August 2017

A Markov Model of Disease Progression and Cost-Effectiveness for Type 2 Diabetes

Technical Report

Prepared for

Centers for Disease Control and Prevention
2920 Brandywine Road, Room 3000 (GPO)
Atlanta, GA 30341-5539
Contract No. 200-1997-00621

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Executive Summary

This technical report describes how we constructed the model of disease progression and cost-effectiveness for type 2 diabetes. Our model consists of three related modules:

- Diabetes Progression: Type 2 diabetes progresses along five disease complication paths from time of normal clinical diagnosis of diabetes to death. Patients may receive different interventions meant to reduce the incidence of complications related to diabetes.
- Early Diabetes Progression: Patients diagnosed with diabetes before time of normal diagnosis are followed from diagnosis though time of normal diagnosis. Patients receive early diagnosis if they are participating in the Diabetes Prevention Program (DPP) intervention and develop diabetes. After this module, patients enter the Diabetes Progression module.
- Impaired Glucose Tolerance (IGT) / DPP: Follows patients with IGT from diagnosis of IGT to diagnosis of diabetes, or death, whichever comes first. Patients may receive the DPP intervention during this module. If diabetes develops, the patient moves on to the Early Diabetes module and then the Diabetes Progression module.

Using these modules, the user will be able to perform analyses on the impact of implementing different interventions relevant to diabetes. Table ES-1 describes those analyses and the modules associated with each. All analyses include the Diabetes Progression module; other modules are included if the analysis begins prior to the normal clinical diagnosis of diabetes.

Table ES-1. Intervention Analyses and Associated Model Modules

Intervention of Interest	Associated Modules
Interventions for reducing the incidence of complications related to diabetes	Diabetes Progression
Diabetes Prevention Program (DPP)	IGT / DPP Early Diabetes Progression Diabetes Progression

ES.1 Diabetes Progression Module

The Diabetes Progression module models how type 2 diabetes progresses along five disease complication paths. Since clinical diagnosis of diabetes normally takes place well after onset, the model allows this module (and, hence, diabetes complications) to begin several years after the onset of diabetes. Each stage along the five paths is associated with a distinct set of costs for treatment and complications; the model allows us to aggregate these costs over the course of a patient's lifetime. The model includes several types of treatment interventions: intensive glycemic control, tight blood pressure control, cholesterol reduction,

smoking cessation, polypill (a currently hypothetical pill containing aspirin and generic blood pressure and statin medications), bariatric surgery, influenza vaccination, and a generic intervention that can be customized by the user. The model calculates the incremental costs and outcomes, measured in quality-adjusted life years (QALYs), associated with each intervention relative to baseline treatment. The resulting incremental cost-effectiveness (CE) ratios can be compared across interventions to help policy makers decide on treatment strategies for patients with type 2 diabetes.

Our model builds on previous diabetes models constructed by Eastman et al. (1997a; 1997b); Dong, Orians, and Manninen (1997); and the CDC Diabetes Cost-Effectiveness Study Group (1998) and a series of RTI projects funded by CDC. We have incorporated much of the structure and many of the parameters from these models within our work. However, our model differs in several ways. First, we employ a Markov model structure to simulate disease progression for patient cohorts; the other models employ Monte Carlo simulation of individual patients. Second, we have extended the previous models to put more emphasis on cardiovascular disease (CVD) and CVD interventions such as hypertension control, cholesterol reduction, and smoking cessation. Third, the Markov structure allows us to introduce interdependencies between different diabetes progression paths that provide a richer description of disease progression. For example, in the present version, persons with microalbuminuria develop hypertension. In addition, persons with hypertension are allowed to develop nephropathy and retinopathy complications more quickly than persons without hypertension.

Finally, most of the key transition probabilities and intervention effects in our model are based on data on patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) that were not available when the earlier models were created. The models instead used data on type 1 patients from the Diabetes Control and Complications Trial (DCCT). Although glycemic control is expected to slow development of complications for both type 1 and type 2 diabetes, the magnitude of effect may differ across types. Therefore, for our model of disease progression for type 2 patients, the UKPDS data are preferable. The UKPDS also provides information on hypertension control that we incorporate within our model.

ES.2 Early Diabetes Progression Module

Patients follow the Early Diabetes Progression module if they are diagnosed with diabetes before the time of normal clinical diagnosis (upon which the Diabetes Progression module begins). The model assumes that disease progression and complication development rates may be different during this time than after the time of normal clinical diagnosis. Patients receive this early diagnosis if they are involved in the DPP and develop diabetes; due to

regular screening for all DPP participants, the disease would be detected almost immediately.

The parameters that determine early diabetes progression are based on data on complication incidence at diabetes onset in patients in the DPP study who develop diabetes, as well as UKPDS data on complication incidence at the time of normal clinical diagnosis.

ES.3 IGT / DPP Module

The IGT / DPP module follows patients from the time of diagnosis of IGT to diagnosis of diabetes, or death, whichever comes first. Patients receive either a control intervention or one of two DPP interventions – one based on intensive lifestyle changes (Lifestyle) and the other on the antihyperglycemic drug Metformin. The model assumes that diagnosis occurs at disease onset because of regular screening of all DPP participants, including the control group.

Persons with IGT may already have some complications at IGT diagnosis and also may experience CHD, stroke, early stages of nephropathy and neuropathy, or death while IGT. They may also develop high blood pressure, high cholesterol, or diabetes. Most of the model's disease progression parameters are based on data on patients in the DPP study.

The software incorporating the model is flexible and user-friendly. Users can modify key model parameters to perform sensitivity analyses and incorporate new data. The model itself can be expanded to include additional interventions. For example, the model originally included only the Diabetes Progression module and was later expanded to include the other two modules.

Most of this document, Sections 1 through 9, is dedicated to describing the Diabetes Progression module since it is the original and main portion of the model. Also for that reason, in those sections, "the model" refers to the Diabetes Progression portion of the model. The sections are specifically organized as follows: Section 1 lays out the basic Markov structure for the model, and Section 2 provides a detailed description of the interventions incorporated in the model. The initial distribution of patients across cohorts is presented in Section 3, and race/ethnicity differences are discussed in Section 4. Section 5 describes the costs of regular and intensive diabetes care, and Section 6 describes the costs of diabetes complications, normal death and other medical costs. Section 7 provides a detailed outline of an alternative multiplicative cost calculation option. QALY values are contained in Section 8, and model computations are described in Section 9. Section 10 then describes all aspects of the other two modules in the model, IGT / DPP and Early Diabetes Progression.

1. MODEL STRUCTURE AND PARAMETERS

In the Markov model, a series of cohorts progress through the model. Each cohort is determined by the following demographic characteristics:

- Age (in 10-year groupings, 25 to 94),
- Sex (male/female),
- Race/Ethnicity (non-Hispanic White, African-American, Hispanic, Native-American, Asian),
- Hypertension (normal/above normal),
- Cholesterol (normal/above normal), and
- Current Smoking (no/yes).

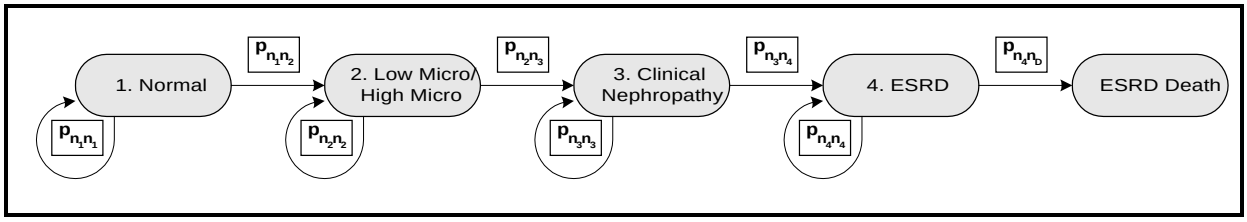
This produces a total of 560 cohorts (7 ages × 2 sexes × 5 race/ethnicity groups × 2 hypertension groups × 2 cholesterol groups × 2 smoking groups).

The model has also been expanded to allow for cohorts aged 5–14 and 15–24. To use these cohorts, however, users must provide their own age-specific parameters to model disease progression. Users may also perform analyses where all patients start at the same age. The time from onset of diabetes to normal diagnosis is set to 10 years in our initial model. This parameter, like most others in the model, can easily be adjusted. All patient cohorts entering the model are assumed to have been newly diagnosed with diabetes. Cohorts are followed along the disease paths until they turn 95 years old, when they are assumed to die.

Cohort members progress simultaneously on five different disease paths. Disease paths and disease states in each path for Model 1 are as follows:

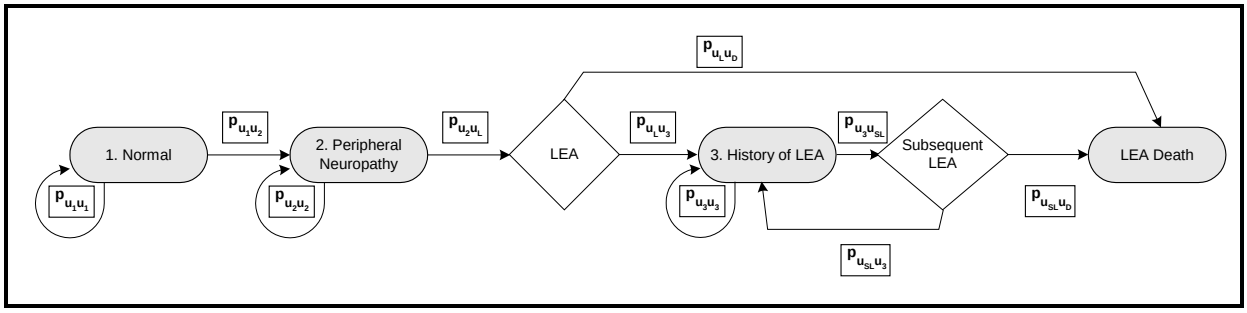
- Nephropathy (shown in Figure 1-1)
  - Normal (n_1)
  - Low microalbuminuria/high microalbuminuria (n_2)
  - Clinical nephropathy (n_3)
  - End stage renal disease (ESRD) (n_4)
  - ESRD death (n_D)

Figure 1-1. States and Transition Probabilities: Nephropathy



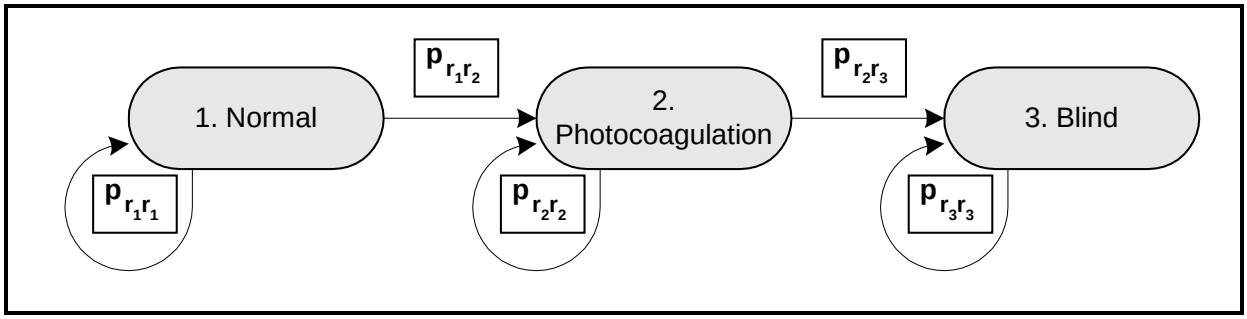
- Neuropathy (shown in Figure 1-2)
  - Normal
  - Peripheral neuropathy (u_2)
  - History of LEA (u_3)
  - LEA death (u_D)

