metabolic complications (National Institutes of Health, 1995; The Expert Committee, 1997). Macrovascular complications include coronary heart disease, stroke, and peripheral vascular disease. Microvascular complications include nephropathy, retinopathy, and peripheral neuropathy, and metabolic complications include diabetic ketoacidosis (DKA), hyperosmolar nonketotic
coma (HNC), lactic acidosis, and hypoglycemia. The Diabetes Control and Complications Trial (1993) demonstrated that aggressive control of IDDM can prevent or prolong the major complications of the disease.

The reported prevalence of heart disease was 37% and 51% in non-Hispanic men and women with diabetes respectively, and 30% and 45% in Hispanic men and women with diabetes respectively in one community-based study (Rewers, Shetterly, Baxter, Marshall, & Hamman, 1992). In fact, the reported risk ratio for heart disease varies from 1.7 to 2.3 for men and 2.9 to 3.2 for women (National Institutes of Health, 1995). It is unclear if the type of diabetes is a factor in determining the risk of heart disease, although the risk may be higher in IDDM (National Institutes of Health, 1995).

Patients with diabetes are also at an estimated 2.5-fold higher risk for cerebrovascular accidents compared to non-diabetic patients (Kittner, White, Losonczy, Wolf, & Hebel, 1990). Elevated blood pressure, increased LDL concentrations, and smoking are all major risk factors for stroke (National Institutes of Health, 1995). The first two conditions are often associated with diabetes.

In addition to having increased risk of heart disease and strokes, people with diabetes are also at increased risk of skin ulceration, especially in the lower extremities. This is due to the peripheral vascular complications associated with diabetes. According to data from the 1995 National Hospital Discharge Survey 6% of all hospital discharges between 1983 and 1990 also listed an ulcer condition in a lower extremity; the length of hospital stay was 59% longer for diabetic patients with lower extremity ulceration than for patients with diabetes and no ulceration; the incidence of amputation among patients
with diabetes ranges from 0.4% to 0.8% per year; and the major risk factors for amputation include hyperglycemia, long duration of diabetes, older age, peripheral vascular disease, and foot ulcers.

Nephropathy and retinopathy also affect many people with diabetes and place a significant economic burden on the health care system. Diabetic nephropathy is responsible for 35% of all new end stage renal disease cases, and cost nearly $2 billion to treat annually (National Institutes of Health, 1995). Diabetic retinopathy is the leading cause of new cases of blindness in the U.S. (National Institutes of Health, 1995). After 15 years of diabetes nearly 90% of patients with IDDM, 80% of those with NIDDM being treated with insulin, and 55% of those with NIDDM not on insulin will have evidence of retinal damage (National Institutes of Health, 1995).

The principal co-morbid conditions of concern are hypertension, obesity and hyperlipidemia as these show a strong interrelationship with the diabetes and may, in combination with the disease have particular cost consequences. Hypertension, in particular, may be a risk factor for the development of nephropathy and thus hypertensive diabetics should be screened for microalbuminuria/proteinuria. Obesity, which is a significant risk factor for the development of NIDDM, may also be associated with the high cost of diabetic treatment. Colditz, (1992) estimated that 57% of the costs of NIDDM was attributable to obesity.

A study by Rendell, Kimmel, Bamisedun, O'Donnell, and Fulmer (1993) provides some assistance in identifying the prevalence of complications and co-morbidities and the costs of diabetes treatment in a managed care setting. A review of physician claim
records for the period 1 January 1988-1 January 1989 revealed that ischemic heart
disease, peripheral vascular disease, cerebrovascular disease and hypertension were
between 2 and 4 times more prevalent among the diabetic patient group than the non-
diabetic patient group. It was also discovered that diabetes was associated with twice the
number of physician visits and were ten to fifteen times more likely to be hospitalized for
peripheral vascular disease, ischemic heart disease and cerebrovascular disease than the
non-diabetic patient population (Rendell et al., 1993). They also found that 74% of the
costs of hospitalizations for late complications of diabetes was attributable to
cardiovascular disease and 10% to diabetic renal disease.

**Monitoring Type 2 Diabetes Mellitus**

The American Diabetes Association (1996) recommends that each visit to the
physician's office should include a detailed history and physical examination. In
addition, the following laboratory test should be obtained at the initial visit: fasting
plasma glucose, glycohemoglobin (hemoglobin A1C), fasting lipid profile, serum
creatinine in adults, urinalysis, microalbuminuria test, urine culture (if sediment is
abnormal or symptoms are present), thyroid function tests when indicated, and an
electrocardiogram in adults. A management plan should be established with the patient
that should include (among other things): annual dilated eye and visual field exam,
consultation for podiatry as needed, consultation for specialized services as needed, and
medications which include insulin, oral glucose-lowering agents, glucagon,
antihypertension medication and lipid-lowering agents, other endocrine medications and
any other medications necessary.
Patients on insulin or having trouble meeting their treatment goals should visit the physician quarterly. All others should have semi-annual check-ups. A glycohemoglobin test should be ordered at least quarterly for patients on insulin therapy. Patients with a lipid disorder or family history of a lipid disorder should have a fasting lipid profile done every year (American Diabetes Association, 1996).

**Treatment Options for Type 2 Diabetes Mellitus**

According to the consensus statement, monotherapy should be initiated in patients whose glycemic goals are not met by diet and exercise. Monotherapy with oral sulfonylureas is usually initiated because this class of medications has few side effects; has been on the U.S. market the longest; and generic products are available within this class. The safety and efficacy profiles of agents within this class are comparable, so the selection of a specific sulfonylurea will depend on the pharmacokinetic and pharmacodynamic profile of the agent (American Diabetes Association, 1995). Metformin may also be initiated as a single agent especially in obese patients because it may promote weight loss and has favorable effects on lipid profiles. Insulin therapy consisting of two or more daily injections may be initiated for patients that present with severe hyperglycemia and have signs of diabetes-related complications (American Diabetes Association, 1995).

When glycemic control is no longer maintained with a single agent, combination therapy is recommended because there is little empiric support for switching from one oral agent to another. Sulfonylurea plus metformin or sulfonylurea plus insulin are the two most studied and frequently used combinations (American Diabetes Association,
If insulin is used, it is generally given as an intermediate (NPH) or long-acting (lente) preparation at bedtime.

If the glycemic goals are not met with combination therapy then the patient should be switched to a multi-injection insulin regimen (American Diabetes Association, 1995). The actual regimen should be tailored to the glycemic control goals and lifestyle of each individual. At least two injections per day are recommended using regular or intermediate insulin preparations.

In 1995, the four classes of medications available for treating patients with diabetes included insulin, sulfonylureas, biguanides, and alpha-glucosidase inhibitors. Insulin is reserved for the treatment of type 1 diabetes, uncontrolled type 2 diabetes, and pregnant women. The dose of insulin has to be adjusted for each patient to achieve the desired glucose control. If insulin is used as monotherapy, multiple daily injections are usually required. The primary side effect of insulin is hypoglycemia.

Sulfonylureas have been on the market for over forty years. Newer agents such as glyburide and glipizide have improved side-effect profiles compared to the first generation sulfonylureas and have taken over most of the market. Sulfonylureas appear to act by potentiating insulin secretion and increasing insulin sensitivity at the tissue receptor site (American Diabetes Association, 1995). Weight gain and hypoglycemia are the primary side effects of this class.

Metformin is the only representative of the biguanide class available in the U.S.. Although the exact mechanisms of action of this class are unknown, a reduction in hepatic glucose production; increase in peripheral insulin sensitivity; and a decrease in
glucose absorption from the intestine appear to play a role (American Diabetes Association, 1995). Biguanides do not cause weight gain and improve the lipid profile of diabetic patients. Self-limiting GI side effects are common when therapy is initiated, and patients with renal or hepatic failure should not use this medication.

No matter what therapy is selected, the goal of treating people with Type 2 diabetes is to lower the hemoglobin A1c below 7%. The preprandial blood glucose concentration should be in the 80-120 mg/dl range and the bedtime glucose concentration should be in the 100-140 mg/dl range (American Diabetes Association, 1996).

According to the American Diabetes Association (1995), the initial therapy for patients with type 2 diabetes consists of diet and exercise. If glycemic control is not achieved then mono-therapy with sulfonylureas is recommended. If the patient is obese, metformin should be considered for first line monotherapy. If type 1 diabetes is suspected or the fasting glucose levels are extremely elevated then insulin should be used as first-line monotherapy. No matter what pharmacological agent is selected for initial therapy, the response to that agent will decrease with time.

If the glycemic goals are not met with oral monotherapy, then one of the following combinations should be initiated: sulfonylurea + metformin, sulfonylurea + insulin, or sulfonylurea + alpha-glucosidase inhibitor. If combination therapy fails, then the patient should be switched to a multidose insulin therapy (American Diabetes Association, 1995).
Preventing Complications of Type 2 Diabetes Mellitus

The American Diabetes Association (1996) states that the objective of diabetes treatment is to normalize blood glucose concentrations because it has been shown that this reduces the potential for diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome. Glucose normalization also reduces the incidence of vaginitis or vulvovaginitis and decreases the symptoms of polyuria, polydipsia, fatigue, blurred vision, and weight loss. The risks of development or progression of retinopathy, nephropathy, and neuropathy are also reduced (American Diabetes Association, 1996).

Economic and Database Analyses in Diabetes

The 1992 direct medical costs associated with diabetic care in the United States are reported to range from $45 billion to $85.7 billion (Ray, Wills, Thamer et al., 1992; Rubin, Altman, & Mendelson, 1994). Using a combination of multiple claims databases from the state of Texas and national survey data, Warner et al. (1992) estimated the 1992 direct and indirect costs of diabetes in the state of Texas to be $4 billion. They divided the direct cost estimated into those clearly attributable to diabetes, clearly plus probably attributable, and all costs for patients with diabetes. The first group of costs included those costs that were absolutely related to diabetes and filed on claims containing and ICD-9-CM diagnostic code for diabetes (250.xx). The second group also included costs associated with probable complications and common co-morbidities.

The drug costs were taken from Medicaid vendor drug estimates. Those in the "clearly related to diabetes" category included the following AHFS drug groups: insulin, oral antidiabetic agents, and glucagon. Those in the related category included cardiac
drugs, antilipemic agents, hypotensive agents, vasodilating agents, and diuretics. Other costs and resource use estimates came from national and state surveys.

Using a database of Medicare claims (for Parts A and B) from three states, Weiner et al. (1995) conducted a claims data "profiling" study to measure the quality of office based care provided to those over 65 years of age. They were able to demonstrate that practice patterns varied across the states and from rural to urban areas.

Glauber and Brown (1992) evaluated the use of medications by patients with diabetes enrolled in a large health maintenance organization using a computerized diabetes registry maintained by the company. They determined that diabetic patients receive, on average, 31.2 dispenses per year compared to 11.5 for a matched control group. This pattern was consistent for cardiovascular drugs, hypolipidemic drugs, antibiotics, and dermatologic products. In addition, the diabetic patients had more outpatient visits compared to the control group (11.3 vs. 6.5 per year) and more hospitalizations, 366 per year vs. 105 per year in the control group.

The study by Rendel et al. (1993) using the claims database of a large insurance company produced similar results, namely that insured patients with diabetes had twice as many office visits and 2.5 times more physician hospital visits. Most of the increases in physician care between patients with diabetes and the control group were associated with the following conditions: ischemic heart disease, peripheral vascular disease, eye disease. Diabetic patients were more likely to receive cardiac catheterizations, vascular surgery, and ophthalmologic procedures.
CHAPTER 3

METHODS

After questions of safety and efficacy have been answered for a given medication, the arguments for and against adding it to a formulary often center on the estimated cost-effectiveness of the medications. Because logistic and financial constraints limit the usefulness of randomized controlled trials in answering questions of effectiveness and cost-effectiveness, decision makers often rely on models to estimate the cost-effectiveness of new medications (Motheral & Fairman, 1997). Guidelines for the inclusion of data derived from pharmacoeconomic analyses with formulary submissions have been developed for both public government and private formularies. However, the accuracy of costs and effectiveness estimates produced by models is rarely, if ever, assessed. Therefore, this research was conducted to determine if a decision analytic based deterministic model and a regression analytic based stochastic model could produce unbiased estimates of the average diabetes-specific costs following the addition of metformin to the formulary of a managed care organization.

The “gold standard” against which the models were compared was the diabetes-specific costs incurred by Intergroup of Arizona while treating patients with type 2 diabetes that had continuous pharmacy and medical coverage during the entire two-year study period (May 1, 1994 to April 30, 1996). These costs were the amount paid by the managed care organization (allowed amount minus the patient co-payment) for pharmacy and medical claims submitted by providers.
Subjects

The study subjects were patients enrolled in a group model HMO that serves Arizona and parts of Utah. The HMO had a total enrollment of 395,466 in 1995 and 412,207 in 1996. Of these members, 159,669 were eligible for benefits for all of 1995 and 134,826 were eligible for benefits for all of 1996. The subjects were all Arizona residents who had a diagnosis of or were receiving treatment for type 2 diabetes mellitus and were continuously enrolled in the managed care organization between May 1, 1994 and April 30, 1996. The subjects were identified from the pharmacy and medical claims databases maintained by the managed care organization. The data extraction methods used to identify the subjects were similar to those presented by Armstrong and Manuchehri (1997).

The data were extracted from two different time frames. The first was the 12-month period prior to the addition of metformin to the formulary, which began May 1, 1994 and ended April 30, 1995. This period shall be referred to as year 1. The second time frame was the 12-month period following the availability of metformin, which runs from May 1, 1995 through April 30, 1996. This period shall be referred to as year 2.

To identify potential subjects the pharmacy and medical claims data were aggregated over each one-year period for each potential study subject. Each member has a unique member identification number which is used in the medical claims, pharmacy claims, and eligibility databases. The member numbers were used exclusively, so no patient names were ever seen by the researcher. Separate yet identical procedures were carried out for year 1 and year 2.
A unique list of member numbers was created for all people with a medical claim containing an ICD-9-CM diagnostic code for diabetes (250.xx) in any of the eight diagnosis fields during the year under study. Next a unique list of member numbers was created for all people with a pharmacy claim for an oral anti-diabetic agent (AHFS code: 68:20.20), or insulin (68:20.08) filed during the year under study. Then these lists were combined into a single list of unique member numbers. The patient's enrollment eligibility was assessed to determine if they were eligible for pharmacy and medical benefit coverage for the entire year. Those eligible for the entire 12 month period were deemed full-year members, while those eligible only part of the year were deemed part-year members. This procedure was carried out independently for year 1 and year 2. Then a new unique membership list was created which included only those members who were full year members in both years 1 and 2.

The next step was to identify the full year members who had a diagnosis of type 2 diabetes mellitus. The ICD-9-CM diagnostic codes listed on the medical claims and the pharmacy claims data were used in this process. The first three digits of the ICD-9-CM diagnostic code identify the disease state. The fourth and fifth digits are used to further describe the disease by specifying specific complications or affected body parts. In the case of diabetes mellitus, the first three digits are 250, the fourth digit identifies a specific complication or condition, and the fifth digit identifies the type of diabetes. A zero or a two in the fifth digit indicates type 2 diabetes, and a one or a three is used to indicate type 1 diabetes. Often the fifth digit is not recorded, or a patient may have a medical claim that contains an ICD-9-CM code for type 1 diabetes at one visit and one that indicates
type 2 diabetes at another visit. Therefore the following algorithm was used to identify subjects with type 2 diabetes mellitus.

First, the subjects that had only diabetes ICD-9 codes with a zero or a two in the fifth digit were identified as patients with type 2 diabetes. Patients with no diabetes ICD-9-CM diagnostic codes who were receiving oral anti-diabetes medications alone or in combination with insulin therapy were also included in the type 2 diabetes group. Then those with medical claims containing an ICD-9-CM diagnostic code for both type 1 and type 2 diabetes and who were receiving an oral anti-diabetes medication alone or in combination with insulin therapy were also included in the study.

The integrity of the data was assessed by examining the ages of all the study members to ensure they were within a reasonable range. Because type 2 diabetes is most commonly diagnosed after the age of 40 years, patients under 20 years of age who were not receiving oral anti-diabetes agents during year one were excluded from this study. Gender specificity was assessed, when possible, by ensuring that all people with medical claims for benign prostatic hypertrophy or prostate cancer were male, and that those with medical claims for pregnancy, breast cancer, and ovarian cancer were female. Reversed and duplicate claims were identified and removed to avoid double counting of resource utilization.
Independent Variable

The independent variable in this analysis was model type. This variable has two levels, a deterministic model and a stochastic model. The deterministic model will be described next, followed by a discussion of the stochastic model used in this research.

The Deterministic Model

The decision tree is the deterministic model used in this study. Two decision trees were constructed. The first one represented the therapies available to patients in the managed care organization during year 1, namely sulfonylureas and insulin. The second tree, representing year 2, was patterned after the first tree, but included metformin. The trees were created using the techniques recommended by Detsky, Naglie, Krahn, Naimark et al. (1997); Detsky, Naglie, Krahn, Redelmeier et al. (1997); Naglie et al. (1997); and Weinstein and Fineburg (1980). They were constructed within an equilibrium framework based on the 1995 treatment recommendations of the American Diabetes Association (1995). The initial year 1 distribution of patients among the various treatment regimens was based on the actual distribution of patients during the first two months of year 1 obtained from the managed care organization’s pharmacy claims database. The probabilities used in the model were derived from the clinical literature, and the costs used in this model were averaged costs from the pharmacy and medical claims databases of the managed care organization.
Constructing the Decision Tree

The following six recommendations by Detsky, Naglie, Krahn, Redelmeier et al. (1997) were used to construct the decision trees: 1) The tree must be balanced, 2) Only two branches should extend from a chance node, 3) The decision tree should not contain any embedded decision nodes, 4) The branches should be linked with one another, 5) The decision tree must have symmetry, and 6) The order of the branches does not matter.

The year one decision tree has four main branches representing people that were on insulin mono-therapy, sulfonylurea mono-therapy, a combination of insulin and sulfonylurea therapy, or diet alone during the first two months of year one. Patients that were on insulin mono-therapy are assumed to either respond or fail to respond to this therapy initially. It is assumed that patients who do not respond will remain on insulin mono-therapy, but consume more resources because they will be monitored more closely as described in the resource section below.

Patients in the combination therapy branch who fail to respond to therapy will be switched to multi-dose insulin mono-therapy. Patients who fail to respond to insulin mono-therapy will remain on insulin but will consume more resources because they will have to be monitored more closely.

Patients who fail to respond to oral sulfonylurea therapy initially will have a single dose of insulin added to their therapy. If they fail to respond to combination therapy then they will be switched to multi-dose insulin therapy as in the previous arm. Patients who do not respond to the multi-dose insulin will remain on the insulin regimen, but will require closer monitoring as above.
Figure 2  Year 1 Decision Tree
Patients that are not taking any medication initially will be started on oral sulfonylurea mono-therapy if their blood glucose concentration is no longer controlled with diet therapy. Insulin will be added to the sulfonylurea therapy for those not responding as in the previous arms. If the patient fails combination therapy, then a multi-dose insulin regimen will be initiated as described in previous arms.

The year 2 decision tree is similar to the year one tree except that a metformin mono-therapy branch has been added. Metformin therapy branches have also been added to the combination arm, the sulfonylurea arm, and the diet arm. It is assumed that a portion of patients that were maintained on diet therapy during year one will be started on metformin mono-therapy initially. If they fail to respond, then either insulin or a sulfonylurea will be added to the metformin therapy. If the patient fails to respond to either of these combination therapies, then a multi-dose insulin regimen will be initiated.

Patients who fail diet therapy during year 2 can be started on either metformin or a sulfonylurea. If either of these mono-therapies fails, then insulin will be added to the regimen. If the patient does not respond favorably to the combination therapy, then a multi-dose insulin regimen will be initiated.

Three medication classes are present in the year 2 decision tree, the sulfonylureas, metformin, and insulin. Although patients may rarely be placed on triple combination therapy is not recommended and is not included in the model. In this model it is assumed that patients may be on sulfonylurea and insulin, metformin and insulin, or metformin and sulfonylurea combination therapy. As described above, a multi-dose insulin regimen
will be initiated for any patients that fail to achieve glycemic control with one of the three combination treatment regimens.