Figure 1-2. States and Transition Probabilities: Neuropathy



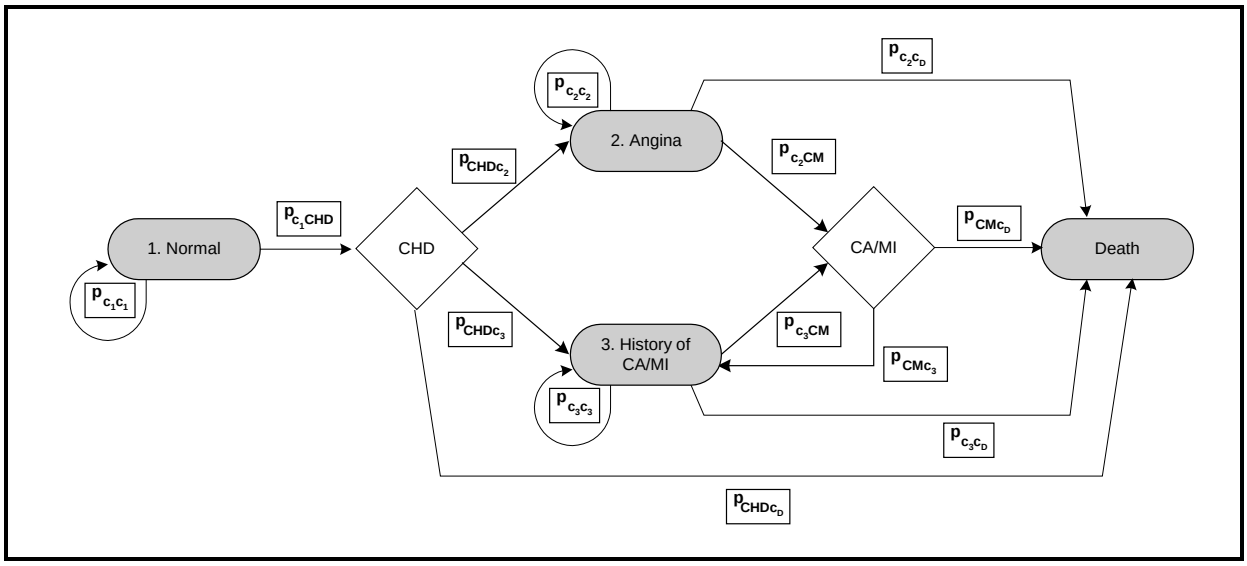
- Retinopathy (shown in Figure 1-3)
  - Normal (r_1)
  - Photocoagulation (r_2)
  - Blind (r_3)

Figure 1-3. States and Transition Probabilities: Retinopathy



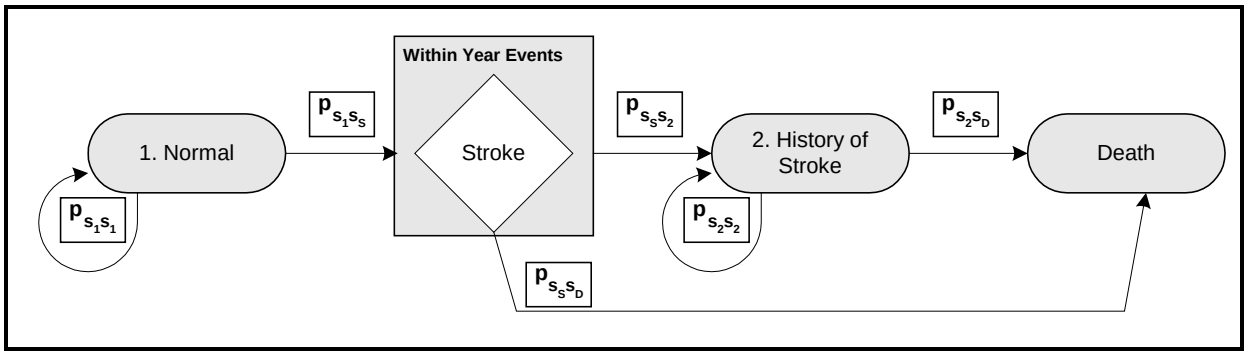
- Coronary Heart Disease (CHD) (an abbreviated version is shown in Figure 1-4 and described in detail in Section 1.2.1)
  - Normal (c_1)
  - Angina (c_2)
  - History of Cardiac Arrest (CA)/Myocardial Infarction (MI) (c_3)
  - CHD death (c_d)

Figure 1-4. States and Transition Probabilities: Coronary Heart Disease



- Stroke (shown in Figure 1-5)
  - Normal (s_1)
  - History of Stroke (s_2)
  - Stroke death (s_D)

Figure 1-5. States and Transition Probabilities: Stroke



At the end of any period, the cohort occupies one state on each of the disease paths. For the simulation, transitions between states take place at discrete time intervals 1 year apart. Thus, at the end of each 1-year period, portions of the cohort can move from one disease state to another or stay in the same disease state. The simulation program determines what proportion of the cohort will move from one state to another based on the transition probability.

In several cases, an individual can experience a complication event that the patient either dies from or survives during the period. On the neuropathy path, a patient with neuropathy can undergo an LEA and either die or survive. Similarly, a person with a history of LEA may undergo an additional LEA and either die or survive. On the CHD path, patients can experience a CHD event (angina, CA/MI, or recurrent CA/MI). Finally, on the stroke path, patients can either survive or die from a stroke suffered within a period.

Such events are incorporated within the overall Markov model by bridge models (Weinstein et al., 1987). Each bridge model covers the incidence and probabilities of death and survival from the event within one period. These values are incorporated into the transition probabilities between model states. The events themselves are not model states, though they are closely related. To see the distinction, consider a patient who is in the peripheral neuropathy state on the neuropathy path at time t. During the next period, the patient may experience an LEA. If the patient survives the LEA, he or she progresses to the state History of LEA at time t+1. Alternatively, if the patient dies from the LEA, he or she progresses to the Death state at t+1. The Markov model keeps track of the number of patients who are in each state in each period. It also keeps track of the cumulative incidence of patients who have undergone complication events such as LEA, angina, CA/MI, and stroke. In the diagrams, events within the bridge models are represented by diamonds, and the states are numbered and represented by ovals.

The initial distribution of the cohort among disease states within each stage is shown in Tables 1-1 through 1-5. For example, the model assumes that 3.5 percent of persons have peripheral neuropathy when they are diagnosed with diabetes, and the remaining 96.5 percent are in the Normal state for neuropathy. The initial distributions for neuropathy and nephropathy come from Eastman et al. (1997b); for retinopathy, MI, and stroke, the model assumes that the entire cohort begins in the Normal state. The initial distributions are the same for all cohorts.

Table 1-1. Initial Distribution of Cohort in Nephropathy

Disease State	Initial Distribution (%)
Normal	89.5
Microalbuminuria	10.5
Nephropathy	0.0
End Stage Renal Disease	0.0

Source: Eastman et al. (1997b), who calculate the value from data in Klein, Klein, and Moss (1993).

Table 1-2. Initial Distribution of Cohort in Neuropathy

Disease State	Initial Distribution (%)
Normal	96.5
Peripheral Neuropathy	3.5
Lower Extremity Amputation	0.0
Subsequent Lower Extremity Amputation(s)	0.0

Source: Eastman et al. (1997b), citing Eastman (1995).

Table 1-3. Initial Distribution of Cohort in Retinopathy

Disease State	Initial Distribution (%)
Normal	100.0
Photocoagulation	0.0
Blind	0.0

Source: Assumption.

Table 1-4. Initial Distribution of Cohort in Coronary Heart Disease

Disease State	Initial Distribution (%)
Normal	100.0
History of Cardiac Arrest/Myocardial Infarction	0.0
History of Angina	0.0
Congestive Heart Failure	0.0

Source: Assumption.

Table 1-5. Initial Distribution of Cohort In Stroke

Disease State	Initial Distribution (%)
Normal	100.0
History of Stroke	0.0

Source: Assumption.

We specify the mathematical model based on the Markov model using transition probabilities. The transition probability $p_{i,j}(t)$ is the probability that the patient in state i at time t will be in state j at time t+1. The hazard rates and hence the transition probabilities are dependent on a variety of variables including the following:

- time since diagnosis of diabetes,
- time between onset of diabetes and diagnosis,
- age,
- sex,
- race/ethnicity,
- glycemic levels,
- smoking,
- cholesterol levels, and
- hypertension.

In the model, age, sex, smoking, and cholesterol level affect only the transition probabilities associated with CHD and stroke. The time between onset of diabetes and diagnosis affects only the glycemic level at the time of diagnosis. Time since diagnosis of diabetes, glycemic level, and hypertension affect all of the transition probabilities. The impact of race/ethnicity affects glycemic levels and death probabilities. Glycemic level has a multiplicative effect on the baseline hazard rates, which in turn determine the transition probabilities used in the model.

In this report, we distinguish between the related terms “hazard rates” and “transition probabilities.” Hazard rate shows the rate at which individuals change from one state to the next; this rate can take values between 0 and ∞. Transition probability is the probability that an individual patient makes the transition between states during one period. The transition probability has a range between 0 and 1. The relationship between the hazard rate (r) and the transition probability (p) for time period t is given by

$$p = 1 - e^{-rt} . \quad (1)$$

Although p and r are fairly close when r is near zero (as is the case for most of the hazard rates in the tables), they are not equal.

1.1 Parameters for Nephropathy, Neuropathy, and Retinopathy

We show the hazard rates for nephropathy, neuropathy, and retinopathy in Tables 1-6a through 1-8a. For comparison, we show the corresponding transition probabilities in Tables 1-6b through 1-8b. These numbers illustrate the slight differences that are present between the hazard rates and the transition probabilities. The baseline transition probabilities for each state in each disease path are calculated in the model itself. Most numbers displayed in the software program input screens are hazard rates; in a few cases, however, it is more convenient to display transition probabilities.

1.1.1 Nephropathy

Table 1-6a shows the baseline hazard rates for nephropathy. The microalbuminuria and clinical nephropathy rates are derived from the transition probabilities reported in Figure 1 in UKPDS 64 (Adler et al., 2003; UKPDS 33, 1998; UKPDS 38, 1998). We converted the probabilities reported in the figure into hazard rates using Equation (1). Calculation of the clinical nephropathy rates was more complicated, because we needed hazard rates conditional on having had microalbuminuria. We first simulated the number of patients who had progressed to microalbuminuria at each year. We then calculated the clinical nephropathy transition probability necessary to yield the number of patients who had progressed to nephropathy by the end of the study period. Finally, we converted this transition probability into a hazard rate.

Table 1-6a. Baseline Hazard Rates: Nephropathy

	Years Since Diagnosis		
	0–11	12–19	20+
Normal to Microalbuminuria (No Hypertension)	0.0202	0.0202	0.0202
Normal to Microalbuminuria (Hypertension)	0.0202	0.0202	0.0202
Microalbuminuria to Clinical Nephropathy No Hypertension)	0.0284	0.0284	0.0284
Microalbuminuria to Clinical Nephropathy (Hypertension)	0.0284	0.0284	0.0284
Clinical Nephropathy to ESRD	0.02327	0.02327	0.02327

Source: See text.

The hazard rates for ESRD were estimated by Eastman et al. using data reported in Humphrey et al. (1989). The same rates are applied to both nonhypertensive and hypertensive patients.

Table 1-6b shows the baseline transition probabilities for nephropathy. These numbers can be compared to the hazard rates in Table 1-6a to show the differences between hazard rates and transition probabilities in the nephropathy disease path. For example, the baseline hazard rate for microalbuminuria 0 to 11 years after diagnosis for persons without hypertension is 0.03253, while the corresponding transition probability is 0.03201. Because the hazard rate in this case is close to zero, its difference from the corresponding transition probability is small. The baseline hazard rate for clinical nephropathy 0 to 11 years after diagnosis for persons with hypertension is 0.1505, while the corresponding transition probability is 0.1397. The difference between the hazard rate and the transition probability is greater in this case because the hazard rate is larger to begin with.

Table 1-6b. Baseline Transition Probabilities: Nephropathy

	Years Since Diagnosis		
	0–11	**12–19**	**20+**
Normal to Microalbuminuria (No Hypertension)	0.02	0.02	0.02
Normal to Microalbuminuria (Hypertension)	0.02	0.02	0.02
Microalbuminuria to Clinical Nephropathy No Hypertension)	0.028	0.028	0.028
Microalbuminuria to Clinical Nephropathy (Hypertension)	0.028	0.028	0.028
Clinical Nephropathy to ESRD	0.023	0.023	0.023

Source: See text.

1.1.2 Neuropathy

Our neuropathy path includes the four states and two intermediate events that are shown in Figure 1-2. An individual who begins in the Normal state may progress to peripheral neuropathy with probability $P_{u_1u_2}$ or may remain in the Normal state with probability $P_{u_1u_1}$. An individual with peripheral neuropathy may experience an LEA with probability $P_{u_2u_L}$. At this point, the individual enters the bridge model and—within the time period—either dies and moves to LEA Death with probability $P_{u_Lu_D}$ or survives and moves to the History of LEA state with probability $P_{u_Lu_3}$. Once an individual reaches the History of LEA state, she will remain there ($P_{u_3u_3}$) unless she experiences a subsequent LEA event. The individual will enter the subsequent LEA bridge model with probability $P_{u_3u_{SL}}$. At this point, the individual either dies and moves to LEA Death with probability $P_{u_{SL}u_D}$ or survives and returns to the History of LEA with probability $P_{u_{SL}u_3}$.

Table 1-7a shows the baseline hazard rates for neuropathy. The hazard rate for peripheral neuropathy is derived from the 9-year value in Figure 8 in UKPDS 33 (1998) using Equation (1). The hazard rate for peripheral neuropathy to subsequent LEA was calculated from data

in UKPDS 33 (UK Prospective Diabetes Study Group (UKPDS 33), 1998). The probability for a subsequent LEA and the mortality rate for LEA come from Tables 18.8 and 18.10, respectively, in Reiber, Boyko, and Smith (1995). Separate hazard rates for persons with hypertension are not available from the UKPDS hypertension study; therefore, we apply the same rates to persons with and without hypertension.

Table 1-7a. Baseline Hazard Rates: Neuropathy

	Years Since Diagnosis			
	0–7	8–12	13–18	19+
Normal to Peripheral Neuropathy	0.03600	0.03600	0.03600	0.03600
Peripheral Neuropathy to LEA	0.0067	0.0067	0.0067	0.0067
History of LEA to Subsequent LEA(s) (Transition Probability)	0.11	0.11	0.11	0.11
Death from LEA (Transition Probability)	0.105	0.105	0.105	0.105
Probability of Foot Ulcers (States of Neuropathy and History of LEA)	0.04	0.04	0.04	0.04

Individuals in the neuropathy and History of LEA states are also assumed to face a 4 percent annual incidence of diabetic foot ulcers. This incidence rate is assumed to be independent of past history of foot ulcers. Estimates of the incidence of diabetic foot ulcers for the entire type 2 population include 2.6 percent for 1 year (Moss et al., 1992) and 5.8 percent cumulative incidence for 3 years (Ramsey et al., 1999). Most (78 percent) foot ulcers occur among persons with neuropathy (Reiber et al., 1995). Assuming that the annual incidence rate for all persons with type 2 diabetes is 2 percent, persons with neuropathy account for 80 percent of foot ulcers, and about 40 percent of persons with type 2 diabetes have neuropathy yields an estimated annual incidence of 4 percent for persons with neuropathy.

Table 1-7b shows the baseline transition probabilities for neuropathy. A comparison of these numbers to Table 1-7a shows the differences between hazard rates and transition probabilities in the neuropathy disease path. For example, the baseline hazard rate for peripheral neuropathy 0 to 7 years after diagnosis is 0.03600, while the corresponding transition probability is 0.03536. Because the hazard rate is close to zero, its difference from the corresponding transition probability is small. The baseline hazard rate for LEA 19+ years after diagnosis is 0.1399, while the corresponding transition probability is 0.1306. In this case, the difference between the hazard rate and transition probability is greater because the hazard rate is larger to begin with.

Table 1-7b. Transition Probabilities for Neuropathy

	Years Since Diagnosis			
	0–7	8–12	13–18	19+
Normal to Peripheral Neuropathy	0.03536	0.03536	0.03536	0.03536
Peripheral Neuropathy to LEA	0.00668	0.00668	0.00668	0.00668
History of LEA to Subsequent LEA(s) (Transition Probability)	0.11	0.11	0.11	0.11
Death from LEA (Transition Probability)	0.105	0.105	0.105	0.105
Probability of Foot Ulcers (States of Neuropathy and History of LEA)	0.04	0.04	0.04	0.04

1.1.3 Retinopathy

Table 1-8a shows the baseline hazard rates for retinopathy. The photocoagulation rate for persons with no hypertension is taken directly from Figure 5 in UKPDS 33 (1998), while the rate for persons with hypertension is taken directly from Figure 8 in UKPDS 38 (1998). Data from Figure 5 in UKPDS 38 were also used to derive the hazard rate for blindness, conditional on photocoagulation. We combined data from persons with intensive glycemic control and conventional glycemic control in the calculation, under the assumption that the hazard rate for blindness—conditional on photocoagulation—is the same for both groups. We also assumed that this rate was the same for persons with and without hypertension. We first simulated the number of patients who had progressed to photocoagulation at each year. We then calculated the blindness transition probability necessary to yield the number of patients who had progressed to blindness by the end of the study period. Finally, we converted this transition probability into a hazard rate.

Table 1-8b shows the baseline transition probabilities for retinopathy. These can be compared to the hazard rates in Table 1-8a to show the differences between hazard rates and transition probabilities.

Table 1-8a. Baseline Hazard Rates: Retinopathy

Years Since Diagnosis	Normal to Photocoagulation (No Hypertension)	Normal to Photocoagulation (Hypertension)	Photocoagulation to Blindness
All years	0.01100	0.01660	0.10650

Table 1-8b. Transition Probabilities for Retinopathy

Years Since Diagnosis	Normal to Photocoagulation (No Hypertension)	Normal to Photocoagulation (Hypertension)	Photocoagulation to Blindness
All years	0.01094	0.01646	0.1010

1.2 Cardiovascular Disease

Cardiovascular diseases, including CHD and stroke, are leading causes of mortality for persons with diabetes. In our model, CHD and stroke are treated as separate disease components using (1) probabilities generated from Anderson et al. (1990) and Weinstein et al. (1987); (2) the UKPDS risk engine, presented in UKPDS 56 and UKPDS 60 (1987), as well as other data sources; (3) a risk equations including obesity estimated by Wilson et al. (2008); or (4) the American College of Cardiology/American Heart Association (ACC/AHA) Pooled CVD Risk Equation (Goff et al., 2014). We first present the original CHD and stroke risk models from (1) in Sections 1.2.1 and 1.2.2, followed by separate sections for (2), (3), and (4).

Finally, we have created a congestive heart failure module for the model, but because of varying definitions of this condition and uncertain data, we have not validated parameters for its disease progression. Users may enter their preferred parameters.

1.2.1 Coronary Heart Disease

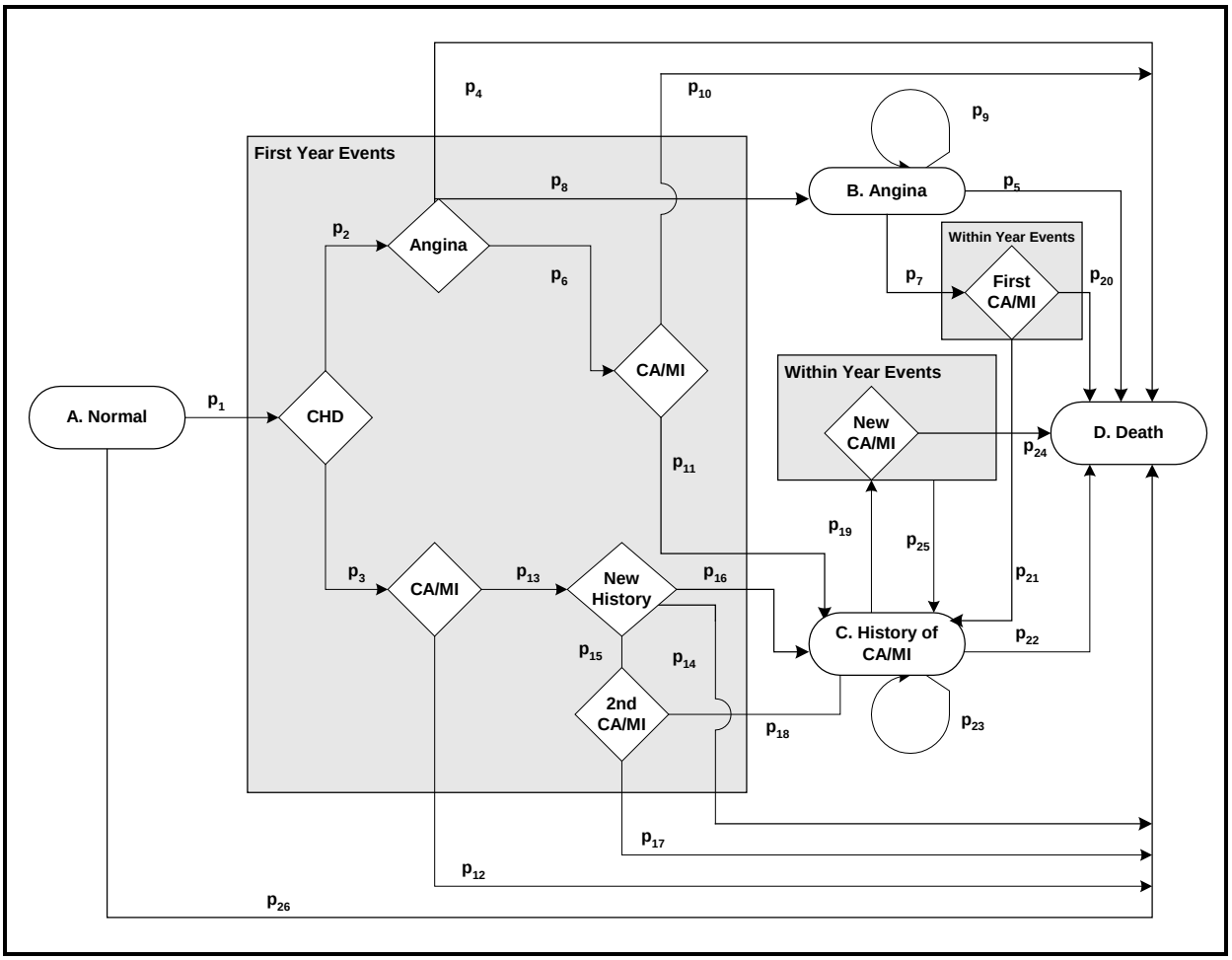
The original CHD component of our model is an abbreviated version of the Coronary Heart Disease Policy Model developed at Harvard University by Weinstein et al. (1987). The complete version of the Coronary Heart Disease Policy Model has 12 CHD states. We simplified the model by eliminating the states associated with coronary artery bypass graft surgery and by combining the CA and MI states into a single state. As a result, our model includes four CHD states: Normal, Angina, History of CA or MI, and Death. Due to the very low survival rates associated with CA, the transition probabilities given a history of CA/MI are those given a history of MI; however, mortality rates associated with CA are incorporated as appropriate. Most of the probabilities in the model are derived from the probabilities outlined by Weinstein et al. (1987) and its updated version in Hunink et al. (1997).

The basic structure for the CHD component is shown in Figure 1-6. The states labeled A (Normal), B (Angina), C (History of CA/MI), and D (Death) represent the states where individuals end up at the end of each year; these are the actual states that are programmed in the model. The remaining diamonds and arrows show what happens to the individual within the course of each year as they move between states (hence the shading for “First

Year Events" and "Within Year Events"). These events are incorporated within the model's transition probabilities, as described below.

Consider an individual beginning at A in the Normal state. With probability P_1, the individual may experience a CHD event. Otherwise, the individual either dies from a non-CHD event or remains in the Normal state. This part of our model corresponds to the Demographic–Epidemiologic model component of the Coronary Heart Disease Policy Model, so named because P_1 depends on demographic and epidemiologic factors such as age, sex, blood pressure, and cholesterol levels. Unlike the Coronary Heart Disease Policy Model, the P_1 in our model includes a variable for the presence of diabetes. P_1 is calculated from Framingham data using estimation equations developed by Anderson et al. (1990).

Figure 1-6. States and Transition Probabilities: Coronary Heart Disease, Detailed View



Following the Coronary Heart Disease Policy Model, we carefully model what happens to an individual in the first 30 days following their first CHD event. This corresponds to the bridge

model component of the Coronary Heart Disease Policy Model. If an individual experiences a first CHD event, the event may be either angina with probability P_2 or CA/MI with combined probability P_3. If the first event is angina, there is a cost associated with the immediate treatment of angina but no immediate other events. If the first event is CA or MI, the individual may either die within 30 days with probability P_{12} or survive to move to the new History of CA/MI box with probability P_{13}.

The Coronary Heart Disease Policy Model allows surviving individuals to incur a second CHD event during the remainder of the year (11 months) following the first 30 days of the first CHD event (this is part of the model's Disease History model component), and we have also incorporated this possibility within our model. Thus, an individual whose first event is angina may either die from angina-related causes (with probability P_4), experience a CA/MI (P_6), or continue on with angina (P_8) during the remainder of the year following the first CHD event. If they experience a CA/MI, they may either die within 30 days (P_{10}) or survive (P_{11}). An individual who survives an initial CA/MI may experience a second CA/MI (P_{15}), die from chronic conditions related to MI (P_{14}), or continue on with no further events (P_{16}). An individual who experiences a second CA/MI will either die within 30 days (P_{17}) or survive (P_{18}).