**Estimating the Probabilities**

The probabilities associated with the chance nodes in each decision tree were gathered from the clinical literature following the procedures recommended by Naglie et al. (1997). Clinical trials were identified through a computerized literature search conducted on MEDLINE (Copyright 1996 Ovid Technologies, Inc.). The name of each anti-diabetes medication on formulary was used as a Medical Subject Heading (MeSH term) or as a text word if it was not available as a MeSH term. Then each term was limited to the following publication types published between 1990 and 1995: randomized controlled trial, human subjects, English language. Further studies were identified from the references obtained in the Medline search.

Next, any study that was not conducted in a type 2 diabetes population was excluded. Studies not reporting the number or percentage of patients reaching the glycemic control were also excluded.

Next all baseline effectiveness probability estimates were obtained by calculating a weighted average of the percent of people reaching their target glycemic control for each therapeutic regimen. This was done by summing the total number of patients reaching the target glycemic control and dividing by the sum of the number of patients in each treatment group. The most extreme estimate of effectiveness from the studies was used as the outer confidence limit in the probabilistic sensitivity analysis. Because over 90% of the study subjects who were on sulfonylurea therapy were using glipizide or
glyburide, which are second generation sulfonylureas, and because the efficacy of these agents at the recommended doses has been shown to be equivalent, these are collapsed into one category called oral sulfonylurea therapy.

Since these models are being conducted within an equilibrium framework, the initial distribution of patients across the various treatment regimens had to be determined. This distribution is analogous to the probability of entering a given branch. It was derived from the pharmacy claims database by determining the percentage of study subjects that were using insulin mono-therapy, sulfonylurea mono-therapy, combination therapy, or no therapy at all during the first two months of year 1 (May 1, 1994 through June 30, 1994).

The distribution of patients across the various treatment regimens for the year 2 model was obtained by the estimated distribution of patients at the end of the year 1 model. It was assumed that only patients that were in the diet group in year 1 will be placed on metformin mono-therapy. An estimate of the percentage of patients started on metformin mono-therapy in year 2 was obtained by multiplying the number of people in the diet group at the end of year 1 by the probability of failing diet therapy.

The techniques proposed by Doubilet et al. (1985) were used to conduct the probabilistic sensitivity analysis. These techniques were selected because they were the most explicit and could be conducted with The SAS System for Window, version 4.0.1111, release 6.2, which was the statistical software packaged used for this analysis.

The probabilistic sensitivity analysis was conducted by randomly assigning each probability a value from its assumed distribution and calculating the expected cost of
treatment by "folding back" the decision tree. This process was repeated 2,951 times (once for each study member).

For mathematical convenience, the distribution of the probabilities is assumed to be log-normal, that is the logit transformation of each probability (\( \log[\text{prob}/(1-\text{prob})] \)) is assumed to be normally distributed. Assuming this distribution for the probabilities has two advantages. First, the normal distribution associated with the transformed variable, logit(\( \text{prob} \)), is determined by its mean (\( \mu \)) and standard deviation (\( \sigma \)). Second, the random selection of a value, \( p \), from the distribution, \( \text{prob} \), is accomplished by randomly choosing a value, \( N \), (between \(-\infty\) and \(+\infty\)) from the associated normal distribution and then taking \( p \) to be the value whose logit is \( N \), that is, \( p = e^N/(1 + e^N) \).

The mean and standard deviation of the probabilities obtained from the literature are not the same as the mean and standard deviation of the distribution of the transformed probabilities. However, the mean (\( \mu \)) and standard deviation (\( \sigma \)) of the transformed probabilities are derived from the baseline estimate of the mean and the upper or lower bound of the estimate derived from the literature. The weighted mean of those responding to each treatment was used as the baseline mean estimate, \( X \), and the most extreme value was used as the outer limit, \( L \). The mean and standard deviation of the distribution of the transformed probabilities is calculated as follows:

\[
\mu = \frac{B - E \times \sqrt{B^2 - M^2 + M^2 E^2}}{1 - E^2}, \text{ where}
\]

\[
M = \log \left[ \frac{X}{1 - X} \right],
\]
The term \(\phi^{-1}(X)\) is the number, \(Z\), (between \(-\infty\) and \(+\infty\)) for which the normal distribution function with mean of zero and standard deviation of one, evaluated at \(Z\) equals \(X\). \(E\) is conveniently calculated as \(E = \frac{1.96}{\phi^{-1}(X)}\); using the SAS probit function. Once the mean of the logit transformation is obtained, the standard deviation, \(s\), is calculated as follows:

\[
s = \frac{|\mu - B|}{1.96}.
\]

After \(\mu\) and \(s\) are calculated for each probability used in the decision tree, a variable called, \(N\), was created as \(N = \mu + (s \times \text{rannor(seed)})\); using the SAS random number generator which selects a random number from a normal distribution.

The probability, \(p\), for each branch is then obtained from the following equation:

\[
p = \frac{e^N}{1 + e^N}.
\]

**Estimating the Costs**

The resources used in each branch of the decision tree are based on the standards of care proposed by the American Diabetes Association (1996). The initial and annual physician visit should include a thorough history and physical, glycohemoglobin, fasting plasma glucose, fasting lipid profile, serum creatinine, urinalysis (check for glucose,
ketones, protein, and sediment), determination of microalbuminurea (in adults who have had diabetes for more than four years), a thyroid function test, and an electrocardiogram (for adults). Patients on insulin therapy or those not meeting their glycemic control goals should have physician visits every three months (more often if needed) at which time the patient should have a glycohemoglobin test and a fasting plasma glucose. Patients controlled on medications should be seen by the physician every 6 months unless otherwise needed. Each visit should include a glycohemoglobin test and a fasting plasma glucose. Patients controlled on diet alone should be seen every six to twelve months and only require a fasting plasma glucose test.

Patients initiating insulin therapy should be in close contact with their provider (as often as daily) by phone or office visit until their optimal regimen is obtained. Patients initiating diet or oral agents may need to be in weekly contact until glycemic control is achieved.

The decision tree covers a 12-month time frame. For the purpose of assigning resources to the decision trees, it was assumed that once a patient was started on any agent, they will be on it for two months before they are switched to the next level of treatment. This two-month period allows for dosage titration.
<table>
<thead>
<tr>
<th>Branch Description</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin mono-therapy,</td>
<td>60 days worth of insulin, 1 physician visit, 1 glycohemoglobin,</td>
</tr>
<tr>
<td>Initial/annual visit</td>
<td>1 fasting plasma glucose, 1 fasting lipid profile, 1 serum</td>
</tr>
<tr>
<td></td>
<td>creatinine, 1 urinalysis, 1 microalbuminurea test, 1 thyroid function test,</td>
</tr>
<tr>
<td></td>
<td>and 1 electrocardiogram</td>
</tr>
<tr>
<td>Insulin mono-therapy,</td>
<td>305, 245, or 185 remaining days worth of insulin, 1 physician visit</td>
</tr>
<tr>
<td>favorable response</td>
<td>every 3 months, 1 glycohemoglobin every 3 months, 1 fasting plasma glucose</td>
</tr>
<tr>
<td></td>
<td>every 3 months</td>
</tr>
<tr>
<td>Insulin mono-therapy,</td>
<td>305 days worth of insulin, 5 physician visit, 5 glycohemoglobin,</td>
</tr>
<tr>
<td>unfavorable response</td>
<td>5 fasting plasma glucose, 2 fasting lipid profile, 2 serum</td>
</tr>
<tr>
<td></td>
<td>creatinine, 2 urinalysis, 2 microalbuminurea test, 1 thyroid function test,</td>
</tr>
<tr>
<td></td>
<td>1 electrocardiogram</td>
</tr>
<tr>
<td></td>
<td>and 2 electrocardiogram</td>
</tr>
<tr>
<td>Insulin mono-therapy,</td>
<td>60 days worth of insulin, 3 physician visit, 1 glycohemoglobin,</td>
</tr>
<tr>
<td>switched to multidose insulin</td>
<td>1 fasting plasma glucose, 1 fasting lipid profile, 1 serum</td>
</tr>
<tr>
<td></td>
<td>creatinine, 1 urinalysis, 1 microalbuminurea test, 1 thyroid function test,</td>
</tr>
<tr>
<td></td>
<td>and 1 electrocardiogram</td>
</tr>
<tr>
<td>Branch Description</td>
<td>Resources</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Combination</td>
<td>60 days worth of medication, 1 physician visit, 1 glycohemoglobin, 1 fasting plasma glucose, 1 fasting lipid profile, 1 serum creatinine, 1 urinalysis, 1 microalbuminurea test, 1 thyroid function test, and 1 electrocardiogram</td>
</tr>
<tr>
<td>initial/annual visit</td>
<td>1 serum creatinine, 1 urinalysis, 1 microalbuminurea test, 1 thyroid function test, and 1 electrocardiogram</td>
</tr>
<tr>
<td>Combination</td>
<td>305, 245, or 185 remaining days worth of medication, 1 physician visit every 5 months, 1 glycohemoglobin every 5 months, 1 fasting plasma glucose every 5 months</td>
</tr>
<tr>
<td>favorable response</td>
<td></td>
</tr>
<tr>
<td>Switched to combination</td>
<td>60 days worth of medication, 2 physician visits, 1 glycohemoglobin, 1 fasting plasma glucose, 1 fasting lipid profile, 1 serum creatinine, 1 urinalysis, 1 microalbuminurea test, 1 thyroid function test, and 1 electrocardiogram</td>
</tr>
<tr>
<td>Add sulfonylurea</td>
<td>60 days worth of sulfonylurea, 2 physician visit, 1 glycohemoglobin, 1 fasting plasma glucose</td>
</tr>
</tbody>
</table>
Table 3  Resources Associated with each Branch of the Decision Tree (Continued)

<table>
<thead>
<tr>
<th>Branch Description</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet/no Rx therapy, initial visit</td>
<td>1 physician visit, 1 glycohemoglobin, 1 fasting plasma glucose, 1 fasting lipid profile, 1 serum creatinine, 1 urinalysis, 1 microalbuminurea test, 1 thyroid function test, and 1 electrocardiogram</td>
</tr>
<tr>
<td>Diet/no Rx therapy, favorable response</td>
<td>1 physician visit, 1 fasting plasma glucose</td>
</tr>
<tr>
<td>Metformin mono-therapy, initial/annual visit</td>
<td>60 days worth of metformin, 1 physician visit, 1 glycohemoglobin, 1 fasting plasma glucose, 1 fasting lipid profile, 1 serum creatinine, 1 urinalysis, 1 microalbuminurea test, 1 thyroid function test, and 1 electrocardiogram</td>
</tr>
<tr>
<td>Metformin mono-therapy, favorable response</td>
<td>305, 245, or 185 remaining days worth of metformin, 1 physician visit every 6 months, 1 glycohemoglobin every 6 months, 1 fasting plasma glucose every 6 months</td>
</tr>
<tr>
<td>Add metformin</td>
<td>60 days worth of metformin, 2 physician visits, 1 glycohemoglobin, 1 fasting plasma glucose</td>
</tr>
</tbody>
</table>

Published pharmacoeconomic analyses derive cost estimates in one of two ways. When the actual costs are not available from a specific hospital or health system, they are obtained from the literature or taken from allowable reimbursement from programs such as Medicaid or Medicare. However, when the perspective of the analysis is that of a
hospital or health system, and cost data are available, then internal costs derived from hospital accounting systems, claims databases, or derived from charges using cost-to-charge ratios are used. Internally derived costs should provide a better estimate of the cost impact that the intervention being studied has upon the health care system because the point estimates of cost that are included in the model are actually the average costs incurred by the population under study. Although this should increase the internal validity of the analysis, it decreases the external validity.

In this research, internally derived costs were used for several reasons. First, the perspective of this research was that of a third party payer responsible for all treatment costs. The claims filed by physicians, pharmacies, hospitals, and laboratories were the actual costs incurred by the managed care organization, and should maximize the internal consistency of each analysis. Second, the purpose of this study is to compare two models, not to compare different approaches to obtaining cost information. Therefore the average costs for the study population were used in the deterministic model for both pharmacy and medical resources included in the model.

The cost of each resource unit was obtained from the medical or pharmacy claims databases. The cost of a diabetes related physician visit was calculated by averaging all physician assessments filed on claims that contain a 250.xx primary diagnosis code during year 1. Similarly, the costs of a glycohemoglobin test, a fasting plasma glucose test, a fasting lipid profile, a serum creatinine, a urinalysis, a microalbuminurea test, a thyroid function test, and an electrocardiogram were calculated by averaging the amount
paid by the health maintenance organization for each procedure on claims that contain a 250.xx diagnosis code in any of the diagnostic fields.

The medication costs were calculated in a slightly different manner to account for different products and different dosage regimens. A weighted average cost per day was calculated for each class.

The average daily cost of the sulfonylureas was calculated by creating a table that contained the following columns: GENERIC NAME, QUANTITY, DAYS SUPPLY, TOTAL NUMBER OF FILLS, TOTAL COSTS, TOTAL DAYS, and DOSES PER DAY. The columns, TOTAL NUMBER OF FILLS and TOTAL COSTS, were populated by summing the number of prescription fills and the cost of each prescription by each unique combination of generic name, quantity, and days supply. Multiplying the column, TOTAL NUMBER OF FILLS by the column, DAYS SUPPLY populated the TOTAL DAYS column. The DOSES PER DAY column was populated by dividing the column QUANTITY by the DAYS SUPPLY column.

To try to ensure that only valid data were used in the calculation, rows that contained improbable doses per day (e.g., 1.33, 4.8, 40) were eliminated. Once all the questionable rows were removed from the table, the TOTAL COSTS and TOTAL DAYS columns were each summed to yield the GRAND TOTAL COST and GRAND TOTAL DAYS columns respectively. Then the GRAND TOTAL COST column was divided by the GRAND TOTAL DAYS column that produced the average cost per day of therapy weighted by the number of fills for each therapy.
A similar procedure was followed for the insulins. A table was created which contained the following columns: GENERIC NAME, QUANTITY, DAYS SUPPLY, TOTAL NUMBER OF FILLS, TOTAL COSTS, TOTAL DAYS, and UNITS PER DAY. The TOTAL NUMBER OF FILLS and TOTAL COSTS columns were populated by summing the number of prescription fills and the cost of each prescription by each unique combination of generic name, quantity, and days supply. The TOTAL DAYS column was populated by multiplying the column, TOTAL NUMBER OF FILLS, by the DAYS SUPPLY column. The DOSES PER DAY column was populated by dividing the QUANTITY by the DAYS SUPPLY column.

Because the days supply obtained from each vial varies with the dosage regimen, a column called units per day was created. Since the concentration of most insulin is 100 units per ml, and all the quantities were in milliliters, multiplying the quantity (in mls) by 100, then dividing by DAYS SUPPLY yielded units per day. Because few people receive more than 150 units per day, any rows that had greater than 150 units per day were eliminated.

Once all the questionable rows were removed from the table, the TOTAL COSTS and TOTAL DAYS columns were summed to yield the GRAND TOTAL COST and the GRAND TOTAL DAYS COLUMNS, respectively. Next the GRAND TOTAL COST column was divided by the GRAND TOTAL DAYS column which produced the average cost per day of therapy weighted by the number of fills.
The same procedures outlined above were done for patients on combination therapy to get the average daily cost for the sulfonylureas and insulin for this subpopulation.

The cost of a days supply of metformin was taken from the 1994 Redbook for the usual maintenance dose (850mg BID).

The Stochastic Model

Regression analysis was used to build the stochastic model in this study. Regression analysis is used in many disciplines to estimate relationships between variables, test hypotheses involving the relationships, and to forecast the behavior of variables. The model used in this study estimated the relationship between two dependent variables, diabetes-specific and diabetes-related costs, and a number of independent variables in order to forecast the impact of adding metformin to the formulary on the dependent variable.

The stochastic model was a log-linear regression model created from the medical and pharmacy claims databases of the managed care organization. The data extraction methods presented by Armstrong and Manuchehri (1997) were used to obtain the patient-level data. Claims data from the 12-month period prior to the introduction of metformin were used to estimate the regression parameters. The candidates for metformin therapy were pulled from the pool of patients with poorly controlled diabetes. An estimate of the percentage of these people whose diabetes may be controlled by taking metformin was based upon the clinical literature.
The procedures used to formulate the model, extract the data from the claims database, estimate the model, and estimate the impact of adding metformin to the formulary are discussed below.

**Formulating the Stochastic Model**

**Explanatory Variables**

Many of the explanatory variables were included in the model to control for certain characteristics of the patient, treatment, or disease, and can be grouped as such. The first group of explanatory variables is the patient characteristics. These include: age, gender, and the presence of co-morbid conditions.

The age of the patient in years at the beginning of the study period (May 1, 1994). Age is important in this model because the onset of type 2 diabetes is usually in the third or fourth decade of life. As the patient ages, he or she is more likely to experience the complications associated with diabetes and other diseases.

The gender of the patient was also included in the model. Typically the prevalence of diabetes does not differ between males and females. However, cardio-protective qualities associated with being female are eroded by diabetes. Women with diabetes are also more prone to urinary tract and vaginal infections if the disease is not controlled.

To control for the presence of co-morbid conditions, dummy variables were used to indicate the presence or absence of the broad categories of diseases as outlined in the ICD-9-CM Manual (PMIC, 1994). These variables were included to control for
variations in resource utilization (and costs) attributable to the diagnosis and treatment of non-diabetes related conditions.

The disease characteristics were captured by dummy variables indicating the presence or absence of specific complications or co-morbid conditions commonly associated with diabetes.

The presence of nephropathy, retinopathy, neuropathy, and coronary artery disease were included in the model because these are complications of diabetes. These variables serve as proxy measures for the duration of the diabetes and long-term glycemic control. Almost all patients exhibit some degree of neuropathy five to ten years after diagnosis (Nathan, 1993). The loss of sensation in the lower extremities is particularly troublesome because it may contribute to foot trauma and diabetic foot ulcers.

Nephropathy progresses to end-stage renal disease in nearly 20% of the patients with type 2 diabetes (Nathan, 1993). Retinopathy affects roughly 50% of all patients with diabetes within seven years of diagnosis and over 90% after 20 years, and cardiovascular disease occurs at a higher rate and an earlier age in diabetics compared to non-diabetics, especially in women (Nathan, 1993).

The presence of hypertension, dyslipidemia, and obesity were included in the model because these conditions are commonly associated with diabetes. The presence of these disorders can worsen diabetes and its complications leading to an increase in resource utilization.

The final disease characteristic variable is a proxy measure, UNCONT, indicating if a patient's blood glucose is uncontrolled during the second half of year 1. This variable
had to be created because no clinical data (e.g., glycosolated hemoglobin) exists in the claims database. If a patient had any one of the following characteristics, then their diabetes was considered uncontrolled: 1) more than four glycohemoglobin tests per year, 2) more than one UTI or episode of vaginitis per year, 3) therapy change (change in medication class or addition of a second class) in last 6 months of year 1 (November 1, 1994 to April 30, 1995). These criteria were confirmed by a certified diabetes educator.

Not all patients that lack glycemic control are candidates for metformin therapy. It was assumed that only patients whose diabetes was not controlled who were obese or on diet or sulfonylurea therapy alone were candidates for metformin therapy. Since the purpose of the variable UNCONT is to estimate the cost impact of improved clinical outcomes secondary to the addition of metformin on the formulary, this variable was further refined to identify patients with uncontrolled diabetes who are also candidates for metformin therapy. This was accomplished by producing a list of patients that met the UNCONT criteria. All patients identified as obese from the ICD-9-CM diagnostic codes on their medical claims, or those on diet therapy or on oral sulfonylurea mono-therapy were retained on the list, all others were excluded.

The treatment characteristics are captured by dummy variables indicating the type of therapy the patient is using. During year 1 of this study, a patient could have been on no therapy, mono-therapy with an oral agent, combination therapy with a sulfonylurea and insulin, or mono-therapy with insulin. These variables also serve as a proxy for the severity of the disease.
Similarly the presence of a visit to a specialist (ophthalmologist, cardiologist, cardiothoracic surgeon, endocrinologist, registered dietitian, podiatrist) was included in the model. This variable is a proxy for the level of care the patient is receiving, which may be a function of the primary provider and the specific physician group or clinic within which he or she practices.