Thus, at the end of the first year, patients either remain at the Normal state, have angina, have a history of CA/MI, or are dead. The process repeats itself for patients in the Normal state. Patients in the Angina and History of CA/MI states can experience one additional CHD event in the following period. Angina patients can experience a first CA/MI event (P_7), with subsequent probabilities of death (P_{20}) or survival (P_{21}). Alternatively, they may die from angina-related causes (P_5) or continue with angina (P_9). Patients with a history of CA/MI can experience a new CA/MI event (P_{19}), with subsequent probabilities of death (P_{24}) or survival (P_{25}). Alternatively, they may die from chronic conditions related to MI (P_{22}) or survive with no additional CHD event (P_{23}). Naturally, patients in the death state experience no new events.

Below, we describe the derivation and source for each of the probabilities shown in Figure 1-6.

- The user has two options for calculating P_1, the probability of moving from the Normal state to CHD; P_2, the probability that the CHD event is angina; and P_3, the probability that the CHD event is a CA/MI. The two options are the Framingham Equation or the UKPDS Risk Engine. The Framingham Equation is discussed below and the UKPDS Risk Engine in section 1.2.3.

  Framingham Equation.
  Calculating the value of P_1. From Anderson et al. (1990), the probability of a new case of CHD at period t is given by

$CHD(t) = [F(t) - F(t-1)] / [1 - F(t-1)]$

where

$F(t) = 1 - \exp(-\exp\{[\ln(t) - \mu(t)] / \sigma(t)\})$
(the Weibull function)

$\mu = 15.5305 + 28.4441 \times \text{female} - 1.4792 \times \ln[\text{age}(t)] - 14.4588 \times \ln[\text{age}(t)] \times \text{female} + 1.8515 \times \ln[\text{age}(t)]2 \times \text{female} - 0.9119 \times \ln[\text{sbp}(t)] - 0.2767 \times \text{smoker}(t) - 0.7181 \times \ln[\text{totalc}(t) / \text{HDL}(t)] - 0.1759 \times \text{diagnosed diabetes} - 0.1999 \times \text{diabetes} \times \text{female} - 0.5865 \times \text{LVH}(t, \text{gender})$

sbp = systolic blood pressure

totalc = total cholesterol level

HDL = high density lipoprotein cholesterol level

LVH = left ventricular hypertrophy

$\ln(\sigma) = 0.9145 - 0.2784 \times \mu$

Note: In the current model, t was set equal to 8, to estimate an average annual mortality based on the valid range of follow-up (4 to 12 years).

Calculating the value of P_2.

P_2 = P(Angina | CHD) = 1 – P(CA/MI | CHD) = 1 – P3.

See P_3 below.

Source: Hunink et al. (1997)

Calculating the value of P_3.

P_3 = P(CA/MI | CHD) = P(CA | CHD) + P(MI | CHD)

See Table 1-9.

Source: Hunink et al. (1997)

Table 1-9. Probability that Initial Coronary Heart Disease Event is Cardiac Arrest or Myocardial Infarction

Age (years)	Probability (CA | CHD)		Probability (MI | CHD)	
	Male	Female	Male	Female
35–44	0.1024	0.0803	0.6171	0.5864
45–54	0.1070	0.0917	0.5440	0.4942
55–64	0.1085	0.0852	0.4739	0.4199
65–74	0.1297	0.0998	0.4929	0.4916
75+	0.1527	0.1793	0.5101	0.4983

Source: Hunink et al. (1997).

- P_4 = P(Death | History of Angina) * (11/12)

  See Table 1-10.

Source: Weinstein et al. (1987)

Table 1-10. Probability of Death Given a History of Angina

Age (years)	Probability (Death | History of Angina)	
	Male	**Female**
35–44	0.00460	0.00249
45–54	0.01070	0.00618
55–64	0.01841	0.01196
65–74	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al. (1987).

- P_5 = P(Death | History of Angina)

  See Table 1-10.

  Source: Weinstein et al. (1987)

- P_6 = P(CA/MI | Angina) * (11/12) * AgeRisk1

  The age-relative risk of CA or MI given a History of Angina was assumed to be equal to AgeRisk1, the age-relative risk of CA or MI given a History of CHD (Table 1-11).

  Source: Hunink et al. (1997)

Table 1-11. Relative Risk of Cardiac Arrest or Myocardial Infarction Given a History of Angina (AgeRisk1)

Age (years)	Relative Risk
35–44	0.261
45–54	0.630
55–64	1.000
65–74	1.371
75+	1.826

Source: Hunink et al. (1997).

- P_7 = P(CA/MI | Angina) * AgeRisk1

P(CA/MI | Angina) = 0.0303 for males, 0.0120 for females

- $P_8 = 1 - P_6 - P_4$
- $P_9 = 1 - P_5 - P_7$

- P_{10} = P(Death | 1st CA/MI)

  = P(Death | CA) * P(CA | CA/MI) +

  P(Death | 1st MI) * P(MI | CA/MI)

  P(CA | CA/MI) = 0.2

  P(MI | CA/MI) = 0.8

  P(Death | CA) = 1 – [P(Survival to Admission) * P(Survival to Discharge)]

  See Table 1-12.

Table 1-12. Probability of Death Given Cardiac Arrest

Age (years)	Probability		
	Survival to Hospital Admission	Survival to Discharge	Death Given CA
35–44	0.3885	0.6446	0.7496
45–54	0.3316	0.5837	0.8064
55–64	0.2747	0.4974	0.8634
65–74	0.2178	0.3661	0.9203
75+	0.1609	0.1419	0.9772

- P(Death | 1st MI) = Table 1-13

Table 1-13. Probability of Death Given the First Myocardial Infarction

Age (years)	Probability (Death | 1st MI)	
	Male	Female
35–44	0.01155	0.01155
45–54	0.0252	0.0252
55–64	0.05475	0.05475
65–74	0.119025	0.119025
75+	0.221475	0.221475

Source: Hunink et al. (1997) multiplied by 0.75, representing the 25% risk reduction experienced between 1985 and 1997 in the United States. (McGovern et al., 2001).

- $P_{11} = 1 - P_{10}$
- $P_{12} = P_{10}$
- $P_{13} = 1 - P_{12}$
- P_{14} = P(MI Chronic Death) * (11/12)

  See Table 1-14.
- P_{15} = P(Recurrent CA/MI in year of first MI | 1st MI)

  = [P(CA | History of CA/MI) + P(MI | History of CA/MI)] * (11/12) * AgeRisk1

  P(CA | History of CA/MI) = 0.01432 for males, 0.01132 for females

Table 1-14. Probability of Death from Chronic Myocardial Infarction

Age (years)	Probability (MI Chronic Death)	
	Male	Female
35–44	0.00460	0.00249
45–54	0.01070	0.00618
55–64	0.01841	0.01196
65–74	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al. (1987).

P(MI | History of CA/MI) = 0.0573 for males, 0.0453 for females

Source: Hunink et al. (1997)

The age-relative risk of MI given a History of CA/MI is assumed to be equal to AgeRisk1, the age-relative risk of CA or MI given a History of CHD (Table 1-11).

- $P_{16} = 1 - P_{14} - P_{15}$
- P_{17} = P(CA | CA/MI) * P(Death | CA) +

  P(MI | CA/MI) * P(Death | Recurrent MI)

P(CA | CA/MI) = 0.2

P(MI | CA/MI) = 0.8

P(Death | CA) = 1 – [P(Survival to Admission) * P(Survival to Discharge)]

See Table 1-12.

See Table 1-15 for probability of death given recurrent MI.

Table 1-15. Death Rates After Recurrent Myocardial Infarction

Age (years)	Probability (Death | Recurrent MI)	
	Male	Female
35–44	0.0578	0.0578
45–54	0.074667	0.074667
55–64	0.0964	0.0964
65–74	0.124467	0.124467
75+	0.196867	0.196867

See Table 1-13 for probability of death given the first MI.

- $P_{18} = 1 - P17$

- P_{19} = P(CA/MI | History of CA/MI) * AgeRisk1 = [P(CA | History of CA/MI) + P(MI | History of CA/MI)] * AgeRisk1

  P(CA | History of CA/MI) = 0.01432 for males, 0.01132 for females

  P(MI | History of CA/MI) = 0.0573 for males, 0.0453 for females

  Source: Hunink et al. (1997) multiplied by a factor of 0.67, representing the 33% risk reduction experienced between 1990 and 2000 in the U.S.

  The age-relative risk given a History of CA/MI was set equal to AgeRisk1, relative risk of MI or CA given a History of CHD (Table 1-11).

  See Table 1-13 for probability of death given the first MI.

- $P_{20} = P_{10}$
- $P_{21} = 1 - P_{20}$
- P_{22} = P(MI Chronic Death)

  See Table 1-14.

  Source: Weinstein et al. (1987)

- $P_{23} = 1 - P_{19} - P_{22}$
- $P_{24} = P_{17}$
- $P_{25} = 1 - P_{17}$

Finally, there is the chance of death from all other causes, represented by P_{26}, the transition probability from Normal to Death. This probability is incorporated into the overall model as a separate calculation done after all other transitions have taken place for the year.

These transition probabilities are based on the general population rather than on people with diabetes. In order to account for the increased risk of CHD among people with diabetes, we have adjusted the transition probabilities by multiplying them by the relative risk of CHD in a person with diabetes versus a healthy person. Relative risks are shown in Table 1-16. The relative risk of incurring an initial CHD event is already incorporated into P_1 in the form of the coefficients for diabetes.

To calculate the transition probabilities between the lettered states in the computer model, the probabilities of movement between each state must be multiplied together along every possible path between any two lettered states. The transition probability is then the sum of these products (Table 1-17).

Table 1-16. Relative Risk of Coronary Heart Disease Events Among People with Diabetes

Event	Relative Risk		Probabilities Affected
	Male	Female	
Death within 30 days after CA/MI	1.58[a]	2.60[a]	P_{10}, P_{12}, P_{17}, P_{20}, P_{24}
Death within 1 year after CA/MI	1.97[a]	4.17[a]	P_{14}, P_{22}
Second CA/MI	2.00[b]	2.00[b]	P_{15}, P_{19}

[a]Table 3 in Miettinen et al. (1998).

[b]Table 19.8 in Wingard and Barrett-Connor (1995).

Table 1-17. Transition Probabilities Between Coronary Heart Disease States

	A	B	C	D
A	$1 - P_1$	$P_1 * P_2 * P_8$	$P_1 * P_2 * P_6 * P_{11} + P_1 * P_3 * P_{13} * P_{16} + P_1 * P_3 * P_{13} * P_{15} * P_{18}$	$P_1 * P_2 * P_4 + P_1 * P_2 * P_6 * P_{10} + P_1 * P_3 * P_{12} + P_1 * P_3 * P_{13} * P_{14} + P_1 * P_3 * P_{13} * P_{15} * P_{17}$
B	0	P_9	$P_7 * P_{21}$	$P_7 * P_{20} + P_5$
C	0	0	$P_{23} + P_{19} * P_{25}$	$P_{19} * P_{24} + P_{22}$
D	0	0	0	1

1.2.2 Stroke

The stroke component of our model has three states: Normal, History of Stroke, and Death (see Figure 1-5). All individuals begin in the Normal state. The probability of experiencing a stroke is P_{S_s}. The probability of dying from the stroke within the period is given by $P_{S_sS_D}$. If the individual survives the stroke, she progresses to History of Stroke. Thus, at the end of 1 year, individuals may be in the Normal, History of Stroke, or Death states. Once an individual reaches the History of Stroke state, she may remain there ($P_{S_2S_2}$) or may die ($P_{S_2S_D}$).

The user has two options for calculating the transition probability from Normal to Stroke: the Framingham equation (Anderson et al., 1990) and the UKPDS Risk Engine (Kothari et al., 2002); the Framingham Equation is discussed below and the UKPDS Risk Engine in section 1.2.3. The other transition probabilities come from the literature (Table 1-18).

Table 1-18. Transition Probabilities: Stroke

Transition	Probability	Source	Notes
Normal to Stroke	P(S)	Anderson et al. (1990) Kothari et al. (2002)	See Table 1. Diabetes is included as a risk factor in the Anderson et al. model. See text.
Stroke to Death	Immediate (0–6 months): 0.0852	Sacco et al. (1994) multiplied by 0.6 reflecting the 40% reduction in stroke mortality between 1990 and 2000 (Koton et al., 2014)	Sacco et al. include the 1-month, 1-year, and 5-year transition probabilities. Those were converted to hazard rates from which 6-month and 1-year transition probabilities were calculated. Since this study found that history of diabetes was not a significant predictor of stroke recurrence, we chose to use the transition probabilities for the entire cohort. Alternatively, we might have used the admission glucose >140 mg/dl as a proxy for diabetes, as that was found to be a significant predictor of stroke recurrence at $p < 0.05$. However, the rest of the model's parameters are for diagnosed diabetes; therefore, using admission glucose as a proxy would be inconsistent.
History of Stroke to Death	One-year: 0.05490		

Letting s_1 = Normal, s_2 = History of Stroke, and s_D = Death, the equations for the transition probabilities from Normal to History of Stroke and Normal to Death follow:

Starting with the individuals in s_1

- the proportion who experience a stroke and die immediately (within 6 months)

  = P(s) * P(Stroke to Death, immediate) (2)

- the proportion who experience a stroke but do not die immediately

  = P(s) * [1 – P(Stroke to Death, immediate)]

- all others remain in the Normal state.

For individuals with a history of stroke (s_2)

- the percentage who die

  = P(History of Stroke to Death; 1 year)

- all others remain in the History of Stroke state.

Death is an absorbing state. The total number of individuals who have had a stroke are those who pass into state s_2 plus those who transition to death due to stroke with Equation (2).

If the Framingham equation is applied, the probability of a new case of stroke at period t is given by

$$\text{Prob}(S[t]) = [F(t) - F(t \,!\, 1)] \,/\, [1 - F(t \,!\, 1)]$$

where

$F(t) = 1 - \exp(-\exp\{[\ln(t) - \mu(t)] / \sigma(t)\})$ (the Weibull function)

$\mu = 26.5116 + 0.2019 \times \text{female} - 2.3741 \times \ln[\text{age}(t)] - 2.4643 \times \ln[\text{sbp}(t)] - 0.3914\ \text{smoker}(t) - 0.0229 \times \ln[\text{totalc}(t) / \text{HDL}(t)] - 0.3087 \times \text{diagnosed diabetes} - 0.2627 \times \text{diabetes} \times \text{female} - 0.2355 \times \text{LVH}$

$\ln(\sigma) = -0.4312$

This is the equation used for P(s) above.

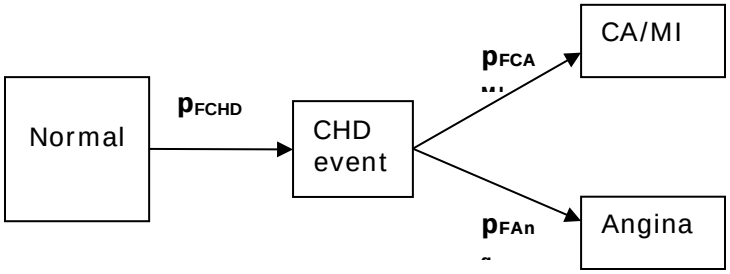
Note: In the current model, t was set equal to 8, to estimate an average annual mortality based on the valid range of follow-up (4 to 12 years).

1.2.3 UKPDS Risk Engine

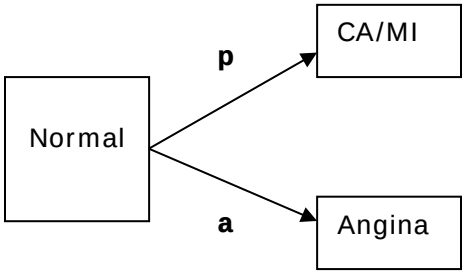
The UKPDS Risk Engine can be applied to calculate the risk of a myocardial infarction or the risk of having a stroke event. The Risk Engine calculations are based on individuals with type 2 diabetes participating in the UKPDS study.

Myocardial Infarction. The UKPDS Risk Engine calculates the probability of a myocardial infarction, whereas the Framingham equation computes the probability of angina or CA/MI. Because our model also incorporates angina as a state of CHD, we will keep the same ratio of angina to CA/MI as with the Framingham. Instead of calculating the probability of a CA/MI event or angina conditional upon a CHD event, we calculate the probability of moving from normal to CA/MI or angina in one step.

Figure 1-7. Progression to Initial CHD Event Using the Framingham Equation and the UKPDS Risk Engine



Framingham equation



UKPDS risk engine

*Calculating the value of **p** using the UKPDS Risk Engine.* From UKPDS 56, the probability of a first myocardial infarction at period t is given by

$$MI(t) = 1 - \exp(-qd^{t-1})$$

where

$$Q = q_0\beta_1^{AGE-55}\beta_2^{SEX}\beta_3^{AC}\beta_4^{SMOK}\beta_5^{h-6.72}\beta_6^{(SBP-135.7)/10}\beta_7^{\ln(LR)-1.59}$$

and

q_0 = Intercept = 0.0112
β_1 = Risk ratio for one year of age at diagnosis of diabetes = 1.059
β_2 = Risk ratio for female sex = 0.525
β_3 = Risk ratio for Afro-Caribbean ethnicity = 0.390
β_4 = Risk ratio for smoking = 1.350
β_5 = Risk ratio for 1% increase in HbA1c = 1.183
β_6 = Risk ratio for 10 mmHg increase in systolic BP = 1.088
β_7 = Risk ratio for unit increase in logarithm of lipid ratio = 3.845
d = Risk ratio for each year increase in duration of diagnosed diabetes = 1.078

and

AGE = Age (yrs) at diagnosis of diabetes

SEX = Individual's sex
1 = female, 0 = male
AC = Indicator of Afro-Caribbean race
1 = Afro-Caribbean,
0 = Caucasian or Asian-Indian
(By default, set to represent African-American)
SMOK = Indicator of smoking status
1 = current smoker at diagnosis of diabetes,
0 = non-smoker at diagnosis of diabetes
H = HbA1c (%), mean of values at years 1 and 2
SBP = Systolic BP, mean of values at years 1 and 2
LR = Total cholesterol/HDL cholesterol ratio, mean of values at years 1 and 2
T = Years since diagnosis

Notes: Regression dilution adjustments were not made, therefore assuming that HbA1c is the mean of 2 values, systolic blood pressure is the mean of 6 values (two groups of three values), and total and HDL cholesterol are each the mean of 2 values. By default, the Afro-Caribbean risk factor in the UKPDS risk engine will be applied to African American cohorts. User may turn off this assumption; in that case the Afro-Caribbean risk factor is not applied to any cohorts.

Calculating the value of **a** using the Framingham Equation.

Let p_{FCHD} = Framingham probability of CHD event,
p_{FCAMI} = P(CA/MI | CHD)
p_{FAng} = P(Angina | CHD)
p = UKPDS risk engine probability of MI
m = P(CA/MI| Normal)
a = P(Angina| Normal)

Then $p_{FCAMI} + p_{FAng} = 1$
$m = p_{FCHD} * p_{FCAMI}$
$a = p_{FCHD} * p_{Fang}$
$a = m * p_{FAng} / p_{FCAMI}$, when using either risk model, based on keeping the rate of angina relative to CA/MI the same
m = p (ignoring the CA-MI distinction)

So, $a = p * p_{FAng} / p_{FCAMI}$,
if $p_{FCAMI} > 0$ and $p * p_{FAng} / p_{FCAMI} <= 1 - p$
$a = 1 - p$, if $p_{FCAMI} = 0$ or $p * p_{FAng} / p_{FCAMI} > 1 - p$

We use one of these two equations to compute the probability of moving from the normal state to the angina state when using the UKPDS risk model. We expect $p_{FCAMI} > 0$ generally, so the second equation will usually be used only when the first equation gives a value that makes the sum (p + a) larger than 1.

Using this calculation strategy, P_1 is never explicitly defined. We assume, though, that $P_1 * P_2 = a$ and $P_1 * P_3 = m$.

Stroke. UKPDS Risk Engine uses the method outlined in UKPDS 60 to calculate the probability of a first stroke (P(s)) during period t. This calculation involves the same equation used to calculate the risk of CHD, except that the value of q is calculated using a slightly different formula and different coefficients.

$$\text{Stroke}(t) = 1 - \exp(-qd^{t-1})$$

where

$$q = q_0\beta_1^{AGE-55}\beta_2^{SEX}\beta_4^{SMOK}\beta_5^{h-6.72}\beta_6^{(SBP-135.5)/10}\beta_7^{LR-5.11}\beta_8^{AF}$$

and

q_0 = Intercept = 0.00186

β_1 = Risk ratio for one year of age at diagnosis of diabetes = 1.092

β_2 = Risk ratio for female sex = 0.700

β_4 = Risk ratio for smoking = 1.547

β_6 = Risk ratio for 10 mmHg increase in systolic BP = 1.122

β_7 = Risk ratio for unit increase in lipid ratio = 1.138

β_8 = Risk ratio for atrial fibrillation = 8.554

d = Risk ratio for each year increase in duration of diagnosed diabetes = 1.145

and

AF Atrial fibrillation at diagnosis of diabetes, 1 = yes, 2 = no

The definitions for AGE, SEX, SMOK, SBP, LR and T are defined in above in the Risk Engine calculations for myocardial infarction.

1.2.4 Wilson Equations

The Wilson CHD and stroke equations (Wilson et al., 2008) enter the model similarly to the original CHD and stroke equations described in Sections 1.2.1 and 1.2.2. The biggest difference is that the Wilson equations include BMI as an explanatory variable.

- The risk of CHD by time t is given by:

  1 – S(t) (note: t is in days)

  where the predicted survival function until time t is:

  $$S(t) = \exp\{ - [t * \exp\{ - L(x)\}]^{1/\Phi}$$

Φ = .7303 and is the Weibull shape parameter

and L(x) = 14.9756 − 0.0159*BMI − 0.0571*Age − 0.4959*current smoker − 0.007044*SBP −.01432*totalc/HDL ratio − 0.3421*diabetes + 0.1539*sex

- Sex (1 if female, 0 if male)
- SBP = systolic blood pressure
- Totalc/HDL ratio = total cholesterol to HDL ratio
- Diabetes (1 if yes, 0 if no)
- Age
- Current smoker (1 if yes, 0 if no)
- BMI = body mass index

The risk of stroke by time t is given by:

1 – S(t) (note: t is in days),

where the predicted survival function until time t is:

$$S(t) = \exp\{ - [t * \exp\{ - L(x)\}]1/\Phi$$

L(x) = 14.6574 − 0.0227*BMI − 0.0450*Age − 0.2584*current smoker − 0.007879*SBP −.0596*totalc/HDL ratio

Φ = .4978 and is the Weibull shape parameter

1.2.5 American College of Cardiology/American Heart Association (ACC/AHA) Pooled CVD Risk Equation (Goff et al., 2014)

Recent studies have suggested that UKPDS-based risk predictions consistently overestimate the risk of CVD and mortality. However, while there appear to be inconsistencies between UKPDS-based predicted risk and real-world observations for macrovascular complications, the mismatch may be due to differences in the underlying population, changing lifestyles, and new treatment options. This mismatch might not be substantial for microvascular complications. Moreover, there are no other sources for developing a risk equation for microvascular complications (CARDIA, ARIC, and CHS do not report these). The Wisconsin Epidemiologic Study of Diabetic Retinopathy, used in the ECHO-T2DM, included a type 1 diabetes population. Therefore, we primarily focused on updating primarily the CVD module.

ACC/AHA recently developed risk equations to estimate the 10-year atherosclerotic cardiovascular disease (ASCVD) risk to guide statin initiation in non-Hispanic black and non-Hispanic white men and women aged 40 to 79 (Goff et al., 2014).

Currently, the CDC-RTI model includes separate equations for CHD and stroke. We decided to use the ACC/AHA equation that calculates a single equation for the first-time ASCVD

event. **A CVD event is defined as nonfatal MI or CHD death or fatal or nonfatal stroke among people free from ASCVD at the beginning of the period**. Angina is not included in this definition of CVD. The authors state that angina (and heart failure) are endpoints with poor reliability. Heart failure was also not included in the composite outcome because the adjudication of heart failure varied considerably across studies. Also, because of geographical variation, self-selection, and physician recommendation biases, coronary revascularization was not included. Goff et al. (2014) do not provide a breakthrough count of the CVD components. Table 1-19 shows the incidence of ASCVD over a 10-year period for people aged 40 to 79 by sex and race.