Data Extraction

Following Armstrong and Manuchehri, 1997, data were extracted as described below.

The time frame for building cost and resource profiles was defined first. The data were extracted from two different time frames. The first was the 12-month period prior to the addition of metformin to the formulary. This period was May 1, 1994 through April 30, 1995. The second time frame was the 12-month period following the availability of metformin, and runs from May 1, 1995 through April 30, 1996. The unit of analysis (the patient, provider, or clinic) was then defined.

The patient is the unit of analysis, so the information at the pharmacy and medical claims level needs to be aggregated over the one-year period for each patient included in the study. Each member has a unique member number which is used in the medical claims, pharmacy claims, and eligibility databases. The member numbers were used exclusively, so no patient names were ever seen by the researcher. Separate yet identical procedures were carried out for year 1 and year 2 as described in the SUBJECTS section at the beginning of this chapter.
All claims for the defined population were then extracted. Using the list of unique member numbers for the study group, all medical and pharmacy claims were pulled for each year. The unique member number linked these two files.

**Assessing The Integrity of the Data**

The ages of all the study members were assessed to ensure that they fell into a reasonable range. Gender specificity was evaluated by ensuring that only males had claims for benign prostatic hypertrophy and male-related cancers, and that only females had claims for female-related cancers and pregnancies whenever possible. Denied, reversed, and duplicate claims were identified and removed to avoid double counting of resource utilization.

**Model Specification**

The following models were specified using the medical and pharmacy claims data from year 1, aggregated to the patient level.

\[
\text{LNDSC} = \alpha + \beta_1\text{AGE} + \beta_2\text{UNCONT} + \beta_3\text{SEX} + \beta_4\text{RENAL} + \beta_5\text{EYE} + \beta_6\text{NEURO} + \beta_7\text{CHF} + \beta_8\text{HTN} + \beta_9\text{LIPID} + \beta_{10}\text{OBES} + \beta_{11}\text{ORALTX} + \beta_{12}\text{INSTX} + \beta_{13}\text{COMBO} + \beta_{14}\text{SPEC} + \beta_{15}\text{DIAG1} + \ldots + \beta_{30}\text{DIAG16} + \epsilon
\]

\[
\text{LNDSMC} = \alpha + \beta_1\text{AGE} + \beta_2\text{UNCONT} + \beta_3\text{SEX} + \beta_4\text{RENAL} + \beta_5\text{EYE} + \beta_6\text{NEURO} + \beta_7\text{CHF} + \beta_8\text{HTN} + \beta_9\text{LIPID} + \beta_{10}\text{OBES} + \beta_{11}\text{ORALTX} + \beta_{12}\text{INSTX} + \beta_{13}\text{COMBO} + \beta_{14}\text{SPEC} + \beta_{15}\text{DIAG1} + \ldots + \beta_{30}\text{DIAG16} + \epsilon
\]
LNDSPC = \alpha + \beta_1 \text{AGE} + \beta_2 \text{UNCONT} + \beta_3 \text{SEX} + \beta_4 \text{RENAL} + \beta_5 \text{EYE} + \beta_6 \text{NEURO} + \beta_7 \text{CHF} + \beta_8 \text{HTN} + \beta_9 \text{LIPID} + \beta_{10} \text{OBES} + \beta_{11} \text{ORALTX} + \beta_{12} \text{INSTX} + \beta_{13} \text{COMBO} + \beta_{14} \text{SPEC} + \beta_{15} \text{DIAG1} + \ldots + \beta_{30} \text{DIAG16} + \varepsilon

LNDRC = \alpha + \beta_1 \text{AGE} + \beta_2 \text{UNCONT} + \beta_3 \text{SEX} + \beta_4 \text{RENAL} + \beta_5 \text{EYE} + \beta_6 \text{NEURO} + \beta_7 \text{CHF} + \beta_8 \text{HTN} + \beta_9 \text{LIPID} + \beta_{10} \text{OBES} + \beta_{11} \text{ORALTX} + \beta_{12} \text{INSTX} + \beta_{13} \text{COMBO} + \beta_{14} \text{SPEC} + \beta_{15} \text{DIAG1} + \ldots + \beta_{30} \text{DIAG16} + \varepsilon

LNDRMC = \alpha + \beta_1 \text{AGE} + \beta_2 \text{UNCONT} + \beta_3 \text{SEX} + \beta_4 \text{RENAL} + \beta_5 \text{EYE} + \beta_6 \text{NEURO} + \beta_7 \text{CHF} + \beta_8 \text{HTN} + \beta_9 \text{LIPID} + \beta_{10} \text{OBES} + \beta_{11} \text{ORALTX} + \beta_{12} \text{INSTX} + \beta_{13} \text{COMBO} + \beta_{14} \text{SPEC} + \beta_{15} \text{DIAG1} + \ldots + \beta_{30} \text{DIAG16} + \varepsilon

LNDRPC = \alpha + \beta_1 \text{AGE} + \beta_2 \text{UNCONT} + \beta_3 \text{SEX} + \beta_4 \text{RENAL} + \beta_5 \text{EYE} + \beta_6 \text{NEURO} + \beta_7 \text{CHF} + \beta_8 \text{HTN} + \beta_9 \text{LIPID} + \beta_{10} \text{OBES} + \beta_{11} \text{ORALTX} + \beta_{12} \text{INSTX} + \beta_{13} \text{COMBO} + \beta_{14} \text{SPEC} + \beta_{15} \text{DIAG1} + \ldots + \beta_{30} \text{DIAG16} + \varepsilon

LNTC = \alpha + \beta_1 \text{AGE} + \beta_2 \text{UNCONT} + \beta_3 \text{SEX} + \beta_4 \text{RENAL} + \beta_5 \text{EYE} + \beta_6 \text{NEURO} + \beta_7 \text{CHF} + \beta_8 \text{HTN} + \beta_9 \text{LIPID} + \beta_{10} \text{OBES} + \beta_{11} \text{ORALTX} + \beta_{12} \text{INSTX} + \beta_{13} \text{COMBO} + \beta_{14} \text{SPEC} + \beta_{15} \text{DIAG1} + \ldots + \beta_{30} \text{DIAG16} + \varepsilon
LNTMC = \alpha + \beta_1 \text{AGE} + \beta_2 \text{UNCONT} + \beta_3 \text{SEX} + \beta_4 \text{RENAL} + \beta_5 \text{EYE} + \beta_6 \text{NEURO} + \beta_7 \text{CHF} + \beta_8 \text{HTN} + \beta_9 \text{LIPOID} + \beta_{10} \text{OBES} + \beta_{11} \text{ORALTX} + \beta_{12} \text{INSTX} + \beta_{13} \text{COMBO} + \beta_{14} \text{SPEC} + \beta_{15} \text{DIAG1} + \ldots + \beta_{30} \text{DIAG16} + \varepsilon

LNTPC = \alpha + \beta_1 \text{AGE} + \beta_2 \text{UNCONT} + \beta_3 \text{SEX} + \beta_4 \text{RENAL} + \beta_5 \text{EYE} + \beta_6 \text{NEURO} + \beta_7 \text{CHF} + \beta_8 \text{HTN} + \beta_9 \text{LIPOID} + \beta_{10} \text{OBES} + \beta_{11} \text{ORALTX} + \beta_{12} \text{INSTX} + \beta_{13} \text{COMBO} + \beta_{14} \text{SPEC} + \beta_{15} \text{DIAG1} + \ldots + \beta_{30} \text{DIAG16} + \varepsilon

Where LNSDC is the natural logarithm of diabetes-specific costs,
LNSMC is the natural logarithm of diabetes-specific medical costs,
LNSPC is the natural logarithm of diabetes-specific pharmacy costs,
LNDRC is the natural logarithm of diabetes-related costs;
LNDRMC is the natural logarithm of diabetes-related medical costs,
LNDRPC is the natural logarithm of diabetes-related pharmacy costs,
LNTC is the natural logarithm of total costs,
LNTMC is the natural logarithm of total medical costs,
LNTPC is the natural logarithm of total pharmacy costs,
AGE is the age of the patient in years at the beginning of the study period
(May 1, 1994);
UNCONT is the presence of uncontrolled diabetes in patients who are potential candidates for metformin therapy as measured by the criteria given above,
(0 = No; 1 = Yes);
SEX is the sex of the patient (0 = male; 1 = female);

RENAL is the presence of nephropathy [ICD-9-CM diagnostic codes 250.4, 583.81, 403.90], (0 = No; 1 = Yes);

EYE is the presence of eye disease including retinopathy [ICD-9-CM diagnostic codes 250.5, 362.01, 362.02, 362.10, 362.12, 362.29], (0 = No; 1 = Yes);

NEURO is the presence of neuropathy [ICD-9-CM diagnostic codes 250.6, 337.9, 355.8, 357.2], (0 = No; 1 = Yes);

CHF is the presence of heart disease including coronary artery disease [ICD-9-CM diagnostic codes 410.0-414.9], (0 = No; 1 = Yes);

HTN is the presence of hypertension [ICD-9-CM diagnostic codes 401-406], (0 = No; 1 = Yes);

LIPID is the presence of dyslipidemia [ICD-9-CM diagnostic code 272], (0 = No; 1 = Yes);

OBES is the presence of obesity [ICD-9-CM diagnostic codes 244.9, 253.8, 255.8, 259.9, 278.0], (0 = No; 1 = Yes);

ORALTX represents the presence of treatment with an oral diabetes medication during the first year of the study period, (0 = No; 1 = Yes);

INSTX is the presence of insulin during the first year of the study period, (0 = No; 1 = Yes);

COMBO is the presence of combination therapy (oral + oral or oral + insulin) during the first year of the study period, (0 = No; 1 = Yes);
DIAG1 = persons reporting at least one claim in ICD-9-CM range 001-139
(Infectious and Parasitic Diseases), (0 = No; 1 = Yes);

DIAG2 = persons reporting at least one claim in ICD-9-CM range 140-239
(Neoplasms), (0 = No; 1 = Yes);

DIAG3 = persons reporting at least one claim in ICD-9-CM range 240-244.89,
245.0-249.99, 251.0-253.79, 253.9-255.79, 255.9-259.89, 260.0-271.99,
273-277.99, 278.01-279 (Endocrine, Nutritional and Metabolic Diseases,
and Immunity Disorders excluding Diabetes, Lipid disorders, and
Obesity), (0 = No; 1 = Yes);

DIAG4 = persons reporting at least one claim in ICD-9-CM range 280-289
(Diseases of the Blood and Blood-Forming Organs), (0 = No; 1 = Yes);

DIAG5 = persons reporting at least one claim in ICD-9-CM range 290-319
(Mental Disorders), (0 = No; 1 = Yes);

DIAG6 = persons reporting at least one claim in ICD-9-CM range 320-337.89,
339-355.79, 355.9-357.19, 357.3-362, 362.3-389 (Diseases of the Nervous
System excluding diabetes-related neuropathies and eye disease),
(0 = No; 1 = Yes);

DIAG7 = persons reporting at least one claim in ICD-9-CM range 390-400.99,
407-409.99, 415-459 (Diseases of the Circulatory System excluding
diabetes related nephropathy, coronary artery disease, and hypertension),
(0 = No; 1 = Yes);
DIAG8 = persons reporting at least one claim in ICD-9-CM range 460-519
(Diseases of the Respiratory System), (0 = No; 1 = Yes);

DIAG9 = persons reporting at least one claim in ICD-9-CM range 520-579
(Diseases of the Digestive System), (0 = No; 1 = Yes);

DIAG10 = persons reporting at least one claim in ICD-9-CM range 580-583.80,
583.82-629 (Diseases of the Genitourinary System), (0 = No; 1 = Yes);

DIAG11 = persons reporting at least one claim in ICD-9-CM range 630-676
(Complications of Pregnancy, Childbirth and the Puerperium),
(0 = No; 1 = Yes);

DIAG12 = persons reporting at least one claim in ICD-9-CM range 680-709
(Diseases of the Skin and Subcutaneous Tissues), (0 = No; 1 = Yes);

DIAG13 = persons reporting at least one claim in ICD-9-CM range 710-739
(Diseases of the Musculoskeletal System and Connective Tissue),
(0 = No; 1 = Yes);

DIAG14 = persons reporting at least one claim in ICD-9-CM range 740-759
(Congenital Abnormalities), (0 = No; 1 = Yes);

DIAG15 = persons reporting at least one claim in ICD-9-CM range 760-779
(Certain Conditions Originating in the Perinatal Period),
(0 = No; 1 = Yes);

DIAG16 = persons reporting at least one claim in ICD-9-CM range 780-799
(Symptoms, Signs and Ill-defined Conditions), (0 = No; 1 = Yes); and
\( \alpha, \beta, \) and \( \epsilon \) are constants.
Interpreting the Parameter Estimates

In a lognormal regression model, a parameter estimate associated with a continuous explanatory variables (multiplied by 100) equals the percentage change in the unit value of the dependent variable (e.g., diabetes-specific costs) per unit change in the explanatory variable. However, the interpretation of a parameter estimate associated with a binary variable is interpreted differently. Halvorsen and Palmquist (1980) point out that if an estimate of the percentage impact is required then the parameter estimate, $b$, needs to be transformed by the following expression: $100 \cdot (e^{b} - 1)$. This adjusted parameter estimate can be interpreted as the percentage increase in average diabetes-specific (or diabetes-related) cost when a particular characteristic is present.

When a characteristic has more than two levels, then the number of binary variables that must be specified for that characteristic is one minus the number of levels. One level must be excluded to avoid inducing perfect multicollinearity into the model. The excluded level becomes the referent value against which the other levels are compared. For instance, the type of therapy has four levels, diet, mono-therapy with an oral agent, mono-therapy with insulin, and combination therapy. To represent this characteristic in the model, three binary variables are included (ORALTX, INSTX, and COMBO). The interpretation of the transformed parameter estimate associated with each of these dummy variables is the percent change in average diabetes-specific cost compared to those patients on diet therapy, the omitted variable.
Data Analysis

As indicated above, the ability of the two models to accurately predict the impact on costs of adding metformin to the formulary was assessed in two ways. First, the actual average diabetes-specific costs incurred during year 2 were calculated from the medical and pharmacy claims of the members included in this study. This figure was then compared to the estimates provided by each model to determine if there was overlap in the 95% confidence limits around the estimated and actual average diabetes-specific costs. The estimated percent change in the average diabetes-specific costs predicted by each model was also assessed against the actual percent change in the average diabetes-specific costs. This was done by using the models to calculate the average diabetes-specific cost estimates for the first and second years and determining the percent change from the first year \(\frac{\text{Avg. Costs}_{\text{year}2} - \text{Avg. Costs}_{\text{year}1}}{\text{Avg. Costs}_{\text{year}1}}\). This formula was also used to calculate the actual percent change in average diabetes-specific costs incurred by the managed care organization. This step was conducted to determine how accurately the models predicted the magnitude of change in average diabetes-specific costs.

The ability of the stochastic model to accurately predict the average diabetes-related costs and percent change average diabetes-related costs was also assessed. This assessment was not conducted for the deterministic model because it only assesses diabetes-specific costs.
Dependent Variables

Calculating the Actual Costs Incurred During Year Two

The diabetes specific costs include the medical claims associated with an ICD-9-CM diagnostic code of 250.xx, which represents diabetes, and pharmacy claims for oral anti-diabetic medications (AHFS code: 68:20.20), insulin (68:20.08), and diabetes supplies such as glucometers, Chem-strips, and syringes.

The diabetes-related costs were calculated by adding the diabetes-specific costs to the medical costs obtained from claims that contain an ICD-9-CM diagnostic code associated with one of the diseases identified as long-term complications of diabetes (Nathan, 1993). The ICD-9-CM codes associated with these complications were augmented with codes listed under the “diabetes, diabetic” subheading in the ICD-9-CM reference manual (PMIC, 1994). These diseases include nephropathy (ICD-9-CM diagnostic codes 250.4, 583.81, 403.90, V56.0), vision disturbances (retinopathy, cataracts, glaucoma (ICD-9-CM diagnostic codes 240.5, 250.5, 362.01, 362.02, 362.10, 362.12, 362.29, 362.83, 365.44, 366.41), diabetic neuropathy (ICD-9-CM diagnostic codes 250.6, 337.9, 355.8, 357.2), coronary artery disease (ICD-9-CM diagnostic codes 410.0-414.9), cerebral vascular disease (ICD-9-CM diagnostic codes 433.0-436), peripheral vascular disease (ICD-9-CM diagnostic codes 250.6, 337.1, 440.2, 443.81), and ulceration of the skin or gangrene (ICD-9-CM diagnostic code 250.7, 785.4, 250.8, 707.9). The following groups of medications were also included in the calculation of diabetes-related costs: cardiac drugs (AHFS code: 24:04), anti-lipemic agents (24:06), hypotensive agents (24:08), vasodilating agents (24:12), and diuretics (40:28).
medication groups were used in a diabetes-related cost study conducted by Warner, et al. (1996). Other agents, such as tricyclic antidepressants are sometimes used to treat diabetic neuropathies. However, they are not included in the calculation of diabetes-related costs because they are much more commonly used to treat other indications.

Calculating the Expected Costs Using the Deterministic Model

The expected diabetes-specific cost of treatment was obtained from the decision tree by "folding back" the tree. Folding back a tree refers to the calculation of the expected cost (or outcome) by multiplying the cost of the resources (or utility of the outcome) in each arm by the probability of entering that arm (Weinstein & Fineberg, 1980). This is done starting at the right hand side of the tree and moving toward the left-hand side (from the last branches of the tree to the first branches). The resultant expected cost is the weighted average diabetes-specific cost of treating a patient with type 2 diabetes. The expected diabetes-related costs before and after the addition of metformin to the formulary were calculated using the year 1 and year 2 models respectively.

Because the procedures followed in this study utilized a system wide equilibrium approach, the expected cost of treating patients with type 2 diabetes before and after metformin was added to the formulary was calculated. The distribution of patients among therapies is based on the year 1 pharmacy claims information. For the year 1 tree, the percentage of patients on each therapy was used as probabilities of entering that therapeutic branch. The average percentage of patients failing to respond to therapy in the "sulfonylurea therapy" and "no Rx therapy" main branches in the year 1 model was used to adjust the proportion of patients in these arms in the year 2 model.
A probabilistic sensitivity analysis was conducted for the two decision trees in this model for two reasons. First, the traditional approach to sensitivity analysis is to vary one or two probabilities at a time to see if the results of the decision change. This process can be cumbersome and less than useful if many probabilities need to be assessed. A probabilistic approach allows for the simultaneous assessment of the uncertainty surrounding all the probabilities (Doubilet et al., 1985). However, the most important reason for using a probabilistic sensitivity analysis is that it allows for the calculation of an expected cost of treatment with a 95% confidence interval.

The probabilistic sensitivity analysis was conducted by randomly assigning each probability a value from its assumed distribution and calculating the expected cost of treatment by "folding back" the decision tree. This process was repeated 2,951 times (once for each study member). The average expected cost and the standard error of the mean were obtained from the simulations and a 95% confidence interval was calculated using the following formula: Mean Expected Cost ± (t_{2,951\text{df}, \alpha=0.05}) \times \text{(SEM)}.

Calculating the Costs With the Stochastic Model

The costs associated with specific procedures were calculated by subtracting the patient co-payment from the amount in the "allowable amount" field. This was the amount that Intergroup paid for the services on the claim filed by a fee-for-service provider. Claims filed by capitated providers contain a market value amount that is populated by Intergroup. This is their best estimate of the cost of the service provided and is the amount they use for actuarial purposes.
The diabetes specific costs were the amount paid by the managed care organization for the treatment and monitoring of diabetes. Any of the following services or tests submitted on a claim containing the ICD-9-CM diagnostic code, 250.xx were included in the diabetes-specific costs: any physician assessment or consultation, glycosylated hemoglobin test, blood chemistry profile, plasma glucose test, urinalysis, urine protein analysis, retinal exam, lipid profile, and serum creatinine test. Pharmacy claims for oral anti-diabetic medications (AHFS code: 68:20.20), insulin (68:20.08), and diabetes supplies such as glucometers, Chem-strips, and syringes paid for by the managed care organization were also be included in the calculation of diabetes-specific costs.

The diabetes-related costs include all the diabetes-specific costs plus the costs associated with the treatment and monitoring of the long-term complications of diabetes. The diabetes-related medical procedures outlined by Nathan (1993) and included in this study are: physician assessment, ophthalmoscopy, fundus photography, fluorescent angiography, 24-hour urinalysis, glomerular filtration rate creatinine clearance, electrophysiologic studies, gastrointestinal studies (barium swallow or radio-labeled scan), and cardiac studies (stress tests, electrocardiography). To be included as diabetes-related, the procedures had to be filed on claim containing a 250.xx ICD-9-CM code or a code for one of the following complications: nephropathy (ICD-9-CM diagnostic codes 250.4, 583.81, 403.90, V56.0), vision disturbances (retinopathy, cataracts, glaucoma (ICD-9-CM diagnostic codes 240.5, 250.5, 362.01, 362.02, 362.10, 362.12, 362.29, 362.83, 365.44, 366.41), diabetic neuropathy (ICD-9-CM diagnostic codes 250.6, 337.9, 355.8, 357.2), coronary artery disease (ICD-9-CM diagnostic codes 410.0-414.9),
cerebral vascular disease (ICD-9-CM diagnostic codes 433.0-436), peripheral vascular disease (ICD-9-CM diagnostic codes 250.6, 337.1, 440.2, 443.81), and ulceration of the skin or gangrene (ICD-9-CM diagnostic code 250.7, 785.4, 250.8, 707.9). The following groups of medications were also included in the calculation diabetes-related costs: cardiac drugs (AHFS code: 24:04), anti-lipemic agents (24:06), hypotensive agents (24:08), vasodilating agents (24:12), and diuretics (40:28).

The two predictor variables used in this model are natural logarithm of the diabetes-specific costs and the natural logarithm of the diabetes-related costs. The natural log transformation is used to transform the distribution of the dependent variable from a lognormal to a normal distribution.

**Estimating the Impact of Adding Metformin**

The mean value of the dummy variables represents the proportion of patients with that characteristic. For instance, the mean value of UNCONT is the proportion of patients whose diabetes is not controlled with the current diabetes medication regimen. These are the candidates for metformin therapy.

The new distribution of patients was determined by taking the change in the percentage of patients on each treatment (DIET, INSTX, COMBO, and ORALTX) between the first and last two months of year 1. It was assumed that this change would be constant during year 2. It was also assumed that the percent increase in sulfonylurea and sulfonylurea + insulin therapy observed in year 1 would be split with metformin and metformin + sulfonylurea, respectively, during year 2. The proportion started on metformin during year 2 was then multiplied by the mean probability of responding to
metformin to yield the proportion of uncontrolled patients that become controlled in year 2 after being started on a metformin therapy regimen. The same calculations were done for combination therapy with metformin and a sulfonylurea agent. The proportion that failed initial metformin mono-therapy but responded to metformin plus insulin was added to those that responded to metformin mono-therapy. The mean proportion (and the 95% confidence interval) of those responding to metformin therapy was the same used in the year 2 decision tree. The mean proportion was used as the baseline estimate and the upper and lower bounds of the 95% confidence interval was used to calculate the range of predicted average costs.

Once the proportion that were expected to be controlled in year 2 due to metformin therapy was obtained, that figure was subtracted from the mean value of UNCONT in the year 1 regression. This represents the change in proportion of those controlled. Similarly, the mean values of ORALTX, INSTX, and COMBO were adjusted to reflect the predicted distribution of patients in year 2.

The regression analysis holds all patient characteristics and treatment characteristics constant, so to calculate the percent change in the estimated year 2 average cost, the estimated year 2 mean values for UNCONT, ORALTX, INSTX, and COMBO were multiplied by their respective parameter estimates and added the intercept term and the parameter estimate for AGE since the average age increased by one unit from year 1 to year 2. The equation for the percent change in average costs from year 1 to year 2 is:

\[ b_0 + (b_1 \times 1) + \left( b_2 \times \text{UNCONT} \right) + \left( b_{11} \times \text{DIETTX} \right) + \left( b_{12} \times \text{INSTX} \right) + \left( b_{13} \times \text{COMBO} \right) \]
The estimated percent change in average cost was then multiplied by the year 1 average cost to yield the new estimate of the year 2 average costs. This was done for the baseline estimate first, then for the upper and lower 95% confidence interval of the response to metformin therapy. This was done for the diabetes-specific costs, diabetes-specific medical costs, diabetes-specific pharmacy costs, diabetes-related costs, diabetes-related medical costs, diabetes-related pharmacy costs, total costs, total medical costs, and total pharmacy costs.

The actual average diabetes-related cost incurred by the managed care organization in year 2 was compared to this estimate to see if the confidence intervals overlap.

**Deterministic Model Assessment**

**Distribution of patients by therapeutic intervention**

The predicted distribution of patients across the various treatment regimens for year 1 and year 2 was calculated by running a cohort of 2,951 simulated patients through each decision tree. The initial distribution for the year 1 decision tree is based on the actual distribution of patients during the first two months of year one. Since it is assumed that a patient will be given two months to determine if he or she is responding to therapy, both year 1 and year 2 are broken down into six 2-month time periods, and the distribution of the cohort at each time period was calculated based on the mean probability estimates used to calculate the expected costs from the decision trees. The 95% confidence interval around the probability estimate was used to obtain the
confidence interval around the point estimate of the distribution of patients at each time period.

The actual distribution of patients was determined from the pharmacy claims data. First, the specific diabetes medication class that each study member had filled during year 1 was listed. Then the beginning and ending date of that therapy was listed. Next, the distribution of patients across the diabetes medication classes was determined for each of the 2-month time periods. The same procedures were conducted for year 2.

Resources Consumed

The predicted and actual number of office visits and the number of hemoglobin A1C tests were used to assess how well the model predicted diabetes-specific medical resource consumption. The predicted number of visits and tests were derived by multiplying the number of visits or tests in each branch of the decision tree by the probability of entering that branch. This procedure is similar to the one used to calculate the expected costs. The mean probability estimate is used as the baseline estimate and the 95% confidence interval is used to obtain the range of office visits and hemoglobin A1C tests predicted by the model.

The actual number of office visits and hemoglobin A1C tests was obtained from the medical claims database using the appropriate CPT code on claims that also contained the ICD-9-CM diagnostic code for diabetes.
Stochastic Model Assessment

The calculations used to predict the year 2 means associated with ORALTX, INSTX, COMBO, and oral mono-therapy have been described. The actual year 2 distribution is taken from the last two months of year two that was obtained to evaluate the deterministic model.

The total cost, diabetes-related cost, and diabetes-specific cost models were assessed to determine if the data conform to the assumptions of the GLM. The first assumption is that the dependent variable is a linear combination of a set of independent variables. This can be violated if key independent variables are excluded from the model, a non-linear relationship exists, or the parameters are not constant over time.

It is possible that key independent variables are excluded from the models since no clinical data were available. Examples of variables that would have been good to have in the model are weight, hemoglobin A1C values, and ethnicity. However, because these variables are not available, there is no way to assess the impact of their exclusion.

The regression models used in this analysis are basically ANCOVA models since all the variables in the model, with the exception of age, are dummy variables. To test the linearity of the relationship between age and the natural logarithm of costs the sample was separated into three age groups, those less than 30 years of age, those 31-60 years of age, and those over 60 years. Separate regressions were run for each group as recommended by Kennedy (1996). The results of the regressions were compared to determine if any changes in the parameter estimates were observed.
A histogram of the residuals was visually inspected to determine if they are normally distributed.

The stability of the parameter estimates over time was also assessed as described below. This assessment is done because it is possible that the introduction of a new therapy may alter the stability of the year one estimates.

Another assumption of the GLM is that the expected value of the error terms is zero. If this assumption is violated, the intercept is biased. There is no reason to suspect that the average of the error terms is not equal to zero. The best estimate of this to assess the average of the residuals of each model.

The third assumption of the GLM is that the variance of the error terms is constant. The SPEC option within the SAS System for Windows was used to test for heteroscedasticity. This produces performs a test that the first and second moments of the model are correctly specified.

The next assumption of the GLM is that the independent variables are considered fixed in repeated samples and are uncorrelated with the error terms. This assumption is difficult to assess, but since no lagged variables are included in the model this assumption should not be violated.

The last assumption states that no perfect linear relationship exists between the independent variables. Violations of this assumption lead to multicollinearity. Because all the patients that had diabetes-specific or diabetes-related costs also saw a specialist, this variable was excluded from the model to avoid perfect multicollinearity.
Multicollinearity within the total cost, diabetes-related cost, and diabetes-specific cost models was assessed using the procedure outlined by Hair, Anderson, Tatham, and Black (1995) using options within The SAS System for Windows. First, the TOLERANCE and the variance inflation factor (VIF) values were requested for the explanatory variables in each model. Essentially, each explanatory variable is regressed against all the other explanatory variables in the model. The tolerance value is the amount of variability in the selected explanatory variable that is NOT explained by the other explanatory variables in the model, and the VIF is the inverse of the tolerance value. Small tolerance values (or large VIF values) indicate high collinearity. Tolerance values less than 0.10 (VIF values greater than 10) are generally accepted as the cutoff point which indicates a collinearity problem (Hair et al., 1995).

The next step was to invoke the COLLIN option in The SAS System for Windows, which provides a condition index and a regression coefficient variance-decomposition matrix. The condition index represents the collinearity of combinations of explanatory variables in each model, and the regression coefficient variance-decomposition matrix provides the proportion of variance for each parameter estimate attributable to each condition index (Hair et al., 1995). To assess multicollinearity, first, identify all condition indices above 30, which is the most commonly used cutoff value (Hair et al., 1995). Then identify the explanatory variables with variance proportions above .50, for all condition indices exceeding 30. A problem is indicated if a conditional index identified in the first step accounts for a substantial proportion of variance (> .90) for two or more coefficients (Hair et al., 1995).
Stability of Parameter Estimates

Occasionally a structural change will occur in the relationship between the independent and dependent variables over time. In a pharmacoeconomic model such a change may arise following the introduction of new diagnostic tests or treatments or changes in treatment guidelines. If the intent of a model is to predict the costs in a future time period, but the parameter estimates are not stable over that period of time then the prediction may not be accurate.

The Chow test is one of the most popular test to assess the stability of the parameters over time (Kennedy, 1996). To conduct the Chow test, separate regressions are run for the two time periods. Then the observations are combined and a large single regression is run. \( F_c \), with \( K \) and \((T_1 + T_2 -2K)\) degrees of freedom, is then calculated as:

\[
\frac{[SSE(\text{constrained}) - SSE(\text{unconstrained})]/K}{SSE(\text{unconstrained})/(T_1 + T_2 -2K)}
\]

where \( K \) is the number of parameters, \( T_1 \) is the number of observations in the first period and \( T_2 \) is the number of observations in the second period. SSE(unconstrained) is the sum of the SSEs from the two separate regressions. SSE(constrained) is the SSE from the overall regression. It is constrained because the parameter estimates are forced to be equal. If \( F_c \) exceeds \( F^*_{k,(T_1 + T_2 -2K)} \) then reject the null hypothesis that there is no structural change.

Limitations

This research was based upon people with type 2 diabetes who were continuously enrolled in a managed care organization for a two year period. It is assumed that the
benefits offered to these patients remained the same during the two year period. It is possible that a change in benefits could alter resource utilization from one year to the next, and interfere with the predictive capability of the models. If benefits are increased in year 2 then the models based on year 1 data will underestimate year 2 utilization. Likewise if benefits are decreased in year 2 then the models will overestimate resource utilization. An attempt was made to limit the impact of changing benefit packages by limiting the study group to those continuously enrolled for the two year period.

A Medicare managed care plan is offered to those over 65 years of age. This plan limits the amount the managed care organization will pay for prescription medication. If the patient reaches their cap, they are responsible for paying for their own medication. It is impossible to determine which study patients are enrolled in this plan or how many patients have reached their cap. The deterministic model will overestimate medication use for those who reach their cap since the estimates produced by this model were compared to the actual amount spent in year 2. The actual amount spent was based upon paid claims. The cap could cause the stochastic model estimates to be higher, lower, or unaffected depending upon when or if the patients reach the cap each year.

Limitations specific to each model are discussed next.

**Deterministic Model**

The probability estimates used in the deterministic models were derived from clinical trials reported in the literature. The characteristics of the patients included in the trials may not be identical to the patient characteristics of the local treatment population. Although the clinical trials generally followed the ADA treatment guidelines, these
treatment patterns may not be identical to the treatment patterns of local providers. Furthermore, since the number of patients responding to therapy is not always reported, the number of studies from which probabilities could be derived is limited. This may affect the robustness and interpretability of the results.

The assumption of constant costs has to be made when working with deterministic models because each branch in the decision tree is associated with only one cost no matter what proportion of patients “enter” the branch or what co-morbid conditions they have. Because it is assumed that everyone that “enters” that branch will incur the same cost, marginal costs are equal to average costs. To minimize the potential bias that this assumption may have on the expected cost estimates, internal costs were used. Thus the point estimate for the cost associated with each branch is the actual mean cost of medical and pharmacy supplies.

Unfortunately, the internal costs derived from the medical and pharmacy claims databases are subject to coding errors of omission (i.e., services were provided, but no claim was submitted) and errors of commission (i.e., more services or higher level services were billed for than were provided). In addition to these errors, internal costs are also associated with measurement errors. For example, the QUANTITY or DAYS SUPPLY fields in the pharmacy claims may not have been populated accurately by the pharmacy.

In order to conduct the probabilistic sensitivity analysis, a log-normal distribution of probabilities was assumed. It is impossible to know if the assumed distribution or if another distribution, such as the poisson distribution, is correct. The log-normal
distribution was selected because it had the characteristics necessary to easily estimate the mean and standard deviation of the proposed distribution using the mean and extreme limit of the proportion of patients that responded to therapy that was reported in the literature. A probability could then be randomly selected from the proposed distribution.

Although the decision tree is based on the clinical guideline put forth by the American Diabetes Association, it may be over simplified. It only encompasses diabetes-specific-treatment costs and does not take into account the costs of treating diabetes complications which often occurs in the emergency department or in the hospital.

**Stochastic Model**

It is assumed that the diagnostic codes, procedure codes, NDC codes, member numbers, provider numbers, and all other information contained in the databases is accurate. Errors in the database will lead to errors in forecasting.

The claims database used in this study contained limited demographic information on the patients and contained no clinical information. Ethnicity, weight, and glycohemoglobin values are key variables to include in a stochastic model of diabetes. Unfortunately no proxy measures were available for ethnicity nor weight, unless the patient had an ICD-9 code for obesity. Using the proxy measure for control, rather than having the actual glycohemoglobin values most likely introduced error into the model. This was assessed.

It is assumed that metformin will be added to current therapy so that patients on any mono-therapy will move to the combination therapy group and patients in the combination group will remain in the group.
It is assumed that the parameters are stable over the two-year period. This is unlikely especially for the parameter estimate associated with COMBO. The only therapy combination that existed in year 1 was sulfonylurea + insulin. In year 2 the sulfonylurea + metformin combination also existed which may have altered the relationship between COMBO and the natural log of the diabetes-related (or diabetes-specific) costs and make the parameter estimate unstable. The stability of the parameter estimates over time was assessed using a Chow test to compare the year 1 and 2 parameter estimates.
CHAPTER 4

RESULTS

Subjects

This research did not include study subjects in the usual sense that subjects are used in an experimental design. Because the independent variable in this study was model type, the subjects used in this research represented the managed care sample upon which the models were based. The subjects modeled in this study are Arizona residents continuously enrolled in a managed care organization (Intergroup Health System) for the entire 24-month study period who had medical claims containing an ICD-9-CM diagnostic code for type 2 diabetes mellitus or were receiving oral anti-diabetic medications.

Between May 1994 and April 1996, the total enrollment in the managed care organization grew from 278,445 to 328,246. These numbers are a monthly snap-shot of enrollment and do not necessarily reflect continuous enrollment during the 24-month period. As shown in Table 4, a total of 15,460 members had at least one medical claim containing a diabetes ICD-9-CM diagnostic code of 250 or a pharmacy claim for a diabetes medication or supply between May 1, 1994 and April 30, 1996. During the first 12-month period, pharmacy or medical claims were filed for 9,766 people and for 12,988 during the second 12-month period. Of the 15,460 people with diabetes claims, only 4,201 were continuously enrolled for the entire 24-month period. One thousand two
hundred forty one of these were type 1 diabetics leaving 2,951 people included in this analysis.

The cost and resource utilization estimates used in the two models are based on these patients. Full year members were used in this study so annual cost and resource utilization information could be gathered. This also ensured that the same people would form the basis of the estimates during both study periods, thus minimizing the potential for selection bias associated with membership turnover.

The 15,460 potential study members initially identified represent somewhere between 4.7% and 5.6% of the total population of the managed care organization. This is comparable to the U.S. prevalence rate of Type 2 diabetes in the U.S., which is 1.3% for those between the ages of 18 and 44 years, 6.2% for those between 45 and 64 years, and 10.4% for those 65 years and older (National Institutes of Health, 1995).

Forty-seven percent of the study subjects were female, which is lower than the national estimate of 58% (National Institutes of Health, 1995).
Table 4 Study Subjects

<table>
<thead>
<tr>
<th>Data Extraction Step</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with a diagnosis of or receiving treatment for diabetes</td>
<td>15,460</td>
</tr>
<tr>
<td>People not continuously enrolled during study period</td>
<td>11,259</td>
</tr>
<tr>
<td>Continuously enrolled members classified as type 1 or unclassifiable</td>
<td>1,241</td>
</tr>
<tr>
<td>Continuously enrolled members, classified with type 2 diabetes, under 20 years of age</td>
<td>9</td>
</tr>
<tr>
<td>not receiving oral anti-diabetes medications</td>
<td></td>
</tr>
<tr>
<td>Study subjects</td>
<td>2,951</td>
</tr>
</tbody>
</table>

The ages of the study members ranged from 10 to 95 years, with a mean and standard deviation of 58.35 and 12.85 years respectively. This age distribution is consistent with national average age estimates of people with Type 2 diabetes since the average age at diagnosis is 52 years in Caucasians, 49 years in African Americans, and 45 years in Mexican Americans (National Institutes of Health, 1995). The age distribution is depicted in Figure 4.
Overview of Total Medical and Pharmacy Resource Use

A total of 18,823 unique ICD-9-CM diagnostic codes were recorded on the medical claims of the 2,951 study subjects during year 1. Each person had an average of 6.4 unique ICD-9 codes (standard deviation, 5.5). The range of unique ICD-9 codes per person was 0 to 45. One hundred ninety one people had pharmacy claims, but no medical claims in year 1. One hundred nine had medical claims, but no pharmacy claims during year 1.

The 2,951 study subjects had a total of 20,428 office visits in year 1. This is the total number of office visits for which claims were submitted and paid by the managed care organization and are not restricted to diabetes-related visits. The number of visits per person ranged from 0 to 87 with a mean and standard deviation of 6.9 and 7.2 visits respectively.
Claims were filed for a total of 659 distinct visits to the emergency department during year 1, with a range of 0 to 16 visits per person. On average, each person had 0.22 emergency department visits during year 1 (standard deviation, 0.74).

Eight hundred ninety five hospitalizations were recorded for the 2,951 people during year 1. The number of hospitalizations per person ranged from 0 to 26 with a mean of 0.30 and a standard deviation of 1.1.

The managed care organization spent over $8.3 million to provide care to the study subjects during year 1 (May 1, 1994 to April 30, 1995). Payment of medical claims accounted for nearly 80% of this expenditure while the remainder was spent on the payment of pharmacy claims. The average total health care cost per study member was $2,835, which is nearly three times higher than the average cost per member for the entire managed care organization. For calendar year 1995, the average total health care cost for all members (including the study members) who were eligible for benefits for the entire year, was $933. The average medical cost for these patients in calendar year 1995 was $767 and the average pharmacy cost was $165.