Table 1-19. 10-Year Incidence of ASCVD in the Pooled ACC/AHA Sample by Sex and Race

Category (40–79 yrs)	ASCVD	No ASCVD	Total	10 year %
White women	902	10,338	11,240	8%
White men	1,259	7,839	9,098	14%
Black women	290	2,351	2,641	11%
Black men	238	1,409	1,647	14%

Source: Appendix 4, Description of the derivation and validation of the Pooled Cohort Equations. A web-based application enabling estimation of 10-year and lifetime risk of ASCVD is available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx

The ACC/AHA risk equations have been assessed for calibration and discrimination by at least two studies: Muntner et al. (2014), using data from the REGARDS study, and DeFilippis et al. (2015), using data from the MESA study. The benefit of the ACC/AHA is that it has been tested on both white and black and on both men and women, irrespective of diabetes status (diabetes is one risk factor). The ACC/AHA equations use the most recent 10-year data from the Coronary Artery Risk Development in Young Adults (CARDIA), Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), and Framingham studies to predict macrovascular outcomes.

Goff et al. (2014) use an exponential model. This means constant risk over time. The hazard function (instantaneous chance of failure at time t conditional on having survived to time t) is:

$$h(t) = h_o(t)\exp(\beta_j x_j) = \exp(\lambda + \beta_j x_j)$$

The cost-effectiveness model requires the annual incidence rate. The parameters needed to calculate the annual probability of an event in the model are: $\lambda, \beta,$ and t (i.e., time over which the model has been estimated).

The unconditional probability of an event occurring between time t and t + 1 can be calculated using the integrated hazard:

$$H(t) = \exp\left(\lambda + \beta_j x_j\right) t$$

The 1-year probability is then estimated as follows:

$$\hat{H} = 1 - \exp(H(t) - \mathrm{H}(t+1))$$

Table 1-20 shows the ACC/AHA equations.

Table 1-20. The ACC/AHA Equations Parameters of the Pooled Cohort Equations for Estimation of 10-Year Risk of CVD

Factors	White Women	Black Women	White Men	Black Men
Ln Age	-29.80	17.114	12.344	2.469
(Ln Age)^2	4.88	0	11.853	0.302
Ln Total cholesterol	13.54	0.94	0	0
Ln Age x Ln Total cholesterol	-3.11	0	-2.664	0
Ln HDL-C	-13.58	-18.92	-7.99	-0.307
Ln Age x Ln HDL- C	3.15	4.475	1.769	0
Ln Treated Systolic BP	2.02	29.291	1.797	1.916
Ln Age × Ln Treated Systolic BP	0.00	-6.432	0	0
Ln Untreated Systolic BP	1.96	27.82	1.764	1.809
Ln Age × Ln Untreated Systolic BP	0.00	-6.087	0	0
Current Smoker	7.57	0.691	7.837	0.549
Ln Age × Current Smoker	-1.67	0	-1.795	0
Diabetes	0.66	0.874	0.0658	0.645
Mean (Coeff x Value)	-29.18	86.61	61.18	19.54
Baseline Survival	0.9665	0.9533	0.9144	0.8954

Because the ACC/AHA equation estimates the combined probability of MI, CHD death, and nonfatal and fatal strokes, the model divides the first event between MI/CHD and stroke. The user can set this distribution by age and sex. The default split is 0.5/0.5.

Angina is not included as an outcome in the ACC/AHA risk equation. Therefore, when using the Pooled Risk CVD equation, model users should set CHDl parameters to ensure that angina does not occur. This can be done by setting the initial distribution of angina to zero and setting the sum of the CA-given CHD and MI-given CHD parameters equal to 1 (to

access these parameters, choose Input→Disease parameters→Coronary heart disease and choose the respective tabs.

1.2.6 Congestive Heart Failure

The model includes a module for congestive heart failure (CHF). Users can set hazard rates by age and sex; by hazard rate ratios for diabetes, hypertension, angina, and history of CA/MI; or by mortality rates, and costs. Because definitions of CHF vary and there is limited data on CHF progression, default values for the hazard rates and hazard rate ratios are currently set to 0.

1.3 Death

In this model the patient can die from five different causes:

- ESRD,
- LEA,
- CHD,
- stroke, and
- other causes.

The first four causes of death are all related to disease paths specific to patients with diabetes. The final mode of death is the general, nonspecific population death rate from other causes. Patients who have ESRD face a higher mortality risk than patients without ESRD. Patients who require LEA have a risk of dying from the surgical procedure. Patients with CHD can die from CA, MI, or sudden death. Once a patient has experienced a CHD event, they face a higher mortality risk than patients who have not had one. Patients experiencing stroke can die immediately; if they survive, they face higher mortality rates in subsequent periods.

Mortality rates from ESRD are a function of the cohort's age, sex, and race/ethnicity as shown in Table 1-21. We assume that a person does not die during the period in which he or she develops ESRD.

Table 1-21. Mortality Rate for End Stage Renal Disease

	Male (%)					Female (%)				
Age	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian
0	6.06	8.40	6.06	8.40	6.06	6.49	10.42	6.49	10.42	6.49
5	6.06	8.40	6.06	8.40	6.06	6.49	10.42	6.49	10.42	6.49
10	6.06	8.4	6.06	8.4	6.06	6.49	10.42	6.49	10.42	6.49
15	4.85	8.4	4.85	8.4	4.85	7.3	10.42	7.3	10.42	7.3
20	16.3541	16.472	16.3541	16.472	16.3541	12.8484	9.3351	12.8484	9.3351	12.8484
25	6.3472	10.0662	6.3472	10.0662	6.3472	9.5803	11.8274	9.5803	11.8274	9.5803
30	7.8117	9.032	7.8117	9.032	7.8117	6.7261	9.1256	6.7261	9.1256	6.7261
35	7.6914	8.4827	7.6914	8.4827	7.6914	7.7624	10.6717	7.7624	10.6717	7.7624
40	8.6004	9.3365	8.6004	9.3365	8.6004	8.8369	11.0483	8.8369	11.0483	8.8369
45	10.836	11.4307	10.836	11.4307	10.836	11.4072	13.0393	11.4072	13.0393	11.4072
50	13.4325	11.8147	13.4325	11.8147	13.4325	15.114	14.9905	15.114	14.9905	15.114
55	16.7303	14.3244	16.7303	14.3244	16.7303	18.7829	15.4213	18.7829	15.4213	18.7829
60	20.9754	16.2196	20.9754	16.2196	20.9754	22.1453	16.8661	22.1453	16.8661	22.1453
65	25.1463	19.6442	25.1463	19.6442	25.1463	25.6583	19.4291	25.6583	19.4291	25.6583
70	29.7632	23.3343	29.7632	23.3343	29.7632	29.5196	23.1637	29.5196	23.1637	29.5196
75	35.4557	28.1839	35.4557	28.1839	35.4557	34.9875	27.1324	34.9875	27.1324	34.9875
80	39.6129	33.4248	39.6129	33.4248	39.6129	38.6878	31.5088	38.6878	31.5088	38.6878
85	49.5909	42.6955	49.5909	42.6955	49.5909	43.3882	40.0003	43.3882	40.0003	43.3882
90	49.5909	42.6955	49.5909	42.6955	49.5909	43.3882	40.0003	43.3882	40.0003	43.3882
95	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Source: Dong, Orians, and Manninen (1997).

The mortality rate from LEA in the United States was found in Table 18.10 in Reiber, Boyko, and Smith (1995) and is not dependent on any other variables. The 1-year probability of death from LEA is

$$P(LEA\_M) = 10.5 \text{ percent}$$

The portion of individuals in U_2 who

- have an LEA and then die immediately from the LEA

$$= P(LEA) * P(LEA\_M) \quad (3)$$

- have an LEA and survive the initial operation

= P(LEA) * [1 – P(LEA_M)]

- all others remain in the peripheral neuropathy state.

The probability of having a subsequent amputation in the United States was found in Table 18.8 in Reiber, Boyko, and Smith (1995). We averaged two estimates from studies conducted in the United States to calculate our estimate. The probability of a subsequent amputation is

P(Subsequent LEA) = 11 percent

The proportion of individuals in u_3 who

- have a subsequent LEA and die immediately from the LEA

  = P(Subsequent LEA) * P(LEA_M)

- have a subsequent LEA and survive

  = P(Subsequent LEA) * [1 – P(LEA_M)]

- remain in u_3

  = 1 – P(Subsequent LEA)

We assume that the probability of death after a subsequent LEA is equal to the probability of death after the initial amputation. We also assume that the costs of any subsequent amputation are equal to the costs of the initial amputation. We make no distinction between the second, third, fourth, etc. amputations in terms of probabilities or costs. The total number of individuals who have had an LEA are those who are in state u_3 at the end of the simulation plus those individuals who have transitioned to death from LEA or subsequent LEA.

CHD mortality is calculated as described in Section 1.2.1, and stroke mortality is calculated from Table 1-18. The model calculates the mortality rate from other causes by first subtracting CVD mortality (i.e., CHD + stroke mortality) from all-cause mortality and then allowing for the possibility that other cause mortality is higher for persons with diabetes than for persons without diabetes, using the following steps.

1. Divide total all-cause mortality into two parts: CVD mortality and other-cause (OC) mortality.
   a. Total mortality = CVD mortality + OC mortality
2. Focus on OC mortality. The model estimates CHD and stroke mortality separately, so we do not have to worry about that.
   a. OC mortality = OCt = Total mortality – CVD mortality

b. Use mortality rates by cause to calculate 2a by age, sex, race

3. We can rewrite OC mortality as

OCt = θ OC diabetes + (1 − θ) OC − no diabetes = θ OCd + (1 − θ) OCnd, where θ = probability of having diabetes.

We can write OCd = RR OCnd, where RR ≥ 1 is the relative risk for persons with diabetes

Then, OCnd = OCd/RR, so

OCt = θ OCd + (1 − θ) OCd/RR =

$$OCd\,\frac{\theta RR + 1 - \theta}{RR} = OCd\,\frac{1 + \theta(RR - 1)}{RR}$$

Then solving for OCd, we get $OCd = OCt\,\frac{RR}{1 + \theta(RR - 1)}$ =

$$(TotMort - CVDMort)\,\frac{RR}{1 + \theta(RR - 1)}$$

Note that the second term =1 if RR=1 or θ=0.

If 0 < θ <1, then the second term is > 1 if RR > 1.

U.S. all-cause mortality is shown in Table 1-22, and CVD mortality is shown in Table 1-23.

Table 1-22. All-Cause Mortality Rate

	Age						
Sex	Minimum	Maximum	White	African American	Hispanic	Asian	Native American
Female	0	0	0.5136	1.1499	0.5351	0.5136	0.5136
Female	1	4	0.0244	0.0409	0.0243	0.0244	0.0244
Female	5	9	0.0116	0.0201	0.0113	0.0116	0.0116
Female	10	14	0.0142	0.0219	0.0127	0.0142	0.0142
Female	15	19	0.0404	0.0407	0.0297	0.0404	0.0404
Female	20	24	0.0443	0.067	0.0339	0.0443	0.0443
Female	25	29	0.0488	0.0947	0.0377	0.0488	0.0488
Female	30	34	0.0643	0.1295	0.0442	0.0643	0.0643
Female	35	39	0.0989	0.1926	0.0686	0.0989	0.0989
Female	40	44	0.1566	0.3157	0.1098	0.1566	0.1566
Female	45	49	0.238	0.4701	0.1707	0.238	0.238
Female	50	54	0.3381	0.6764	0.2561	0.3381	0.3381
Female	55	59	0.5276	0.9438	0.4179	0.5276	0.5276
Female	60	64	0.8556	1.3763	0.639	0.8556	0.8556

(continued)

Table 1-22. All-Cause Mortality Rate (continued)

Sex	Age		White	African American	Hispanic	Asian	Native American
	Minimum	Maximum					
Female	65	69	1.3381	1.9655	1.0277	1.3381	1.3381
Female	70	74	2.1532	2.8998	1.6342	2.1532	2.1532
Female	75	79	3.4563	4.3885	2.6699	3.4563	3.4563
Female	80	84	5.8177	6.5782	4.3343	5.8177	5.8177
Female	85	93	13.4509	12.8969	9.253	13.4509	13.4509
Female	94	94	100	100	100	100	100
Male	0	0	0.6316	1.4142	0.6365	0.6316	0.6316
Male	1	4	0.0294	0.0486	0.0302	0.0294	0.0294
Male	5	9	0.0151	0.0231	0.0138	0.0151	0.0151
Male	10	14	0.0206	0.0286	0.0198	0.0206	0.0206
Male	15	19	0.0871	0.121	0.0965	0.0871	0.0871
Male	20	24	0.1291	0.2101	0.1309	0.1291	0.1291
Male	25	29	0.1232	0.2447	0.1088	0.1232	0.1232
Male	30	34	0.1308	0.2599	0.1097	0.1308	0.1308
Male	35	39	0.1809	0.3236	0.1515	0.1809	0.1809
Male	40	44	0.2728	0.4671	0.2223	0.2728	0.2728
Male	45	49	0.4123	0.7668	0.3433	0.4123	0.4123
Male	50	54	0.6078	1.1866	0.518	0.6078	0.6078
Male	55	59	0.8558	1.6687	0.7067	0.8558	0.8558
Male	60	64	1.3437	2.3744	1.1182	1.3437	1.3437
Male	65	69	2.0559	3.2427	1.6068	2.0559	2.0559
Male	70	74	3.2193	4.5873	2.5141	3.2193	3.2193
Male	75	79	5.1232	6.747	3.9901	5.1232	5.1232
Male	80	84	8.2144	9.2292	6.105	8.2144	8.2144
Male	85	93	15.2507	14.4525	9.9328	15.2507	15.2507
Male	94	94	100	100	100	100	100

Source: CDC Wonder, 2004 all-cause mortality.