Probabilities Used in The Deterministic Model

Overview of Studies

Over 60 potential articles were identified from the initial search of Medline and International Pharmaceutical Abstracts. A review of the abstracts and articles reduced the number to 13 studies that were conducted in type 2 diabetic patients, included the medications used in the decision tree, and reported the percent or number of patients responding to therapy. Two of these studies were excluded because the reported
treatment period was greater than two years and were not consistent with the decision
trees used in this study. An additional study was excluded because it reported the
analysis of data collected at a single site from a previously published multi-center study.

Some of the studies that were used to develop the probability estimates were
conducted outside of the United States. However, they were conducted in clinics
associated with teaching hospitals and used similar inclusion criteria, exclusion criteria,
and outcome measures as those studies conducted within the United States. The
definition of glycemic control used in the studies was consistent with the
recommendations of the American Diabetes Association. Because the normal range of
the glycosylated hemoglobin test varies from one laboratory to another, the number or
proportion of responders reported in the article was used because that figure is the
response rate at that particular setting.

The treatment groups studied, duration of treatment, number treated and number
reaching the desired goal are reported in Table 5. The treatment setting and patient
characteristics of each study will be described briefly.

Floyd, Funnell, Kazi, and Templeton (1990) conducted a feasibility trial of an
insulin-treatment algorithm to determine if they could conduct a long-term trial to assess
if successful practice could result in better metabolic control. The subjects were between
the ages of 30 and 70 years of age, had no chronic or debilitating diseases, no signs of
heart disease, or autonomic neuropathy, were not taking antipsychotic or anticonvulsive
medications, and were attending a diabetes clinic at the University of Michigan Medical
Center. Fifty-two percent of the subjects were male and the average hemoglobin A1C concentration was 8.8% for the experimental group and 9.1% for the control group.

Abraira et al. (1995) conducted a feasibility study in five VA medical centers comparing single dose insulin therapy, multi-dose insulin therapy, and insulin plus glipizide in 153 males. The subjects were between the ages of 40 and 60 years of age, had diabetes for at least 15 years, and had failed sulfonylurea therapy as indicated by a hemoglobin A1C over 6.55%. Exclusion criteria included renal failure, current or previous diabetes-related gangrene, clinically evident autonomic neuropathy, other serious illnesses, or poor compliance. Those with controlled cardiovascular diseases or retinopathy were included in the study.

Birkeland, Furuseth, Melander, Mowinckel, and Vaaler (1994) studied glipizide, glyburide, and diet therapy in type 2 diabetic patients who had failed to respond to diet therapy alone (HbA1C > 7%). Patients were excluded from the study if they had cardiac, hepatic, renal, or pulmonary disease or any other severe illness. The average age of the study sample was 59 (± 7) years. Forty-eight percent of the sample was male, and the average duration of diabetes was 3.5 years. Target glycemic control was set at HbA1C < 7.5% or a fasting plasma glucose less than 8.0 mmol/L.

DeFronzo, Goodman, and the Multicenter Metformin Study Group (1995) examined the effects of diet, metformin, glyburide, and a combination of the two agents in obese patients with type 2 diabetes who had fasting plasma glucose concentrations greater than 140mg/dl after being treated with diet or 8 weeks of glyburide. The exclusion criteria included uncontrolled hypertension, cardiovascular, hepatic, or renal
disease, symptomatic diabetes, use of metformin during the previous six months, or the use of excessive alcohol or illicit drugs. Those less than 40 years and greater than 70 years of age were also excluded. The average weight was 93kg, and the average duration of diabetes was 7 years. Forty six percent of the study sample was male.

Chow, Tsang, Sorensen, and Cockram (1995) studied insulin plus sulfonylureas, insulin plus metformin, and insulin alone in patients with type 2 diabetes at a Hong-Kong teaching hospital. Subjects had to have fasting plasma glucose concentrations greater than 7.7 mmol/L after being treated with maximum doses of sulfonylureas or metformin. Patients with cardiac, hepatic, renal or peripheral vascular disease were excluded as were patients with proliferative retinopathy, severe maculopathy, type 1 diabetes, insulin therapy, or excessive alcohol intake. The average age of the sample was 54 years; the average duration of diabetes was 9 years; and 66% of the sample was female. Failure to respond to therapy was given as a HbA1C greater than 8.8%.

Chaisson et al. (1994) studied metformin, sulfonylureas (glyburide), insulin, and diet therapy in type 2 diabetics who received care in one of seven university-affiliated, community-based, tertiary care diabetes centers in Canada. The subjects had to have a HbA1C concentration greater than 7% and a diagnosis of type 2 diabetes for greater than six months to be included. Furthermore, patients on beta-blockers, thiazide diuretics, lipid-lowering agents, gastro-intestinal motility agents, or those with gastro-intestinal disorders were excluded. The mean age of the sample was 57 years, 60% were male and 92% were Caucasian. Response to therapy was defined as a HbA1C < 7% or a 15% decrease in the HgA1c value.
Hermann et al. (1994) studied people with type 2 diabetes who were treated at one of five primary care centers in Sweden. Patients had to have fasting plasma glucose concentrations greater than 6.7 mmol/L. Insulin treatment was the only exclusion criterion listed. The average age of the study sample was 60 years. Fifty seven percent of the sample was obese, 63% were male, 42% had hypertension, 12% had coronary artery disease, 6% had neuropathy, 40% were on beta-blockers, and 28% were on diuretics. The average duration of diabetes was 4 years.

Giugliano et al. (1993) studied insulin and insulin plus metformin in obese patients with type 2 diabetes who were poorly controlled on at least 3 months of insulin therapy. The study was conducted in a university hospital in Italy. Patients with cardiac, hepatic, or renal disease were excluded. In addition, patients with other endocrine disorders were also excluded as were patients over the age of 70 years. The average age of the study sample was 60 years, and the average duration of diabetes was 12 years. The study sample was comprised of 62% females and the average HbA1c was 12%. Response to the study medications occurred within the first two months and was maintained throughout the study period. Response was defined as a fasting plasma glucose less than 10 mmol/L.

Jennings et al. (1991) compared the effects of continuous subcutaneous insulin and conventional insulin therapy, in patients with type 2 diabetes who were poorly controlled on sulfonylurea therapy. The study was conducted in a diabetes clinic associated with a hospital in the United Kingdom, and included all white patients between the ages of 40 and 65 years who were treated with maximum dose sulfonylurea
therapy and still had hemoglobin A1C concentrations greater than 11.2%. The patients had to be on sulfonylurea therapy for at least one year and show no signs of type 1 diabetes. Other exclusion criteria included severe retinopathy, neuropathy, or cardiovascular disease; renal failure, other uncorrected endocrine disorders, or other life-threatening diseases.

**Combined Probabilities**

The weighted mean, mean, and median combined probability estimates are presented in Table 6 along with the lower and upper extreme estimates. The upper and lower extreme estimates are the highest and lowest response rates reported within a given treatment group. The upper extreme estimate was the farthest from the weighted mean probability within each treatment group. This mean estimate was used with the weighted mean to calculate the mean and standard deviation of the distribution of the transformed probabilities as outlined by Doubilet et al. (1985). The mean and standard deviation of the distribution of the transformed probabilities were used to select the probability used in the Monte Carlo simulations as described by Doubilet et al. (1985). Only one study was identified that reported the results of insulin plus metformin combination therapy, so an extreme value of 0.779 was used.
Table 5 Sources of Probabilities

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Treatment Group</th>
<th>Months of Tx</th>
<th>Number Reaching Goal</th>
<th>Number Treated</th>
<th>Percent Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Abraira, et al.</td>
<td>Sulfonylurea + Insulin</td>
<td>11</td>
<td>18</td>
<td>66</td>
<td>0.273</td>
</tr>
<tr>
<td>1994</td>
<td>Birkeland, et al.</td>
<td>Sulfonylurea</td>
<td>15</td>
<td>8</td>
<td>15</td>
<td>0.533</td>
</tr>
<tr>
<td>1994</td>
<td>Birkeland, et al.</td>
<td>Sulfonylurea</td>
<td>15</td>
<td>11</td>
<td>15</td>
<td>0.733</td>
</tr>
<tr>
<td>1994</td>
<td>Chaisson</td>
<td>Metformin Following Sulfonylurea Failure</td>
<td>12</td>
<td>7</td>
<td>39</td>
<td>0.179</td>
</tr>
<tr>
<td>1994</td>
<td>Chaisson</td>
<td>Insulin (1-2 doses)</td>
<td>12</td>
<td>12</td>
<td>44</td>
<td>0.273</td>
</tr>
<tr>
<td>1994</td>
<td>Chaisson</td>
<td>Diet</td>
<td>12</td>
<td>5</td>
<td>37</td>
<td>0.135</td>
</tr>
<tr>
<td>1995</td>
<td>Chow</td>
<td>Insulin (1-2 doses)</td>
<td>6</td>
<td>19</td>
<td>26</td>
<td>0.731</td>
</tr>
<tr>
<td>1995</td>
<td>Chow</td>
<td>Sulfonylurea + Insulin</td>
<td>6</td>
<td>20</td>
<td>27</td>
<td>0.741</td>
</tr>
<tr>
<td>1995</td>
<td>DeFronzo, et al.</td>
<td>Metformin</td>
<td>6</td>
<td>31</td>
<td>143</td>
<td>0.217</td>
</tr>
<tr>
<td>1995</td>
<td>DeFronzo, et al.</td>
<td>Metformin Following Sulfonylurea Failure</td>
<td>6</td>
<td>6</td>
<td>210</td>
<td>0.029</td>
</tr>
<tr>
<td>1995</td>
<td>DeFronzo, et al.</td>
<td>Diet</td>
<td>6</td>
<td>9</td>
<td>146</td>
<td>0.062</td>
</tr>
<tr>
<td>1995</td>
<td>DeFronzo, et al.</td>
<td>Metformin + Sulfonylurea</td>
<td>6</td>
<td>47</td>
<td>213</td>
<td>0.221</td>
</tr>
<tr>
<td>1990</td>
<td>Floyd, et al.</td>
<td>Multidose Insulin</td>
<td>6</td>
<td>18</td>
<td>26</td>
<td>0.692</td>
</tr>
<tr>
<td>1990</td>
<td>Floyd, et al.</td>
<td>Multidose Insulin</td>
<td>6</td>
<td>12</td>
<td>27</td>
<td>0.444</td>
</tr>
<tr>
<td>1993</td>
<td>Giugliano</td>
<td>Metformin + Insulin</td>
<td>6</td>
<td>14</td>
<td>27</td>
<td>0.519</td>
</tr>
<tr>
<td>1994</td>
<td>Hermann, et al.</td>
<td>Sulfonylurea</td>
<td>1.5</td>
<td>21</td>
<td>34</td>
<td>0.618</td>
</tr>
<tr>
<td>1994</td>
<td>Hermann, et al.</td>
<td>Metformin</td>
<td>1.5</td>
<td>25</td>
<td>38</td>
<td>0.658</td>
</tr>
<tr>
<td>1994</td>
<td>Hermann, et al.</td>
<td>Metformin + Sulfonylurea</td>
<td>1.5</td>
<td>54</td>
<td>72</td>
<td>0.750</td>
</tr>
<tr>
<td>1991</td>
<td>Jennings, et al.</td>
<td>Multidose Insulin</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>0.800</td>
</tr>
<tr>
<td>1991</td>
<td>Jennings, et al.</td>
<td>Multidose Insulin</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>0.300</td>
</tr>
</tbody>
</table>
Table 6 Combined Probability of a Favorable Response to Each Therapy Used in the Decision Tree

<table>
<thead>
<tr>
<th>Probability Group</th>
<th>Weighted Mean</th>
<th>Mean</th>
<th>Median</th>
<th>Extreme Estimate</th>
<th>Extreme Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>Mean p Used</th>
<th>Standard Deviation in the Decision Tree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>0.625</td>
<td>0.628</td>
<td>0.618</td>
<td>0.533</td>
<td>0.733</td>
<td></td>
<td></td>
<td>0.623</td>
<td>0.059</td>
</tr>
<tr>
<td>Metformin</td>
<td>0.309</td>
<td>0.437</td>
<td>0.309</td>
<td>0.217</td>
<td>0.658</td>
<td></td>
<td></td>
<td>0.314</td>
<td>0.155</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.443</td>
<td>0.502</td>
<td>0.502</td>
<td>0.273</td>
<td>0.731</td>
<td></td>
<td></td>
<td>0.446</td>
<td>0.143</td>
</tr>
<tr>
<td>Multidose Insulin</td>
<td>0.562</td>
<td>0.559</td>
<td>0.568</td>
<td>0.440</td>
<td>0.800</td>
<td></td>
<td></td>
<td>0.562</td>
<td>0.131</td>
</tr>
<tr>
<td>Diet</td>
<td>0.077</td>
<td>0.098</td>
<td>0.098</td>
<td>0.062</td>
<td>0.135</td>
<td></td>
<td></td>
<td>0.078</td>
<td>0.025</td>
</tr>
<tr>
<td>Metformin +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>0.354</td>
<td>0.485</td>
<td>0.485</td>
<td>0.221</td>
<td>0.750</td>
<td></td>
<td></td>
<td>0.357</td>
<td>0.184</td>
</tr>
<tr>
<td>Sulfonylurea + Insulin</td>
<td>0.370</td>
<td>0.412</td>
<td>0.333</td>
<td>0.242</td>
<td>0.741</td>
<td></td>
<td></td>
<td>0.376</td>
<td>0.175</td>
</tr>
<tr>
<td>Metformin +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0.519</td>
<td>0.519</td>
<td>0.519</td>
<td>0.519</td>
<td>0.779</td>
<td></td>
<td></td>
<td>0.518</td>
<td>0.139</td>
</tr>
</tbody>
</table>

**Unit Costs Used in the Deterministic Model**

The unit costs used in the deterministic model were derived from the pharmacy and medical claims databases. The point estimates presented in Table 7 are the average
costs of each item based on the pharmacy or medical claims filed for the 2,951 study members.

### Table 7 Cost Estimates Used in the Deterministic Model

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office Visit</td>
<td>52</td>
</tr>
<tr>
<td>Blood Glucose</td>
<td>10</td>
</tr>
<tr>
<td>Cholesterol Screen</td>
<td>15</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>11</td>
</tr>
<tr>
<td>Microalbuminemia</td>
<td>16</td>
</tr>
<tr>
<td>Thyroid Function</td>
<td>30</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>7</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>31</td>
</tr>
<tr>
<td>Glycosylated Hemoglobin</td>
<td>16</td>
</tr>
<tr>
<td>Overall Average Cost Per Day for Sulfonylurea Therapy</td>
<td>0.62</td>
</tr>
<tr>
<td>Overall Average Cost Per Day for Insulin Therapy</td>
<td>0.93</td>
</tr>
<tr>
<td>Overall Average Cost Per Day for Combo Therapy</td>
<td>1.82</td>
</tr>
</tbody>
</table>

### Medical Resource Costs

The average cost of an office visit for the 2,951 study participants was calculated from 2,182 medical claims filed during year one. These were claims filed for physician services in an outpatient setting. The average amount paid per claim was $51.89 (standard deviation, 34.68).
The average cost of a blood glucose test was estimated from 342 medical claims containing the CPT codes for a blood glucose test. The average cost of a test was $10.43 (standard deviation, 3.12). The mean and standard deviation of a cholesterol screen was $14.70 and 2.83 respectively and was based on 658 medical claims. The costs of a serum creatinine test and a thyroid function test (TSH) were estimated from 66 and 344 claims respectively. The average amount paid for a serum creatinine test was $10.57 (standard deviation, 4.41) and $29.78 (standard deviation, 9.17) for a thyroid function test.

The mean cost of a microalbuminemia test was $15.92 (standard deviation, 7.45) based on 13 claims. The mean cost (and standard deviation) of a urinalysis was $6.56 (2.15) and was based on 1,125 claims. Four-hundred-four claims containing the CPT code for an electrocardiogram were filed during year 1. The average cost (and standard deviation) of an electrocardiogram was $30.72 (5.88).

Several factors account for the variation in the costs of the medical resources. First is the fact that several CPT codes may be used for a given procedure. The different codes reflect the intensity of the actual test or service performed. This is especially true of physician services. For instance, a physician receives more money for working up a new patient with several diagnoses than he or she does for a routine follow-up visit. Another factor that may account for the variation in costs is the contractual relationship between the provider and the managed care organization. Reimbursement rates may differ from one physician group to another.
Pharmacy Costs

Because prescribed medication classes were modeled in the decision trees, the average cost per day for each class was estimated from the pharmacy claims database. The average daily cost for each class is presented in Table 7. This process took into account the specific agents that the study members used as well as the specific doses and dosing frequencies most commonly used by the study members.

Diabetes-Specific Costs

The first research objective was to compare the predicted average diabetes-specific costs obtained from the deterministic and stochastic models to the actual average diabetes-specific costs incurred during the 12 month period following the addition of metformin to the formulary of the managed care organization (year 2). The three hypotheses associated with this objective were:

Hypothesis 1a: \( \mu_{DSC-DM} = \mu_{DSC-SM} = \mu_{DSC-Actual} \)

Hypothesis 1b: \( \mu_{DSCM-DM} = \mu_{DSCM-SM} = \mu_{DSCM-Actual} \)

Hypothesis 1c: \( \mu_{DSPC-DM} = \mu_{DSPC-SM} = \mu_{DSPC-Actual} \)

The expected diabetes-specific costs obtained from the two models are presented in Table 8 along with the actual average diabetes-specific costs obtained from the medical and pharmacy claims filed during year 2. The point estimate is presented with the 95% confidence interval in parentheses.
Because some of the study members did not incur diabetes-specific costs during year 2, two average cost estimates are given for year 2. The first is the cost per study member and the second is the cost per member who actually had diabetes-specific costs. The average cost estimates displayed in Table 8 focus on predicting the year 2 diabetes-specific costs. Another way to assess the models is to see how well they predict the magnitude of the change in average costs from year 1 to year 2. This is presented as the percent change in diabetes-specific costs in the last row of Table 8.

Hypotheses 1a, 1b, and 1c were all rejected because the 95% confidence interval around the average costs predicted by the deterministic and stochastic models never overlapped. The confidence interval associated with the deterministic model is less than five dollars and the confidence interval associated with the stochastic model is one dollar.

The estimate produced by the deterministic model is based on all 2,951-study members. The estimate produced by the stochastic model is based upon those who had diabetes-specific costs in year 1. Since the dependent variable is the natural logarithm of the diabetes-specific costs, those with zero costs were treated as missing data points and excluded from the model. To obtain estimates that were comparable to the deterministic model, the average costs for all members was calculated by multiplying the average cost estimate by the number of members included in the model and dividing by 2,951. Both of the estimates are included in Table 8.
Table 8  Estimated and Actual Year 2 Average Diabetes-Specific (DS) Costs for All Study Members and Those with Diabetes-Specific Costs Greater than Zero

<table>
<thead>
<tr>
<th></th>
<th>Deterministic Model</th>
<th>Deterministic Model</th>
<th>Stochastic Model</th>
<th>Stochastic Model</th>
<th>Actual Model</th>
<th>Actual Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate* (All Members)</td>
<td>Estimate* (All Members)</td>
<td>Average Year 2 Cost* (All Members)</td>
<td>Average Year 2 Cost* (All Members)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS Total Costs*</td>
<td>1,010 (1,008-1,012)</td>
<td>809 (809-809)</td>
<td>989 (850-1127)</td>
<td>1,308 (1,308-1,308)</td>
<td>1,486 (1,282-1,689)</td>
<td></td>
</tr>
<tr>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 1,825)</td>
<td>(n = 1,964)</td>
<td></td>
</tr>
<tr>
<td>DS Medical Costs*</td>
<td>614 (613-616)</td>
<td>416 (416-416)</td>
<td>836 (698-973)</td>
<td>684 (684-684)</td>
<td>1,256 (1,052-1,459)</td>
<td></td>
</tr>
<tr>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 1,793)</td>
<td>(n = 1,964)</td>
<td></td>
</tr>
<tr>
<td>DS Pharmacy Costs*</td>
<td>396 (395-397)</td>
<td>72 (72-72)</td>
<td>153 (145-161)</td>
<td>119 (119-119)</td>
<td>230 (220-240)</td>
<td></td>
</tr>
<tr>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 2,951)</td>
<td>(n = 1,791)</td>
<td>(n = 1,964)</td>
<td></td>
</tr>
<tr>
<td>Year 1 to 2 Change in Total Costs</td>
<td>22.7%</td>
<td>5.7%</td>
<td>29.4%</td>
<td>5.7%</td>
<td>20.1%</td>
<td></td>
</tr>
</tbody>
</table>

* Presented as Mean $, (95% CI), (n)
Actual Year 2 Diabetes-Specific Cost

The total diabetes-specific cost that the managed care organization incurred treating the study members during year 2 was $2,917,602. When all study members are used in the denominator, the average diabetes-specific total cost is $989. When only the 1,964 study members that had diabetes-specific costs during year 2 are included in the denominator then the average diabetes-specific total cost is $1,486.