Table 1-23. CVD Mortality

Sex	Age		White	African American	Hispanic	Asian	Native American
	Minimum	Maximum					
Female	0	14	0	0	0	0	0
Female	15	19	0.0003	0	0	0.0003	0.0003
Female	20	24	0.0006	0	0	0.0006	0.0006
Female	25	29	0.0014	0.0068	0	0.0014	0.0014
Female	30	34	0.0034	0.0098	0.0013	0.0034	0.0034
Female	35	39	0.008	0.0169	0.0045	0.008	0.008
Female	40	44	0.0162	0.0507	0.0107	0.0162	0.0162
Female	45	49	0.0291	0.0871	0.0231	0.0291	0.0291
Female	50	54	0.0469	0.1445	0.0386	0.0469	0.0469
Female	55	59	0.0821	0.2118	0.0748	0.0821	0.0821
Female	60	64	0.1474	0.332	0.1453	0.1474	0.1474
Female	65	69	0.2549	0.514	0.2539	0.2549	0.2549
Female	70	74	0.4686	0.8082	0.4599	0.4686	0.4686
Female	75	79	0.8657	1.3358	0.8842	0.8657	0.8657
Female	80	84	1.7154	2.1886	1.5862	1.7154	1.7154
Female	85	94	4.673	4.5843	4.0875	4.673	4.673
Male	0	14	0	0	0	0	0
Male	15	19	0.0003	0	0	0.0003	0.0003
Male	20	24	0.0011	0.0018	0	0.0011	0.0011
Male	25	29	0.0035	0.0076	0.0012	0.0035	0.0035
Male	30	34	0.008	0.0183	0.0047	0.008	0.008
Male	35	39	0.0187	0.0357	0.0117	0.0187	0.0187
Male	40	44	0.0439	0.0763	0.028	0.0439	0.0439
Male	45	49	0.083	0.1598	0.0574	0.083	0.083
Male	50	54	0.1417	0.287	0.1156	0.1417	0.1417
Male	55	59	0.2169	0.441	0.1903	0.2169	0.2169
Male	60	64	0.348	0.6665	0.3118	0.348	0.348
Male	65	69	0.5291	0.9079	0.4988	0.5291	0.5291
Male	70	74	0.8459	1.3185	0.8238	0.8459	0.8459
Male	75	79	1.4272	1.9181	1.3228	1.4272	1.4272
Male	80	84	2.482	2.6966	2.1165	2.482	2.482
Male	85	94	5.0345	4.4287	3.916	5.0345	5.0345

Source: CDC Wonder, 2004 CVD mortality, except for Hispanic rates which are based on 2003 data.

Prevalence estimates (θ *100) are shown in Table 1-24. Users may set the relative risk of death for persons with diabetes as a multiple of the risk for persons without diabetes. The default value is 2 based on NHANES analyses by Gregg et al. (2007).

Table 1-24. Prevalence by Age

		Age					
		0–24	25–44	45–64	65–74	75+	0–44
Race	Sex	Rate	Rate	Rate	Rate	Rate	Rate
White	Male	0.33	2.2	10.1	20.0	16.4	1.3
	Female	0.36	2.5	8.6	15.4	13.4	1.4
Black	Male	0.54	3.8	16.9	26.6	22.0	1.7
	Female	0.36	3.4	15.9	28.7	29.1	1.7
Hispanic	Male	0.17	2.4	13.3	31.2	22.7	1.1
	Female	0.29	2.6	15.9	27.7	22.3	1.3

Source: http://www.cdc.gov/diabetes/statistics/prev/national/fig2004.htm; prevalence for ages 0–24 and 25–44 were estimated from overall 0–44 rate.

2. INTERVENTIONS

The model considers a series of interventions including intensive glycemic control, interventions for each CVD risk factor (hypertension, high cholesterol, and smoking), the polypill (a proposed single pill containing a statin, three drugs that lower blood pressure, aspirin, and folic acid), and bariatric surgery. Users can specify costs and effectiveness for the generic intervention.

2.1 Glycemic Control

Intensive glycemic control is incorporated into the model by adjusting the baseline hazard rate using the ratio between HbA_{1c} under intensive control and HbA_{1c} under conventional treatment raised to an exponent that varies across progression steps. The adjusted hazard rates are given by

$$h^*_{i,j}(t) = h_{i,j}(t) \times [g(t)/G(t)]^{\beta i,j}$$

where

$h^*_{i,j}(t)$ = the adjusted hazard rate for going from state i to state j at time t,
$h_{i,j}(t)$ = the baseline hazard rate for going from state i to state j at time t,
$g(t)$ = the glycemic level under intensive glycemic control,
$G(t)$ = the glycemic level under conventional glycemic control, and
$\beta i,j$ = a positive exponent associated with the transition from i to j.

The Diabetes Control and Complications Research Group (1995a) shows that progression rates for type 1 diabetes depend on glycemic levels using a similar equation, with the exponents varying between progression steps. Following Eastman et al. (1997a), we assume that this general functional form also holds for type 2 diabetes. This form allows us to analyze the effects of alternative interventions that have smaller or larger effects on glycemic control. The glycemic levels under intensive and conventional glycemic control are approximated by

$$g(t) = \min(mx, ini + rcbf*on - imp + rcaf*t)$$

$$G(t) = \min(mx, ini + rcbf*on - imp + rcaf*t)$$

where

mx = maximum level
ini = initial HbA_{1c} at onset
rcbf = rate of change for HbA_{1c} before treatment
on = time between onset of disease and diagnosis (assumed to be the same for each cohort)

imp = treatment impact
rcaf = rate of change after treatment
t = time since diagnosis

The values for these variables, shown in Table 2-1, are derived from UKPDS 33 (1998) and Dong, Orians, and Manninen (1997).

Table 2-1. Rate of Change of Glycemic Levels

	Conventional Glycemic Control G(t)	Intensive Glycemic Control g(t)	Source
Initial HbA_{1c} at Onset	6.8	6.8	Dong, Orians, and Manninen (1997)
Annual Rate of Change for HbA_{1c} Before Treatment	0.2	0.2	Dong, Orians, and Manninen (1997)
Years Between Onset and Diagnosis	10	10	Assumption
Treatment Impact	–2.0	–2.9	UKPDS 33 (1998)
Rate of Change After Treatment	0.2	0.2	UKPDS 33 (1998)
Max Level Without Treatment	12.0	12.0	Dong, Orians, and Manninen (1997)
Max Level With Treatment	11.0	9.0	Dong, Orians, and Manninen (1997)

Source: Dong, Orians, and Manninen (1997).

Intensive glycemic control has significant effects on the progression rates for microalbuminuria, nephropathy, peripheral neuropathy, and photocoagulation (UKPDS 33, 1998). Table 2-2 shows the differences between conventional and intensive control for each progression step. The relative risk reduction associated with intensive glycemic control is given by the ratio of the hazard rate for intensive control to the hazard rate for conventional control.

Table 2-2. Hazard Rates for Conventional and Intensive Glycemic Control

Health State	Conventional Glycemic Control	Intensive Glycemic Control	Beta
Microalbuminuria	0.032531	0.023709	2.62
Proteinuria	0.07497	0.065611	1.08
Peripheral Neuropathy	0.03600	0.02940	1.67
Photocoagulation	0.01100	0.00790	2.74

Source: UKPDS 33 (1998).

We derived an implied $\beta_{i,j}$ by setting the risk reduction equal to $(7.0/7.9)^{\beta_{i,j}}$ and solving for $\beta_{i,j}$. The average glycemic level for patients with intensive control in the UKPDS is 7.0, and the corresponding level for patients with conventional control is 7.9. For example, in the case of microalbuminuria, we solve $(7.0/7.9)^{\beta_{i,j}} = (0.023709/0.032531)$, yielding a $\beta_{i,j}$ of 2.62.

In the UKPDS, intensive glycemic control was associated with a 16 percent relative risk reduction in MI, and this reduction just missed significance at the 5 percent level ($p = 0.052$). In our baseline model, we assume that intensive glycemic control has no effect on the probability of CHD. In sensitivity analyses, we allow intensive glycemic control to reduce the probability of CHD by 16 percent. The association between intensive glycemic control and stroke did not approach significance in the UKPDS ($p = 0.52$); therefore, we do not include glycemic control effects on stroke in our model.

Two methods can be used to determine the time that tight glycemic control starts – time since diabetes onset and HbA1c level. We assume by default that individuals receive standard control for the first 10 years after onset, then tight glycemic control thereafter.

2.2 Hypertension

In our model, the intensive hypertension control intervention affects the probabilities of CHD and stroke. Intensive hypertension control also reduces the hazard rates for nephropathy and retinopathy. The model only applies this intervention to cohorts who have hypertension.

The percentage of persons with diabetes who have hypertension comes from Appendix 7.19 on p. 149-50 of *Diabetes in America* where hypertension is defined as systolic blood pressure greater than or equal to 160 mm Hg *or* diastolic blood pressure greater than or equal to 95 mm Hg *or* person taking anti-hypertensive medications. Average blood pressure levels by age group are shown in Table 2-3. To estimate these levels, we used NHANES III

data. Levels for persons with hypertension are based on measurements for individuals with diabetes who have hypertension and are not receiving anti-hypertensive medications.

2.2.1 Risk Reduction

The effects of the blood pressure interventions are modeled as a reduction in the risk of a CHD event. The efficacy of the hypertension interventions comes from the United Kingdom Prospective Diabetes Study (UKPDS) (1998). Because the results of the UKPDS showed that an ACE inhibitor and a beta blocker were equally effective in reducing the likelihood of CHD, we present results for a "hypertension intervention" rather than results for individual hypertension drugs. These risk reductions are presented in Table 2-4.

Table 2-3. Blood Pressure Levels, by Age

Age Group	No Hypertension		Hypertension	
	Normal Systolic	Normal Diastolic	Above Normal Systolic	Above Normal Diastolic
25–34	118	73	160	99
35–44	115	74	160	99
45–54	122	76	168	93
55–64	128	74	164	92
65–74	134	71	168	81
75–84	135	70	174	73
85–94	142	72	172	78

Table 2-4. Risk Reduction in Likelihood of Coronary Heart Disease

Treatment	Risk Reduction	Relative to	Source
Moderate	13% (relative to no treatment)	No treatment	Inferred from UKPDS 38
Intensive	0%—base analysis 21%—sensitivity analysis	Moderate treatment	UKPDS 38

According to the UKPDS results, the risk reduction associated with intensive control relative to moderate control is 21 percent. However, this risk reduction was not significant ($p=0.13$). Therefore, in our base analyses of hypertension control, we assume that intensive control does not reduce CHD risk. In sensitivity analyses, we assume that the risk reduction is 21 percent.