The total diabetes-specific medical cost was $2,466,021 for year 2 which yields average diabetes-specific medical costs of $1,256 and $836 for those who had diabetes-specific costs and all study members respectively. The total diabetes-specific pharmacy cost for year 2 was $451,582 resulting in average diabetes-specific pharmacy costs of $230 and $153 for the two groups. The diabetes-specific pharmacy costs accounts for 15% of the total diabetes-specific costs.

Expected Year 2 Diabetes-Specific Cost from the Deterministic Model

The expected cost was estimated 2,951 times and the mean expected cost was obtained from these simulations. Variability was built into the model by treating the probabilities used in the decision trees as variables with their own distribution.

The average diabetes-specific cost estimate obtained from the deterministic model is $1,010. Multiplying this figure by 2,951 yields an estimate of $2,980,510 for the total diabetes-specific costs incurred by the managed care organization as predicted by the deterministic model. This is 1.02% larger than the actual total cost incurred during year 2. The average cost estimate was also 1.02% larger than the average cost per study member.
The average diabetes-specific medical cost estimate produced by the deterministic model was lower than the actual year 2 average, and the confidence intervals did not overlap. The average diabetes-specific medical cost estimate obtained from the deterministic model was $614, which translates into a total diabetes-specific medical cost estimate of $1,811,914. This is 73.5% of the actual diabetes-specific medical cost incurred during year 2. The diabetes-specific medical cost estimate obtained from the model is based on the number of physician visits and laboratory tests used to treat and monitor diabetes. The average cost estimate obtained from the deterministic model is 73.5% of the average cost that includes all study members.

The confidence intervals around the average diabetes-specific pharmacy cost estimate did not overlap the year 2 average diabetes-specific cost confidence intervals either. The average diabetes-specific pharmacy cost estimate is 2.6 times higher than the average cost that includes all study members. The diabetes-specific total pharmacy cost estimate obtained from the model was $1,168,596, which is 2.6 times higher than the actual diabetes-specific total pharmacy costs that the managed care organization incurred during year 2.

**Average Year 2 Diabetes-Specific Cost Estimate from the Stochastic Model**

It is assumed that 50% of the patients who fail diet therapy will be started on sulfonylurea mono-therapy and 50% will be started on metformin mono-therapy. Sixty-six percent (1-pmet) of those started on metformin will not meet the target glycemic control and insulin will be added to the regimen. Fifty-six percent of these will be controlled on this regimen. Of those who fail to respond to sulfonylurea therapy, it is
assumed that 50% will be started on a combination of sulfonylurea plus metformin and 50% will be started on a combination of sulfonylurea plus insulin.

The 95% confidence intervals around the average diabetes-specific costs did overlap the actual average diabetes-specific cost confidence intervals for those who had diabetes-specific costs greater than zero. The average diabetes-specific medical and pharmacy cost estimates produced by the stochastic model were lower than the actual year 2 average diabetes-specific medical and pharmacy costs, respectively, and neither set of confidence intervals overlapped.

The average diabetes-specific cost estimates produced by the stochastic model for all members were lower than the actual average diabetes-specific total, medical, and pharmacy costs. None of the confidence intervals overlapped those associated with the respective actual costs.

The predicted average diabetes-specific total cost for the 1,825 members who had diabetes-specific costs in year 1 was $1,308. When all members are considered, the estimated diabetes-specific cost per member is $809. Based on these predicted average cost estimates, the year 2 total diabetes-specific cost estimate would be, $2.387 million, which is 82% of the actual year 2 diabetes-specific costs actually incurred by the managed care organization for the provision of care to the study members.

Similarly the predicted average diabetes-specific medical costs for year 2 was $684 for those members who actually incurred diabetes-specific costs in year 1, and $416 when all members are considered. This represents a predicted total diabetes-specific
medical cost estimate of $1,226 million, which is 50% of the diabetes-specific medical 
costs actually incurred during year 2.

The year 2 average diabetes-specific pharmacy cost estimates for those who 
actually had year 1 diabetes-specific costs and for all study members was $119 and $72, 
respectively. This equates to a total diabetes-specific pharmacy cost estimate of 
$213,129, which is 47% of the actual diabetes-specific pharmacy costs incurred during 
year 2.

Percent Change in Diabetes-Specific Cost Estimates

The average diabetes-specific total costs increased 20.1% from year 1 to year 2 if 
only those who incurred diabetes-specific costs were considered. The actual percent 
change in the average diabetes-specific total costs when all 2,951 study members were 
considered was 29.4%.

The expected cost estimate obtained from the year 2 decision tree was 22.7% 
higher than that obtained from the year 1 decision tree. All 2,951 study members were 
used in the two decision tree models. The percent change predicted by the stochastic 
model was 5.7%, which is less than the percent change that actually occurred from year 1 
to year 2.
Diabetes-Related Costs

The second research objective was to compare the average diabetes-related cost estimates obtained from the stochastic model to the actual diabetes-related cost incurred during year 2. The three hypotheses associated with this objective are:

Hypothesis 2a: $\mu_{DRC-SM} = \mu_{DRC-Actual}$

Hypothesis 2b: $\mu_{DRMC-SM} = \mu_{DRMC-Actual}$

Hypothesis 2c: $\mu_{DRPC-SM} = \mu_{DRPC-Actual}$

The expected diabetes-related costs obtained from the stochastic model are presented in Table 9 along with the actual average diabetes-related costs obtained from the medical and pharmacy claims filed during year 2. The point estimate is presented with the 95% confidence interval in parentheses.

Hypothesis 2a cannot be rejected because the 95% confidence intervals around the actual and predicted year 2 diabetes-related total costs did overlap for those members who had diabetes-related costs. The 95% confidence intervals around the actual and predicted year 2 diabetes-related total costs for all study members also overlapped. Therefore the conclusion is made that the average diabetes-related total costs predicted by the stochastic model is the same as the actual year 2 diabetes-related costs at the 0.006 alpha level since two 95% confidence intervals overlap at the 0.006 level.

Hypothesis 2b is rejected because there was no overlap of the 95% confidence intervals around the actual and predicted year 2 diabetes-related medical costs for those
with diabetes-related costs or for all members. Therefore the conclusion is made that the average diabetes-related medical costs predicted by the stochastic model is not the same as the actual year 2 diabetes-related medical costs at the 0.005 alpha level.

Hypothesis 2c is also rejected because there was no overlap in the confidence intervals associated with the average diabetes-related pharmacy cost estimates and the actual year 2 average costs. This was true for members who had diabetes-related costs and for all members. Therefore the conclusion is made that the average diabetes-related medical costs predicted by the stochastic model is not the same as the actual year 2 diabetes-related medical costs at the 0.005 alpha level.

The expected diabetes-related costs obtained from the stochastic model are presented in Table 9. Two stochastic model estimates are given in Table 9. The first is the cost per member, using all study members in the denominator. Only those members who had diabetes-related costs in year 1 are used as the denominator in the second average cost estimate. The same regression model and parameter estimates were used to obtain both estimates. The average diabetes-related costs obtained from the pharmacy and medical claims filed during year 2 is also presented in Table 9 as the cost per member with diabetes-related costs and as the cost per each study member. The point estimate is presented with the 95% confidence interval in parentheses. The percent change in total diabetes-related costs from year 1 to year 2 is also presented in Table 9.
Table 9 Estimated and Actual Year 2 Average Diabetes-Related (DR) Costs* for All Study Members and Those with Diabetes-Related Costs Greater than Zero

<table>
<thead>
<tr>
<th></th>
<th>Stochastic Model Estimate (All Members)</th>
<th>Actual Average (All Members)</th>
<th>Stochastic Model Estimate (Costs &gt; 0)</th>
<th>Actual Average (Costs &gt; 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR Total Costs</td>
<td>1,174 (1,174-1,174) (n = 2,951)</td>
<td>1,331 (1,157-1,506) (n = 2,951)</td>
<td>1,899 (1,899-1,899) (n = 1,825)</td>
<td>2,000 (1,744-2,257) (n = 1,964)</td>
</tr>
<tr>
<td>DR Medical Costs</td>
<td>528 (528-528) (n = 2,951)</td>
<td>1,051 (879-1,223) (n = 2,951)</td>
<td>914 (914-914) (n = 1,796)</td>
<td>1,580 (1,325-1,834) (n = 1,964)</td>
</tr>
<tr>
<td>DR Pharmacy Costs</td>
<td>156 (156-156) (n = 2,951)</td>
<td>280 (266-294) (n = 2,951)</td>
<td>253 (253-253) (n = 1,815)</td>
<td>421 (403-439) (n = 1,964)</td>
</tr>
<tr>
<td>Year 1 to 2 Change in Total Costs</td>
<td>6.02%</td>
<td>20.2%</td>
<td>6.02%</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

* Presented as Mean $, (95% CI), (n)

Actual Year 2 Diabetes-Related Cost

The total diabetes-related cost incurred by the managed care organization for the provision of care to the 2,951 study members was $3.928 million. The average diabetes-
related costs was $1,331 when all members were used in the denominator, and $2,000 when only those members who incurred a diabetes-related costs were considered.

The total diabetes-related medical costs were $3.102 million, which yielded average costs of $1,051 and $1,580 for all members and those with diabetes-related costs, respectively. The total diabetes-related pharmacy costs were $826,427 resulting in average diabetes-related pharmacy costs of $280 and $421 for all members and those with diabetes-related costs, respectively.

The diabetes-related pharmacy costs account for 21% of the total diabetes-related costs which is similar to that reported for the diabetes-specific costs.

**Average Year 2 Diabetes-Related Cost Estimate from the Stochastic Model**

As with the diabetes-specific cost model, it is assumed that 50% of the patients who fail diet therapy will be started on sulfonylurea mono-therapy and 50% will be started on metformin mono-therapy. Sixty-six percent (1-pmet) of those started on metformin will not meet the target glycemic control and insulin will be added to the regimen. Fifty-six percent of these will be controlled on this regimen. Of those who fail to respond to sulfonylurea therapy, it is assumed that 50% will be started on a combination of sulfonylurea plus metformin and 50% will be started on a combination of sulfonylurea plus insulin.

The predicted year 2 average diabetes-related costs was $1,899 for the 1,825 members who had diabetes-related costs in year 1, and $1,174 when all study members
were considered. This corresponds to a total year 2 diabetes-related cost estimate of $3,465 million, which is 88% of the actual diabetes-related cost estimate.

The predicted year 2 average diabetes-related medical cost estimates were $528 and $914 for all study members and the 1,825 members who had diabetes-related costs in year 1, respectively. This corresponds to a total year 2 diabetes-related medical cost estimate of $1,642 million, which is 51% of the actual diabetes-related cost.

The predicted year 2 average diabetes-related pharmacy cost estimates were $156 and $253 for all study members and the 1,825 members who had diabetes-related costs in year 1, respectively. This corresponds to a total year 2 diabetes-related pharmacy cost estimate of $459,195, which is 56% of the actual diabetes-related cost.

Percent Change in Diabetes-Related Cost Estimates

The average diabetes-related total costs increased 11.7% from year 1 to year 2 when only those who incurred diabetes-related costs were considered. The percent change in diabetes-related costs when all study members were considered was 20.2%.

The estimated change in diabetes-related costs obtained from the stochastic model was 6.02%. This is nearly one half of the actual percent change when those who had diabetes-related costs are considered, and one quarter of the percent change when all study members are considered.

**Total health care costs**

The third research objective was to compare the average total health care cost estimates obtained from the stochastic model to the actual diabetes-related cost incurred during year 2. The three hypotheses associated with this objective are:
Hypothesis 3a: $\mu_{TC-SM} = \mu_{TC-Actual}$

Hypothesis 3b: $\mu_{TMC-SM} = \mu_{TMC-Actual}$

Hypothesis 3c: $\mu_{TPC-SM} = \mu_{TPC-Actual}$

The expected diabetes-related costs obtained from the stochastic model are presented in Table 10. Two stochastic model estimates are given in Table 10. The first is the cost per member, using all study members in the denominator. Only those members who had diabetes-related costs in year 1 are used as the denominator in the second average cost estimate. The same regression model and parameter estimates were used to obtain both estimates. The average diabetes-related costs obtained from the pharmacy and medical claims filed during year 2 is also presented in Table 10 as the cost per member with diabetes-related costs and as the cost per each study member. The point estimate is presented with the 95% confidence interval in parentheses. The percent change in total health care costs from year 1 to year 2 is also presented in Table 10.

Hypothesis 3a cannot be rejected because the 95% confidence intervals around the actual and predicted year 2 health care total costs overlapped for those members with health care costs. The 95% confidence intervals around the actual and predicted year 2 health care total costs for all study members also overlapped. Therefore the conclusion is made that the average health care total costs predicted by the stochastic model is the same as the actual year 2 health care total costs at the 0.005 alpha level.
Hypothesis 3b cannot be rejected because the 95% confidence intervals around the actual and predicted year 2 health care medical costs for those with health care costs overlapped. The 95% confidence intervals around the actual and predicted year 2 health care medical costs for all study members overlapped as well. Therefore the conclusion is made that the average medical costs predicted by the stochastic model is the same as the actual year 2 diabetes-related medical costs at the 0.005 alpha level.

Hypothesis 3c is rejected because the 95% confidence intervals around the actual year 2 pharmacy costs did not overlap the 95% confidence interval around the predicted year 2 pharmacy costs for all members nor those with health care costs greater than zero.
Table 10 Estimated and Actual Year 2 Average Total Health Care (HC) Costs for All Study Members and Those with Total Health Care Costs Greater than Zero

<table>
<thead>
<tr>
<th></th>
<th>Stochastic Model Estimate (All Members)</th>
<th>Stochastic Model Estimate (Costs &gt; 0)</th>
<th>Actual Avg. Year 2 Cost (All Members)</th>
<th>Actual Avg. Year 2 Cost (Costs &gt; 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC Total Costs</td>
<td>2,979 [2,979-2,979] (n = 2,951)</td>
<td>2,984 [2,984-2,984] (n = 2,946)</td>
<td>3,204 [2,906-3,502] (n = 2,951)</td>
<td>3,205 [2,908-3,503] (n = 2,950)</td>
</tr>
<tr>
<td>HC Pharmacy Costs</td>
<td>579 [579-579] (n = 2,951)</td>
<td>606 [606-606] (n = 2,951)</td>
<td>721 [691-751] (n = 2,951)</td>
<td>721 [691-751] (n = 2,950)</td>
</tr>
<tr>
<td>Year 1 to 2 Change in Total Costs</td>
<td>5.07% (95% CI)</td>
<td>5.07% (95% CI)</td>
<td>13.0% (95% CI)</td>
<td>12.9% (95% CI)</td>
</tr>
</tbody>
</table>

* Presented as Mean $, (95% CI), (n)

Actual Year 2 Total Health Care Cost

The total cost incurred by the managed care organization for the provision of health care to the 2,951 study members was $9,456 million. Medical costs comprised $7.329 million of the total, and pharmacy costs made up the remaining $2.127 million.
The pharmacy costs account for 22.5% of the total costs which is consistent with that reported for the diabetes-specific costs.

The total health care average cost was $3,205 or $3,204 depending on if those with health care costs or all members were used to calculate the average year 2 cost. The average medical costs were $2,485 or $2,484 and the average pharmacy cost was $721.

**Average Year 2 Total Health Care Cost Estimate from the Stochastic Model**

As with the diabetes-specific cost and the diabetes-related cost models, it is assumed that 50% of the patients who fail diet therapy will be started on sulfonylurea mono-therapy and 50% will be started on metformin mono-therapy. Sixty-six percent (1-pmet) of those started on metformin will not meet the target glycemic control and insulin will be added to the regimen. Fifty-six percent of these will be controlled on this regimen. Of those who fail to respond to sulfonylurea therapy, it is assumed that 50% will be started on a combination of sulfonylurea plus metformin and 50% will be started on a combination of sulfonylurea plus insulin.

The predicted year 2 average health care costs was $2,984 for the 2,946 members who had health care costs in year 1, and $2,979 when all study members were considered. This corresponds to a total year 2 diabetes-related cost estimate of $8.79 million, which is 93% of the actual health care costs incurred during year 2.

The predicted year 2 average health care medical cost estimates were $2,378 and $2,352 for those who had health care costs in year 1 and all study members, respectively. This corresponds to a total year 2 medical cost estimate of $6.463 million, which is 88% of the actual year 2 medical costs.
The predicted year 2 average pharmacy cost estimates were $606 and $579 for the those who had diabetes-related costs in year 1 and all study members, respectively. This corresponds to a total year 2 pharmacy cost estimate of $1.709 million, which is 80% of the actual diabetes-related cost.

**Percent Change in Total Health Care Cost Estimates**

The average health care total costs increased 12.9% from year 1 to year 2 when only those who incurred diabetes-related costs were considered. The percent change in health care total costs when all study members were considered was 13.0%

The estimated change in total costs obtained from the stochastic model was 5.07%. This is less than one half of the actual percent change when those who had health care costs or all study members were considered.

**Assessing the Deterministic Model**

The actual and predicted distributions of patients across the diabetes treatment options are presented in Tables 11 and 12 for years 1 and 2, respectively. The initial distribution of patients at the beginning of year one was taken from the actual distribution of patients based on the pharmacy claims filed during the first two months of year 1. For year 1, the model consistently underestimated the proportion of patients on diet therapy.
<table>
<thead>
<tr>
<th>Time Period 1</th>
<th>Diet</th>
<th>Sulfonylurea</th>
<th>Combination</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td>42.9</td>
<td>49.8</td>
<td>2.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Predicted</td>
<td>42.9</td>
<td>49.8</td>
<td>2.2</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>(42.9-42.9)</td>
<td>(49.8-49.8)</td>
<td>(2.2-2.2)</td>
<td>(5.0-5.0)</td>
</tr>
<tr>
<td>Time Period 2</td>
<td>Actual</td>
<td>37.0</td>
<td>55.7</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Predicted</td>
<td>3.3</td>
<td>70.6</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>(3.3-3.4)</td>
<td>(70.5-70.6)</td>
<td>(0.8-0.9)</td>
<td>(25.1-25.3)</td>
</tr>
<tr>
<td>Time Period 3</td>
<td>Actual</td>
<td>32.6</td>
<td>59.4</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Predicted</td>
<td>3.3</td>
<td>55.7</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td>(3.3-3.4)</td>
<td>(55.5-55.9)</td>
<td>(15.7-15.9)</td>
<td>(25.1-25.3)</td>
</tr>
<tr>
<td>Time Period 4</td>
<td>Actual</td>
<td>30.0</td>
<td>61.7</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Predicted</td>
<td>3.3</td>
<td>55.7</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>(3.3-3.4)</td>
<td>(55.5-55.9)</td>
<td>(6.4-6.6)</td>
<td>(34.3-34.7)</td>
</tr>
<tr>
<td>Time Period 5</td>
<td>Actual</td>
<td>25.4</td>
<td>65.2</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Predicted</td>
<td>3.3</td>
<td>55.7</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>(3.3-3.4)</td>
<td>(55.5-55.9)</td>
<td>(6.4-6.6)</td>
<td>(34.3-34.7)</td>
</tr>
<tr>
<td>Time Period 6</td>
<td>Actual</td>
<td>22.0</td>
<td>67.8</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Predicted</td>
<td>3.3</td>
<td>55.7</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>(3.3-3.4)</td>
<td>(55.5-55.9)</td>
<td>(6.4-6.6)</td>
<td>(34.3-34.7)</td>
</tr>
</tbody>
</table>

* Presented as the baseline proportion of patients in each treatment group.
Just as diet therapy was underestimated in year 1, the distribution of patients on insulin therapy was consistently over-estimated in year 1. The distribution of patients on combination therapy was slightly overestimated, while the distribution of patients on sulfonylureas was similar.

The predicted distribution of patients in year 2 is less accurate than the predictions for year 1. The deterministic model predicted that most patients would be on insulin therapy by the end of year 2. Given the nature of the probabilities used in the model, this is to be expected.

Use of Medical Resources

The actual and predicted numbers of office visits and hemoglobin A1C tests is given in Table 13 for years 1 and 2. For year 1, the model overestimated both the mean number of physician office visits and the number of hemoglobin A1C tests. The predicted number of physician visits per member with a visit is 1.79 times higher than the actual average in year 1, and 2.4 times higher in year 2. Similarly, the predicted number of hemoglobin A1C tests, per member who had a test, is 2.2 times higher than the actual number in year 1, and 2.9 times higher in year 2.
Table 12  Actual and Predicted* Year 2 Distribution of Patients
Among Treatment Groups

<table>
<thead>
<tr>
<th>Year 2</th>
<th>Diet</th>
<th>Sulfonylurea</th>
<th>Metformin</th>
<th>Combination</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>24.67</td>
<td>61.37</td>
<td>0.27</td>
<td>6.57</td>
<td>7.12</td>
</tr>
<tr>
<td>Predicted</td>
<td>0.3</td>
<td>55.7</td>
<td>3.0</td>
<td>6.5</td>
<td>34.5</td>
</tr>
<tr>
<td>(0.3-0.3)</td>
<td>(55.7-55.7)</td>
<td>(3.0-3.0)</td>
<td>(6.5-6.5)</td>
<td>(34.5-34.5)</td>
<td></td>
</tr>
<tr>
<td>Time Period 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>15.76</td>
<td>60.62</td>
<td>0.95</td>
<td>7.35</td>
<td>15.32</td>
</tr>
<tr>
<td>Predicted</td>
<td>0.0</td>
<td>34.8</td>
<td>1.1</td>
<td>29.6</td>
<td>34.5</td>
</tr>
<tr>
<td>(0.0-0.0)</td>
<td>(34.7-35.0)</td>
<td>(1.1-1.1)</td>
<td>(29.4-29.7)</td>
<td>(34.5-34.5)</td>
<td></td>
</tr>
<tr>
<td>Time Period 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>9.28</td>
<td>59.47</td>
<td>1.52</td>
<td>21.76</td>
<td>7.96</td>
</tr>
<tr>
<td>Predicted</td>
<td>0.0</td>
<td>34.8</td>
<td>1.0</td>
<td>13.3</td>
<td>50.9</td>
</tr>
<tr>
<td>(0.0-0.0)</td>
<td>(34.7-35.0)</td>
<td>(1.0-1.0)</td>
<td>(13.2-13.4)</td>
<td>(50.8-51.1)</td>
<td></td>
</tr>
<tr>
<td>Time Period 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>11.35</td>
<td>54.08</td>
<td>2.78</td>
<td>24.09</td>
<td>7.69</td>
</tr>
<tr>
<td>Predicted</td>
<td>0.0</td>
<td>34.8</td>
<td>1.0</td>
<td>13.2</td>
<td>51.0</td>
</tr>
<tr>
<td>(0.0-0.0)</td>
<td>(34.7-35.0)</td>
<td>(1.0-1.0)</td>
<td>(13.1-13.3)</td>
<td>(50.8-51.1)</td>
<td></td>
</tr>
<tr>
<td>Time Period 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>5.90</td>
<td>52.25</td>
<td>2.95</td>
<td>30.23</td>
<td>8.68</td>
</tr>
<tr>
<td>Predicted</td>
<td>0.0</td>
<td>34.8</td>
<td>1.0</td>
<td>13.2</td>
<td>51.0</td>
</tr>
<tr>
<td>(0.0-0.0)</td>
<td>(34.7-35.0)</td>
<td>(1.0-1.0)</td>
<td>(13.1-13.3)</td>
<td>(50.8-51.1)</td>
<td></td>
</tr>
<tr>
<td>Time Period 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>2.30</td>
<td>50.15</td>
<td>3.02</td>
<td>35.82</td>
<td>8.71</td>
</tr>
<tr>
<td>Predicted</td>
<td>0.0</td>
<td>34.8</td>
<td>1.0</td>
<td>13.2</td>
<td>51.0</td>
</tr>
<tr>
<td>(0.0-0.0)</td>
<td>(34.7-35.0)</td>
<td>(1.0-1.0)</td>
<td>(13.1-13.3)</td>
<td>(50.8-51.1)</td>
<td></td>
</tr>
</tbody>
</table>

* Presented as the baseline proportion of patients in each treatment group.
Table 13 Predicted and Actual Number of Diabetes-Specific Physician Visits and Hemoglobin A1C Tests per Member Per Year, Year 1

<table>
<thead>
<tr>
<th></th>
<th>Physician Visits</th>
<th>HbA1C Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per Member</td>
<td>Per Study</td>
</tr>
<tr>
<td></td>
<td>with a visit</td>
<td>Member</td>
</tr>
<tr>
<td><strong>Year 1</strong></td>
<td>(n = 1768)</td>
<td>(n = 2,951)</td>
</tr>
<tr>
<td>Actual</td>
<td>2.47</td>
<td>1.48</td>
</tr>
<tr>
<td>Predicted</td>
<td>4.49</td>
<td>4.49</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(4.48-4.50)</td>
<td>(4.48-4.50)</td>
</tr>
<tr>
<td><strong>Year 2</strong></td>
<td>(n = 1764)</td>
<td>(n = 2,951)</td>
</tr>
<tr>
<td>Actual</td>
<td>2.39</td>
<td>1.43</td>
</tr>
<tr>
<td>Predicted</td>
<td>5.84</td>
<td>5.84</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(5.82-5.86)</td>
<td>(5.82-5.86)</td>
</tr>
</tbody>
</table>

Assessing the Stochastic Model

The Regression Models

The results of the nine regression models are presented in Tables 14, 15, and 16 below. Table 14 contains the parameter estimates and adjusted parameter estimates for the total cost, diabetes-related total cost, and diabetes-specific total cost models. Examining the adjusted-$R^2$ for the total cost model reveals that the model explains 48% of the variance in the dependent variable. The diabetes-related and diabetes-specific models account for 35% and 24% of the variance in the dependent variable, respectively.
The variable UNCONT (the presence of uncontrolled diabetes in patients who are potential candidates for metformin, 0 = No; 1 = Yes) is statistically significantly different from zero in all three models presented in Table 14. The interpretation of the adjusted variable in the total cost model is that those whose diabetes is uncontrolled and who are candidates for metformin therapy have 31% higher costs than those whose diabetes is controlled, holding all else constant.

The parameter estimate associated with gender is statistically significantly different from zero in the diabetes-related and -specific models. The interpretation of the adjusted parameter estimate for the diabetes-related cost model is that the average diabetes-related cost is 11% higher for females than males, holding all else constant.

The presence of diabetic neuropathies does not appear to have an impact on the health care expenditures spent on patients with diabetes as indicated by the fact that the parameter estimate associated with NEURO is not statistically significantly different from zero in any of the three models presented in Table 14.

The average total health care costs for those patients using an oral hypoglycemic agent were 29% lower than the average cost of patients treated with diet therapy, holding all else constant. However, the average diabetes-related costs of those treated with oral agents were 28% lower than those on diet therapy alone. One possible explanation for this could be that anyone who did not have a claim for a diabetes medication were classified as being on diet therapy. Perhaps some of those patients actually have advanced disease, but did not fill any prescriptions for diabetes medications within the Intergroup System.
The parameter estimate associated with the insulin therapy variable was not statistically significantly different from zero in either the diabetes-related cost model or the diabetes-specific cost model. The parameter estimate associated with the combination therapy variable therapy was not statistically significantly different from zero in the diabetes-related cost model but it was in the diabetes-specific model.

All the people who had diabetes-related or diabetes-specific costs saw a specialist, therefore this variable was excluded from those two models. However, those patients who did see a specialist during year 1 had 74% higher average total costs than those who did not see a specialist.
## Table 14 Total, Diabetes-Related, and Diabetes-Specific Cost Models

| Variable | Total Cost Model | | | Diabetes-Related Cost Model | | | Diabetes-Specific Cost Model | |
|----------|------------------|------------------|------------------|------------------|------------------|------------------|
|          | Parameter Estimate | Adjusted Parameter | Parameter Estimate | Adjusted Parameter | Parameter Estimate | Adjusted Parameter |
| INTERCEPT | 4.93* | 4.93 | 6.02* | 6.02 | 5.67* | 5.67 |
| AGE      | 0.00# | 0.00 | 0.00# | 0.00 | -0.01* | -0.01 |
| UNCONT   | 0.27# | 0.31 | 0.29# | 0.34 | 0.41* | 0.51 |
| SEX      | 0.04 | 0.04 | 0.11# | 0.12 | 0.10# | 0.11 |
| RENAL    | 0.42* | 0.52 | 0.58* | 0.78 | 0.20 | 0.22 |
| EYE      | 0.30* | 0.35 | 0.20* | 0.22 | 0.19* | 0.21 |
| NEURO    | 0.12 | 0.13 | 0.16 | 0.17 | 0.23 | 0.26 |
| CHF      | 0.45* | 0.57 | 0.52* | 0.68 | 0.39* | 0.48 |
| HTN      | 0.31* | 0.37 | 0.55* | 0.74 | 0.20* | 0.22 |
| LIPID    | 0.14* | 0.15 | 0.34* | 0.41 | 0.11 | 0.11 |
| OBES     | 0.17* | 0.19 | 0.09 | 0.10 | 0.23* | 0.26 |
| ORALTX   | 0.29* | 0.34 | -0.28# | -0.25 | -0.14 | -0.13 |
| INSTX    | 0.54* | 0.72 | -0.03 | -0.03 | 0.26 | 0.30 |
| COMB     | 0.35# | 0.42 | 0.17 | 0.18 | 0.43# | 0.53 |
| SPEC     | 0.74* | 1.09 |          |       |          |       |
| DIAG1    | 0.05 | 0.05 | 0.14# | 0.15 | 0.14# | 0.15 |
| DIAG2    | 0.35* | 0.41 | -0.03 | -0.03 | 0.02 | 0.02 |
| DIAG3    | 0.23* | 0.26 | 0.09 | 0.10 | 0.23* | 0.26 |
| DIAG4    | 0.46* | 0.58 | 0.30* | 0.36 | 0.50* | 0.65 |
| DIAG5    | 0.28* | 0.32 | 0.22* | 0.25 | 0.27* | 0.31 |
| DIAG6    | 0.15* | 0.16 | 0.05 | 0.05 | 0.00 | 0.00 |
| DIAG7    | 0.46* | 0.58 | 0.77* | 1.15 | 0.48* | 0.61 |
| DIAG8    | 0.23* | 0.26 | 0.07 | 0.08 | 0.12# | 0.13 |
| DIAG9    | 0.32* | 0.38 | 0.18* | 0.19 | 0.25* | 0.29 |
| DIAG10   | 0.15* | 0.16 | -0.01 | -0.01 | 0.04 | 0.04 |
| DIAG11   | 0.68* | 0.98 | 0.72# | 1.06 | 0.86# | 1.37 |
| DIAG12   | 0.13* | 0.14 | 0.12# | 0.12 | 0.13# | 0.14 |
| DIAG13   | 0.37* | 0.45 | 0.10# | 0.11 | 0.15* | 0.16 |
| DIAG14   | 0.21 | 0.24 | -0.13 | -0.12 | 0.01 | 0.01 |
| DIAG15   | 0.28 | 0.32 | -0.27 | -0.24 | -0.31 | -0.27 |
| DIAG16   | 0.54* | 0.71 | 0.30* | 0.35 | 0.31* | 0.37 |

<table>
<thead>
<tr>
<th>Dep. Var.</th>
<th>Natural logarithm of total costs</th>
<th>Natural logarithm of diabetes-related costs</th>
<th>Natural logarithm of diabetes-specific costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DV</td>
<td>7.02</td>
<td>6.49</td>
<td>6.06</td>
</tr>
<tr>
<td>Mean Costs</td>
<td>2,840</td>
<td>1,791</td>
<td>1,237</td>
</tr>
<tr>
<td>Total df.</td>
<td>2,946</td>
<td>1,825</td>
<td>1,825</td>
</tr>
<tr>
<td>adj-R2</td>
<td>0.48</td>
<td>0.35</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*p < 0.01  #p < 0.05
Table 15 contains the parameter estimates and adjusted parameter estimates for the total medical cost, diabetes-related medical cost, and diabetes-specific medical cost models. The adjusted-$R^2$ values for the medical cost models were similar to the total cost models presented in Table 14, ranging from 28% to 48%.

The parameter estimates associated with AGE were statistically significant in all three models and inversely related to each dependent variable. The parameter estimates associated with UNCONT are also statistically significant in each model. The presence of heart disease, hypertension, and obesity are associated with higher average costs in all three models.

The parameter estimates associated with insulin and combination therapy were not statistically significant in any of the models, and the estimate associated with oral therapy is significant only in the diabetes-related medical cost model. This indicates that the type of diabetes therapy does not have much impact on average medical costs.

Table 16 contains the parameter estimates and adjusted parameter estimates for the total pharmacy cost, diabetes-related pharmacy cost, and diabetes-specific pharmacy cost models. The adjusted-$R^2$ values for the pharmacy cost models were lower than those of the total cost models presented in Table 14, ranging from 7% to 17%.

A smaller number of parameter estimates are statistically significantly different from zero. Those on combination therapy have higher average pharmacy costs than those on diet therapy.
Table 15 Total, Diabetes-Related, and Diabetes-Specific Medical Cost Models

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERCEPT</td>
<td>5.41*</td>
<td>5.41</td>
<td>5.23*</td>
<td>5.23</td>
<td>5.07*</td>
<td>5.07</td>
</tr>
<tr>
<td>AGE</td>
<td>-0.01*</td>
<td>-0.01</td>
<td>-0.01*</td>
<td>-0.01</td>
<td>-0.01*</td>
<td>-0.01</td>
</tr>
<tr>
<td>UNCONT</td>
<td>0.32*</td>
<td>0.38</td>
<td>0.38*</td>
<td>0.46</td>
<td>0.37*</td>
<td>0.44</td>
</tr>
<tr>
<td>SEX</td>
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<td>0.10</td>
<td>0.12#</td>
<td>0.13</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>RENAL</td>
<td>0.38#</td>
<td>0.47</td>
<td>0.74*</td>
<td>1.09</td>
<td>0.40</td>
<td>0.49</td>
</tr>
<tr>
<td>EYE</td>
<td>0.46*</td>
<td>0.59</td>
<td>0.34*</td>
<td>0.41</td>
<td>0.21*</td>
<td>0.23</td>
</tr>
<tr>
<td>NEURO</td>
<td>0.20</td>
<td>0.22</td>
<td>0.31#</td>
<td>0.37</td>
<td>0.20</td>
<td>0.22</td>
</tr>
<tr>
<td>CHF</td>
<td>0.59*</td>
<td>0.81</td>
<td>0.62#</td>
<td>0.86</td>
<td>0.51*</td>
<td>0.67</td>
</tr>
<tr>
<td>HTN</td>
<td>0.30*</td>
<td>0.35</td>
<td>0.40#</td>
<td>0.49</td>
<td>0.37*</td>
<td>0.45</td>
</tr>
<tr>
<td>LIPID</td>
<td>0.06</td>
<td>0.06</td>
<td>0.20#</td>
<td>0.22</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>OBES</td>
<td>0.25#</td>
<td>0.28</td>
<td>0.33#</td>
<td>0.39</td>
<td>0.36*</td>
<td>0.44</td>
</tr>
<tr>
<td>ORALTX</td>
<td>-0.05</td>
<td>-0.05</td>
<td>-0.14*</td>
<td>-0.13</td>
<td>-0.03</td>
<td>-0.03</td>
</tr>
<tr>
<td>INSTX</td>
<td>0.16</td>
<td>0.17</td>
<td>0.11</td>
<td>0.12</td>
<td>0.17</td>
<td>0.18</td>
</tr>
<tr>
<td>COMB</td>
<td>0.01</td>
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<td>0.01</td>
<td>0.01</td>
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<tr>
<td>DIAG1</td>
<td>0.06</td>
<td>0.06</td>
<td>0.19#</td>
<td>0.21</td>
<td>0.24*</td>
<td>0.27</td>
</tr>
<tr>
<td>DIAG2</td>
<td>0.58*</td>
<td>0.79</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>0.10</td>
</tr>
<tr>
<td>DIAG3</td>
<td>0.36*</td>
<td>0.44</td>
<td>0.27#</td>
<td>0.31</td>
<td>0.29*</td>
<td>0.34</td>
</tr>
<tr>
<td>DIAG4</td>
<td>0.55*</td>
<td>0.74</td>
<td>0.60#</td>
<td>0.83</td>
<td>0.69*</td>
<td>0.99</td>
</tr>
<tr>
<td>DIAG5</td>
<td>0.27*</td>
<td>0.31</td>
<td>0.32#</td>
<td>0.38</td>
<td>0.29*</td>
<td>0.33</td>
</tr>
<tr>
<td>DIAG6</td>
<td>0.23*</td>
<td>0.26</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>DIAG7</td>
<td>0.61*</td>
<td>0.84</td>
<td>1.01#</td>
<td>1.74</td>
<td>0.57*</td>
<td>0.77</td>
</tr>
<tr>
<td>DIAG8</td>
<td>0.26*</td>
<td>0.30</td>
<td>0.15#</td>
<td>0.16</td>
<td>0.14#</td>
<td>0.15</td>
</tr>
<tr>
<td>DIAG9</td>
<td>0.43*</td>
<td>0.54</td>
<td>0.30#</td>
<td>0.34</td>
<td>0.39*</td>
<td>0.48</td>
</tr>
<tr>
<td>DIAG10</td>
<td>0.27*</td>
<td>0.32</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>DIAG11</td>
<td>0.67#</td>
<td>0.95</td>
<td>0.89#</td>
<td>1.43</td>
<td>0.79</td>
<td>1.20</td>
</tr>
<tr>
<td>DIAG12</td>
<td>0.20*</td>
<td>0.22</td>
<td>0.14#</td>
<td>0.15</td>
<td>0.15#</td>
<td>0.16</td>
</tr>
<tr>
<td>DIAG13</td>
<td>0.53*</td>
<td>0.71</td>
<td>0.19#</td>
<td>0.21</td>
<td>0.19#</td>
<td>0.20</td>
</tr>
<tr>
<td>DIAG14</td>
<td>0.27*</td>
<td>0.31</td>
<td>-0.18</td>
<td>-0.16</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>DIAG15</td>
<td>0.37</td>
<td>0.45</td>
<td>-0.11</td>
<td>-0.10</td>
<td>-0.02</td>
<td>-0.02</td>
</tr>
<tr>
<td>DIAG16</td>
<td>0.81*</td>
<td>1.25</td>
<td>0.53#</td>
<td>0.70</td>
<td>0.48*</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Dep. Var. | Natural logarithm of total medical costs | Natural logarithm of diabetes-related medical costs | Natural logarithm of diabetes-specific medical costs |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DV</td>
<td>6.48</td>
<td>5.61</td>
<td>5.46</td>
</tr>
<tr>
<td>Mean Costs</td>
<td>2,256</td>
<td>868</td>
<td>651</td>
</tr>
<tr>
<td>Total df:</td>
<td>2718</td>
<td>1,796</td>
<td>1,793</td>
</tr>
<tr>
<td>adj-R2</td>
<td>0.48</td>
<td>0.38</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*p ≤ 0.01  # p < 0.05
Table 16 Total, Diabetes-Related, and Diabetes-Specific Pharmacy Cost Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cost</th>
<th>Diabetes-Related Cost</th>
<th>Diabetes-Specific Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERCEPT</td>
<td>4.26*</td>
<td>4.50*</td>
<td>4.17*</td>
</tr>
<tr>
<td>AGE</td>
<td>0.01*</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>UNCONT</td>
<td>-0.12</td>
<td>-0.44*</td>
<td>0.06</td>
</tr>
<tr>
<td>SEX</td>
<td>-0.10</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>RENAL</td>
<td>0.11</td>
<td>0.54*</td>
<td>-0.32</td>
</tr>
<tr>
<td>EYE</td>
<td>0.12</td>
<td>0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>NEURO</td>
<td>0.00*</td>
<td>0.05</td>
<td>0.36*</td>
</tr>
<tr>
<td>CHF</td>
<td>0.11</td>
<td>0.10</td>
<td>-0.16</td>
</tr>
<tr>
<td>HTN</td>
<td>0.45</td>
<td>0.80*</td>
<td>-0.05</td>
</tr>
<tr>
<td>LIPID</td>
<td>0.40</td>
<td>0.62*</td>
<td>0.12</td>
</tr>
<tr>
<td>OBES</td>
<td>0.01</td>
<td>-0.13</td>
<td>0.00</td>
</tr>
<tr>
<td>ORALTX</td>
<td>0.73</td>
<td>-0.18</td>
<td>-0.31</td>
</tr>
<tr>
<td>INSTX</td>
<td>1.17*</td>
<td>0.31</td>
<td>0.2*</td>
</tr>
<tr>
<td>COMB</td>
<td>0.96*</td>
<td>0.71*</td>
<td>1.12*</td>
</tr>
<tr>
<td>SPEC</td>
<td>0.07</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>DIAG1</td>
<td>0.09</td>
<td>-0.01</td>
<td>-0.13</td>
</tr>
<tr>
<td>DIAG2</td>
<td>-0.04</td>
<td>-0.10</td>
<td>-0.10</td>
</tr>
<tr>
<td>DIAG3</td>
<td>-0.06</td>
<td>-0.20</td>
<td>-0.05</td>
</tr>
<tr>
<td>DIAG4</td>
<td>0.06</td>
<td>-0.19</td>
<td>-0.06</td>
</tr>
<tr>
<td>DIAG5</td>
<td>0.29</td>
<td>0.03</td>
<td>0.20</td>
</tr>
<tr>
<td>DIAG6</td>
<td>0.02</td>
<td>-0.02</td>
<td>-0.07</td>
</tr>
<tr>
<td>DIAG7</td>
<td>0.23</td>
<td>0.28*</td>
<td>-0.02</td>
</tr>
<tr>
<td>DIAG8</td>
<td>0.16</td>
<td>-0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>DIAG9</td>
<td>0.15</td>
<td>-0.21*</td>
<td>-0.10</td>
</tr>
<tr>
<td>DIAG10</td>
<td>0.00</td>
<td>-0.05</td>
<td>-0.04</td>
</tr>
<tr>
<td>DIAG11</td>
<td>-0.26</td>
<td>-0.51</td>
<td>-0.10</td>
</tr>
<tr>
<td>DIAG12</td>
<td>0.14*</td>
<td>0.14</td>
<td>0.18*</td>
</tr>
<tr>
<td>DIAG13</td>
<td>0.16</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>DIAG14</td>
<td>0.09</td>
<td>0.01</td>
<td>0.23</td>
</tr>
<tr>
<td>DIAG15</td>
<td>0.03</td>
<td>-0.54</td>
<td>-0.77</td>
</tr>
<tr>
<td>DIAG16</td>
<td>0.03</td>
<td>-0.05</td>
<td>-0.11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dep. Var.</th>
<th>Natural logarithm of total pharmacy costs</th>
<th>Natural logarithm of diabetes-related pharmacy costs</th>
<th>Natural logarithm of diabetes-specific pharmacy costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DV</td>
<td>5.83</td>
<td>5.32</td>
<td>4.56</td>
</tr>
<tr>
<td>Mean Costs</td>
<td>579</td>
<td>239</td>
<td>114</td>
</tr>
<tr>
<td>Total df.</td>
<td>2719</td>
<td>1,814</td>
<td>1,791</td>
</tr>
<tr>
<td>adj-R2</td>
<td>0.17</td>
<td>0.16</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* p ≤ 0.01  # p < 0.05
General Linear Model Assumptions

To test the linearity of the relationship between age and the natural logarithm of total costs the sample was categorized into three age groups, those less than 30 years of age, those 31-60 years of age, and those over 60 years. Separate regressions were run for each group as recommended by Kennedy (1996). The results of the regressions were compared and indicated that the relationship may not be linear because the sign of the parameter estimate was not the same in all three models. The parameter estimates associated with age were -0.027 and -0.021 for the 0-29 and 60-99 age groups, respectively. For the 30-59 age group the parameter estimate for age was 0.014. The results were similar for the diabetes-related and diabetes-specific cost models.

A visual inspection of the residuals of the three models indicates that their distribution is normal.

The stability of the parameter estimates over time will be assessed below. This assessment is done because it is possible that the introduction of a new therapy may alter the stability of the year one estimates.

Another assumption of the GLM is that the expected value of the error terms is zero. If this assumption is violated, the intercept is biased. The sum of the residuals in the nine models ranged from 0.028x10^{-13} to 4.793x10^{-11} and the mean, or expected values, ranged from 1.691x10^{-16} to 1.627x10^{-14}, thus the average or expected value of the residuals is nearly zero.

The third assumption of the GLM is that the variance of the error terms is constant. The test for heteroscedasticity invoked by the SPEC option using The SAS
System for Windows produces uncertain results secondary to unreliable degrees of freedom associated with the test due to poor data scaling.

The last assumption states that no perfect linear relationship exists between the independent variables. Violations of this assumption lead to multicollinearity. Because all the patients that had diabetes-specific or diabetes-related costs also saw a specialist, this variable was excluded from the model to avoid perfect multicollinearity.

The TOLERANCE, VIF, and COLLIN options were requested in The SAS System for windows. None of the explanatory variables in either of the three models had tolerance values less than 0.10. Furthermore, none of the condition indices in any of the three models was greater than 30, therefore the conclusion that multicollinearity is not a problem in these models can be made.

Stability of Parameter Estimates

The Chow test is used to assess the structural changes in parameter estimates over time. $F_c$, with $K$ and $(T_1 + T_2 -2K)$ degrees of freedom, is calculated as:

$$F_c = \frac{\text{SSE(constrained)} - \text{SSE(unconstrained)}}{K} \left( \frac{\text{SSE(unconstrained)}}{T_1 + T_2 -2K} \right)$$

$\text{SSE(unconstrained)}$ was obtained by combining the error sum of squares from the regressions run on the year 1 and year 2 regressions separately. The $\text{SSE(constrained)}$ is the error sum of squares from the regression run on the combined year 1 and year 2 data. The results of the Chow tests for each model are presented in Table 17.

At an alpha level of 0.05, the parameter estimates for all the total cost models and the diabetes-related pharmacy cost model are stable from year 1 to year 2. If an alpha
level of 0.01 is adopted then the parameter estimates for the diabetes-related cost and the diabetes-specific pharmacy cost models are stable.

This implies that something is causing the relationship between the dependent and independent variables to differ in year 2 compared to year 1.

<table>
<thead>
<tr>
<th>Table 17 Results of the Chow Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Total Costs</td>
</tr>
<tr>
<td>Total Medical Costs</td>
</tr>
<tr>
<td>Total Pharmacy Costs</td>
</tr>
<tr>
<td>Diabetes-Related Costs</td>
</tr>
<tr>
<td>Diabetes-Related Medical Costs</td>
</tr>
<tr>
<td>Diabetes-Related Pharmacy Costs</td>
</tr>
<tr>
<td>Diabetes-Specific Costs</td>
</tr>
<tr>
<td>Diabetes- Specific Pharmacy Costs</td>
</tr>
<tr>
<td>Diabetes-Specific Pharmacy Costs</td>
</tr>
</tbody>
</table>

Distribution of Patients Among Treatment Groups

The distribution of patients among ORALTX, INSTX, COMBO, and diet therapy is presented in Table 18. Because no one was on metformin during year 1, these patients are included with those treated with oral sulfonylureas during year 2.
Table 18 Actual and Predicted Year 2 Percent Distribution of Patients Among Therapies

<table>
<thead>
<tr>
<th>Year 2</th>
<th>Diet (%)</th>
<th>Oral Mono-therapy* (%)</th>
<th>Combination (%)</th>
<th>Insulin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period 6</td>
<td>Actual</td>
<td>2.30</td>
<td>53.17</td>
<td>35.8</td>
</tr>
<tr>
<td></td>
<td>Predicted, TC Model</td>
<td>5.7</td>
<td>85.8</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Predicted, DR Model</td>
<td>0.1</td>
<td>86.2</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Predicted, DS Model</td>
<td>0.1</td>
<td>86.2</td>
<td>1.8</td>
</tr>
</tbody>
</table>

* This is a combination of the oral sulfonylurea and metformin groups.

Generally speaking, the models overestimated the percentage of people on oral therapy and underestimated the proportion of patients on combination therapy. The total cost model did a better job of predicting the proportion of patients on insulin compared to the diabetes-related and diabetes-specific models. However, the total cost model overestimated the proportion of patients on diet therapy, while the diabetes-related and diabetes-specific models underestimated the percentage of patients on diet therapy by the end of year 2.
CHAPTER 5

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

Discussion

At the inception of this research, it was the intent of the researcher to prove the superiority of one type of model over another. However, it quickly became apparent that these models are both useful tools and each has its place within pharmacoeconomic research. Both models require that certain assumptions are made in order to use them, and both models have limitations as demonstrated by this research.

Summary of Findings

A decision tree was constructed within an equilibrium framework using probabilities obtained from the literature and costs derived from internal sources to predict the expected diabetes-specific cost of providing care to diabetic patients following the addition of metformin to the formulary of a managed care organization. The estimate of the total diabetes-specific cost impact came within five percent of the actual total diabetes-specific cost incurred during the year following the formulary addition.

The decision tree used in this research, constructed from national treatment guidelines using literature-based probabilities and internally derived costs, underestimated the diabetes-specific medical costs and overestimated the diabetes-specific pharmacy costs. The predicted diabetes-specific average medical cost was 73% of the actual average cost. While the predicted diabetes-specific average pharmacy cost was 258% of the actual average diabetes-specific pharmacy cost.
A regression model was also constructed, using medical and pharmacy claims data and a proxy measure for diabetes control to predict the expected diabetes-specific, diabetes-related and total health care costs of providing care to diabetic patients following the addition of metformin to the formulary of a managed care organization. The average total cost estimates produced by the total health care cost model were within seven percent of the actual average costs incurred the year following the addition of metformin to the formulary. The diabetes-related and diabetes-specific cost models produced less accurate results. The estimates produced by these models were within 12% and 18% of the actual costs incurred, respectively.

The total health care, diabetes-related, and diabetes-specific average medical costs produced by the regression models were within 6%, 50%, and 46% of the actual average medical costs respectively. The total, diabetes-related, and diabetes-specific average pharmacy costs produced by the regression models were within 20%, 45%, and 49% of the actual average medical costs respectively.

These results are different than expected. The deterministic model estimates were more accurate than expected given that the model was based upon national treatment guidelines and literature-based probabilities of effect (rather than local treatment practices and efficacy rates). The stochastic models were expected to produce more accurate predictions than they did because they were based on patient level data and controlled for a limited number of patient and provider characteristics.
The Deterministic Model

Although the average diabetes-specific cost predicted by the deterministic model was within $21 of the actual diabetes-specific costs, it is possible that this result was due to chance. The model overestimated the pharmacy costs, and underestimated the medical costs—perhaps one compensated for the other.

Medical costs were underestimated despite the fact that the deterministic model overestimated the number of physician visits and hemoglobin A1C tests ordered. This is probably due to the fact that the deterministic model does not include hospitalization or emergency department costs. Any claim that listed an ICD-9-CM diagnostic code of 250 as the primary diagnosis was included in the calculation of the diabetes-specific medical costs. Some of these were emergency department and hospital claims.

The year 1 model predicted that most people would be on oral therapy or insulin by the end of the first year. The year 2 model predicted that over 50% of the patients would be on insulin therapy and over 30% would be on oral therapy by the end of year 2. At the end of year one, just over six percent were on insulin and over 20% had no claims for prescription medication for diabetes.

The inconsistency of the predicted and actual distribution of patients among the various therapies calls into question the validity of the deterministic model used in this research. These inconsistencies indicate that the probabilities obtained from the literature were not consistent with the treatment practices within this managed care organization. The probabilities were derived from a limited number of clinical trials because few studies reported the number of patients that reached their targeted glycemic control. It is
difficult to know how the inclusion of probabilities from additional studies would affect the mean probabilities used in the decision tree. Increasing the number of subjects upon which the probabilities are derived increases the confidence that mean probability used in the decision tree is actually the probability of response from those who are eligible to participate in a clinical trial. Focusing on this question makes one lose sight of the more important questions such as: 1) Do data derived from clinical trials adequately represent actual clinical practice, and 2) should these data be used to obtain probabilities for decision trees?

Based on the model used in this research, the answer is no, but it is unlikely that this conclusion can be generalized to all decision trees. This model is based on the treatment guidelines of the American Diabetes Association, thus the content of the model is probably valid. However, the development of diabetes care habits requires behavioral modification and consistent motivation, therefore, physicians and patients may not automatically progress to the next level of therapy if glycemic control is not achieved two months after a new diabetes therapy is initiated. Thus, a better source of probabilities for this model may have been the pharmacy claims database or a panel of physicians who treat diabetic patients within the managed care organization.

Another characteristic of this model that makes it different from others is the fact that the sulfonylureas and the insulins were modeled as classes rather than as individual products. This was done to simplify the decision tree and was justified on the basis that the primary drugs used in the sulfonylurea class are glipizide and glyburide and they are both second generation sulfonylureas, which have similar efficacy and side-effect
profiles. The insulins also have similar efficacy and side-effect profiles and the treatment regimen must be tailored to each patient.

**The Stochastic Model**

With the exception of the total health care cost model, the regression models did a poor job predicting the year 2 expected costs. Generally speaking, the more specific the cost used in the model, the worse the model was at predicting the year 2 costs. For example, the model that included total health care costs had the highest adjusted-$R^2$ value and produced an estimate that was within seven percent of the actual health care costs incurred in year 2. However, the model that included diabetes-specific pharmacy costs had the lowest adjusted-$R^2$ value and produced an estimate that was within 49% percent of the actual health care costs incurred in year 2.

This finding supports the argument that key explanatory variables are missing from the models. The regression models used in this study were based solely on medical and pharmacy claims data and contained no clinical data. A proxy measure was used to roughly indicate which patients did not have their diabetes under control. Then using literature based estimates of the percent of patients that would respond to therapy, an estimate was made of the percentage of patients with uncontrolled diabetes that would be controlled following the addition of metformin to their regimen. Ideally a hemoglobin A1C value would have been used as an explanatory variable. Then the percent reduction in hemoglobin A1C, obtained from the clinical literature, could have been used to estimate the impact of the new medication on the level of control and the costs of treatment.
Other explanatory variables that should be included in a diabetes model include ethnicity, body weight, and duration of disease. Unfortunately none of these data were available. The exclusion of key clinical and disease-specific variables from the stochastic model eliminate the advantages gained by using patient level data.

Another potential reason for the poor predictive ability of the diabetes-related and the diabetes-specific regression models is that the parameter estimates are not stable from one year to the next, with the exception of the Diabetes-Related Pharmacy Cost model. Any number of factors could be responsible for altering the relationship between the costs of care and the independent variables included in the model such as the addition of metformin to the formulary or the progression of the disease itself.

The cost of the metformin in the regression model was implicitly assumed to be the same as that of the sulfonylureas because they were lumped into the same category to make the year 2 cost predictions. This is one potential source of cost underestimation. Another came from the fact that the year 2 cost estimates produced by the regression models was based on the people who incurred costs during year 1, and more people incurred diabetes-related and diabetes-specific costs in year 2 than in year 1.

Finally the predicted distribution of patients among the different therapies in year 2 was based upon probabilities derived from clinical trials and was subject to the same problems described under the deterministic model.

The purpose of this research was to compare the average cost predictions made by two models to determine if the predictions were accurate. No reports in diabetes or any other disease have been found in the literature.
The resources used by the diabetic patients in this study are similar to those reported by others. Glauber and Brown (1992) reported that pharmacy costs for diabetic patients was three times higher that those without diabetes. Fifty seven percent of the patients in their study were on an oral hypoglycemic agent, 34% were on insulin and 6% were receiving a combination of the two. During year 1, the subjects included in the current study had average health care costs three times that of the total HMO population and 3.5 times higher average pharmacy costs. At the end of year 1, 68% of the subjects were on oral hypoglycemic agents and 53% the end of year 2. However, only 6.4% and 8.7% of the patients were on insulin at the end of years 1 and 2 respectively. The percentage of patients on combination therapy increased to 36% by the end of year 2, but this figure includes those taking insulin and an oral agent plus those on metformin and a sulfonylurea agent.

Conclusions

Further research is needed to determine which sources of data are best to use in models that estimate the economic impact of adding a medication to the formulary of a managed care organization. However, based on this research, if a managed care organization wants to predict the economic impact of adding a medication to their formulary and they only have medical and pharmacy claims data from the previous year, then they should use a decision tree to predict the disease specific cost impact and a regression model to predict the total health care cost impact. Because the decision tree in this study used literature based probabilities and internal cost data and produced an accurate estimate of the disease-specific average cost, my current recommendation is that
decision trees that are used to predict the disease-specific cost impact should use
literature based probabilities and internally derived cost estimates. Regression models
that are used to predict the total health care cost impact should, at a minimum, control for
age, gender, co-morbid conditions, and specific therapeutic regimens.

The question being asked (i.e., disease-specific or total cost impact), the available
data, and the technical capabilities of the analyst should dictate which type of model is
used. Decision trees are of no use when trying to estimate the total cost impact and
regression models built from administrative claims data, lacking clinical indicators, are of
no use in estimating the disease-related or disease-specific cost impacts.

The decision tree can be constructed and used with cost and probability data from
the literature or internal sources and does not require any special equipment, other than a
spread-sheet or calculator. However, the more data that can be obtained from internal
sources, the better the estimates will reflect the internal constraints of the health system.

The regression model is data intensive and may require special programs to
extract the data and run the analysis. Regression models can incorporate more patient
and treatment characteristics than the decision tree because it uses patient- or
observation-level data. Unfortunately, the type of data available may limit the analysis.

Many people can construct a decision tree or build a regression model and
produce an expected cost. However, the results should be treated with great caution
unless each step in the model building process is assessed (or has the ability to be
assessed) to ensure the model reflects the patient characteristics and treatment patterns
within the managed care organization.
Recommendations for Future Research

One study assessing the accuracy of a model does not provide enough data to improve the model construction. Therefore further studies need to be conducted on both deterministic models and stochastic models to assess the predictive capabilities of the models. The decision tree should be assessed using probabilities derived from the pharmacy claims data base and from an expert panel composed of physicians who treat diabetic patients in the managed care organization. This would help determine the best source of probability data when trying to predict the economic impact of adding a new drug to the formulary of a managed care organization.

The regression model needs to be respecified to include diabetes-specific characteristics such as hemoglobin A1C measures, weight, time since diagnosis, and ethnicity.

Once the optimal deterministic and stochastic models are found, they need to be assessed in other patient populations to see if they produce reliable estimates. These same techniques then could be applied to other chronic diseases such as asthma where the patient can experience acute exacerbations of the disease and must provide daily self-care to prevent or postpone the long-term consequences of the disease. The purpose of these studies is not to build generalizable models that can be used to answer all questions for each disease. Rather, studies that examine each step of the model building process are needed to determine what sources of data and model building techniques produce the best cost-impact estimates.
In addition, there are several specific areas that need to be explored further in the area of claims databases. Constant research is needed to assess the accuracy of the diagnostic, service code information, and medication information contained in the medical and pharmacy claims. On-line adjudication, increasing use of administrative databases for outcomes research, and periodic insurance audits should have a positive impact on the accuracy of the data, but it needs to be continually monitored.

As health systems integrate their computer systems, it will be easier for health services researchers to combine clinical and administrative databases. However, until that technology is in widespread use, studies are needed to develop better proxy measures for clinical and disease severity indicators.
REFERENCES