The risk reduction associated with moderate control relative to no treatment was not calculated in the study. Based on the UKPDS, we have assumed that all persons with hypertension receive at least moderate control. Therefore, the model's default setting is moderate control. We calculated an implied risk reduction for the probability of progressing from Normal to CHD under moderate control using the Framingham equation and the UKPDS data. We first entered the UKPDS population characteristics into the Framingham equation to determine the probability of CHD without treatment. We then calculated the probability of CHD for the moderate control treatment group and again for the intensive control group. We found that 5/12 of the total reduction in risk of CHD is achieved between no control and moderate control and 7/12 of the total reduction is achieved between moderate control and intensive control. We know from the UKPDS results that the reduction in risk from intensive control reduced the probability of progressing from Normal to CHD by 21 percent relative to moderate control (for this calculation, we use the UKPDS point estimate, rather than a zero effect). Therefore, the new absolute level of risk under intensive control

$= (1 – 0.21)(1 – x)$, where x is the risk reduction associated with moderate control

The total change in risk

$= 1 – x + [x – (1 ! 0.21)(1 – x)]$

$= 1 – (1 – 0.21)(1 – x) = 1 – 0.79(1 – x) = 0.21 + 0.79x$

Since we know that the reduction in risk between no control and moderate control is 5/12 of the total reduction in risk,

$x = 5/12(0.21 + 0.79x)$

$x = 0.3292 + 0.0875x$

$x = 0.1304$

Therefore, the reduction in risk due to moderate control is 13.0 percent. Thus, $P_1(\text{moderate}) = P_1(1 – 0.13)$ and $P_1(\text{intensive}) = P_1(1 – 0.13)(1 – 0.21)$.

The reduction in the risk of stroke from a hypertension intervention is modeled in a similar fashion. As above, we calculated an implied risk reduction for the probability of progressing from Normal to Stroke under moderate control using the Framingham equation and the UKPDS data. We again assume that all persons with hypertension receive at least moderate

control. The probability of progressing from Normal to nonfatal or fatal Stroke with moderate control is reduced by 17 percent. Thus, $P_{S_1S_2}(\text{moderate}) = P_{S_1S_2}(1 - 0.17)$.

The reduction in risk of fatal or nonfatal Stroke associated with intensive control comes from the UKPDS. They found that the risk of Stroke was reduced by 44 percent. Thus, $P_{S_1S_2}(\text{intensive}) = P_{S_1S_2}(1 - 0.17)(1 - 0.44)$. These risk reductions are presented in Table 2-5.

Table 2-5. Risk Reduction in Likelihood of Stroke

Treatment	Risk Reduction	Source
Moderate	17% (relative to no treatment)	Inferred from UKPDS 38 (1998)
Intensive (Atenolol or Captopril)	44% (relative to moderate treatment [diuretic])	UKPDS 38 (1998)

Hypertension control for patients with a History of CHD or Stroke (i.e., secondary prevention) has long been accepted practice. Our model assumes that all patients with a History of CHD or Stroke receive hypertension treatment. The effects of this treatment are assumed to be incorporated within the corresponding transition probabilities. The costs of continuing hypertension treatment are included in all post-CHD and post-Stroke stages.

In the UKPDS hypertension study (UKPDS 38, 1998), persons with type 2 diabetes and hypertension had faster rates of progression to microalbuminuria, clinical nephropathy, and photocoagulation than persons with type 2 diabetes and no hypertension. In addition, intensive hypertension control significantly reduced the rates of progression for these complications. In our model, persons with hypertension have higher baseline hazard rates for photocoagulation than persons without hypertension (see Table 1-8a). Intensive hypertension control intervention reduces the hazard rates for these complications, as shown in Table 2-6. Hypertension status has no effect on the other nephropathy, neuropathy, and retinopathy hazard rates in the model.

Table 2-6. Photocoagulation Hazard Rates for Conventional and Intensive Hypertension Control

Transition	Conventional Hypertension Control	Intensive Hypertension Control
Photocoagulation	0.01660	0.01020

Source: UKPDS 38 (1998).

2.3 Cholesterol

In the model, interventions that reduce cholesterol lower the probability of CHD and stroke. Cholesterol reduction interventions are only applied to cohorts with high cholesterol.

In order to identify cohorts with high cholesterol we must define normal and above normal cholesterol levels. We defined normal total cholesterol as less than 200 mg/dL and above normal total cholesterol as greater than or equal to 200 mg/dL. These definitions come from the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (1993). We combined the borderline-high blood cholesterol together with the high-blood cholesterol to provide a conservative estimate for above normal cholesterol. This information was used in the Framingham calculations to determine the risk for MI and stroke. The equation also requires an HDL estimate. We used the average HDL level for persons in the normal and above normal total cholesterol groups in the NHANES III data. Average cholesterol levels by age are shown in Table 2-7.

2.3.1 Primary Prevention

Our estimates of risk reduction achieved with cholesterol reduction come from two studies, the West of Scotland Coronary Prevention Study (pravastatin) (Shepherd et al., 1995) and the Helsinki Heart Study (gemfibrozil) (Huttunen et al., 1988). Both of these were randomized, controlled clinical trials. Unlike the secondary prevention trials, the data we present here are not subgroup analyses of persons with diabetes. We have been unable to find primary prevention cholesterol trials among persons with diabetes. Therefore, we use data for the general population.

Table 2-7. Cholesterol Levels, by Age

Age Group	Normal Total Cholesterol	Normal HDL	Above Normal Total Cholesterol	Above Normal HDL
25–34	168	49	228	49
35–44	172	51	233	48
45–54	174	49	238	49
55–64	175	47	243	52
65–74	174	49	241	52
75–84	175	48	244	53
85–94	175	48	244	53

The risk reductions in major CHD attained in the trials were very similar. Pravastatin and gemfibrozil produced risk reductions of 31 percent and 34 percent, respectively. Because these reductions come from primary prevention trials, they will affect the probability of CHD (P_1).

2.3.2 Secondary Prevention

The cholesterol risk reduction estimates come from two studies, the Cholesterol and Recurrent Events Trial (CARE) (pravastatin) (Goldberg et al., 1998) and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention (VA Hit) (gemfibrozil) (Rubins et al., 1999). Both studies were randomized, controlled clinical trials with significant numbers of enrollees with diabetes. The CARE study published a subgroup analysis of persons with diabetes, which contains the diabetes-specific risk reductions that we present here. The VA Hit study has not published a subgroup analysis of diabetes but included some specific information about the 627 people with diabetes who were enrolled in the study.

The risk reductions in major CHD achieved by each of the interventions were similar. Gemfibrozil and pravastatin reduced major CHD by 24 percent and 25 percent, respectively. Because both of these studies tested secondary interventions, they will affect transition probabilities that follow CHD. These risk reductions will be applied to the following transition probabilities: P_4, P_5, P_6, P_7, P_{14}, P_{15}, P_{19}, P_{22}, and P_{24} (Table 2-8).

Table 2-8. Risk Reduction in Coronary Heart Disease with Cholesterol Treatment

Transition Probability	Fibrate (Gemfibrozil)	Statin (Pravastatin)
Primary (P_1)	34%	31%
Secondary (P_4, P_5, P_6, P_7, P_{14}, P_{15}, P_{19}, P_{22}, P_{24})	24%	25%

2.3.3 Cholesterol and Stroke

We do not model an effect from cholesterol treatment on the likelihood of stroke. The studies that address the possible reduction in risk in stroke have found widely varying results. Although we have not modeled a reduction in risk in stroke from cholesterol treatment, we do allow the user to enter a risk reduction into the model.

2.4 Smoking

There are five possible smoking interventions: (1) a nicotine patch and individual intensive counseling; (2) nicotine gum and individual intensive counseling; (3) individual intensive counseling; (4) full counseling; and (5) brief counseling. The marginal quit rate (over and above the baseline no-intervention quit rate) associated with each of these programs varied, ranging from 16.64 percent to 1.86 percent, as shown in Table 2-9. In addition, we reduced the number of quitters by 45 percent to account for post-follow-up relapse (Cromwell et al., 1997).

The effect of quitting smoking is modeled by reducing the likelihood of CHD and stroke in persons who have not yet experienced these complications. No effect is modeled for persons who have already experienced CHD or stroke. The reduction in risk is realized in the quitter over time. One year after the individual quits smoking, his risk is halved. Fifteen years after the individual quits smoking, his risk is equal to that of a person who has never smoked (US DHHS, 1990). The model assumes that the risk will decline in a linear fashion until reaching the risk of a never-smoker at year 15.

Table 2-9. Smoking Interventions

Intervention	Description of Intervention	Marginal Quit Rate (%)	Post-Follow-Up Relapse Rate (%)	Cost per Intervention (1997$)	Source
Nicotine Patch and Intensive Counseling	Intensive counseling consists of 5 30-minute counseling sessions with a smoking cessation expert.	16.64	45	345	Cromwell, Bartosch, Fiore, Hasselblad, and Baker (1997)
Nicotine Gum and Intensive Counseling	Intensive counseling consists of 5 30-minute counseling sessions with a smoking cessation expert.	11.50	45	525	Cromwell, Bartosch, Fiore, Hasselblad, and Baker (1997)
Intensive Counseling	Intensive counseling consists of 5 30-minute counseling sessions with a smoking cessation expert.	6.62	45	111	Cromwell, Bartosch, Fiore, Hasselblad, and Baker (1997)
Full Counseling	15 minutes of physician time during initial visit with 2 10-minute follow-up visits.	6.20	45	80	Cromwell, Bartosch, Fiore, Hasselblad, and Baker (1997)
Brief Counseling	7 minutes of physician time during initial visit with 1 10-minute follow-up visit	1.86	45	40	Cromwell, Bartosch, Fiore, Hasselblad, and Baker (1997)

2.5 Polypill

The polypill was initially proposed by Wald and Law (2003) as a strategy to reduce cardiovascular risk in the general population by combining common, low-cost medications (a statin, three drugs that lower blood pressure, aspirin, and folic acid) into a single pill. As proposed, the polypill would be efficacious and inexpensive; patients would find it easy to adhere to and suffer few side-effects. However, the polypill is not yet available (Watts, 2008).

Users can select the effect of the polypill on CVD risk and the annual cost of the drug. Default values include an 80% CVD risk reduction based on Wald and Law (2003) and a $100 annual cost. Because interest in the polypill has declined, these numbers have not been updated.

2.6 Bariatric Surgery

Bariatric surgery was added to the cost-effectiveness model to estimate whether surgery in persons with diabetes who were overweight and obese would be cost-effective. The bariatric surgery module covers gastric bypass and banding and has primarily been used to evaluate surgery in persons who already have diabetes. In the module, surgery can lead to diabetes remission (i.e., no longer requiring diabetes medications) or improvement (i.e., requiring fewer medications). Persons entering remission may relapse back into active diabetes. Surgery has a high initial cost and recurring costs in subsequent years, and patients have a slightly elevated mortality rate.

The bariatric surgery model and its parameters are described in detail in Hoerger et al. (2010).

2.7 Generic Intervention

The generic intervention makes it possible to design an intervention that affects multiple parameters. Users can specify the cost of an intervention and its effects on glycemic control, cholesterol reduction, blood pressure reduction, and BMI. Users can also specify which groups receive the intervention, whether patients comply with the intervention, and potential side effects.

3. DISTRIBUTION OF THE POPULATION WITH DIABETES

To run the model for a national cohort of newly diagnosed diabetes patients, it is necessary to determine the distribution of the population among the different population groups as defined by age, sex, race/ethnicity, hypertension status, cholesterol status, and smoking status.

3.1 Distribution in Early Versions of the Model

Although the original distribution in the model is no longer used as the default values, it does provide insights in how to tailor a diabetes population for study. In the early version of the model, the distribution of persons with newly diagnosed diabetes throughout the entire population was determined using the following formula:

(Population in each age, race/ethnicity and sex group) * (Incidence rate) * P(smoking) * P(hypertensive) * P(high cholesterol).

The population in each age, race/ethnicity, and sex group (i.e., African-American, female, ages 25 to 34) came from the U.S. Bureau of the Census (1997). We used the estimate for June 1994 since that is the sixth month of the year.

Using probability data from *Diabetes in America*, a population frequency for each of the cohorts was calculated (Table 3-1). Because the data from these tables did not exactly match our cohorts, we made some adjustments to adapt the data to fit our needs. For example, the tables with the smoking, cholesterol, and hypertension information did not contain a Hispanic category.

Table 3-1. Sources for the Distribution of the Population with Diabetes in Earlier Versions of the Model

Characteristic	Source
Population in Each Age, Race/Ethnicity, and Sex Group, 1994	U.S. Bureau of the Census (1997)
Incidence Rate	CDC (1997), *Diabetes Surveillance,* Table 2.24 – 2.27, Pages 34-35
P (smoking)	Cowie and Harris (1995), Appendix 7.41, Page 158
P (hypertensive)	Cowie and Harris (1995), Appendix 7.16, Page 147
P (high cholesterol)	Cowie and Harris (1995), Appendix 7.34, Page 155

Instead, they provided information about Mexican-Americans, who comprise about 63 percent of the Hispanic population in the United States in 1996 (1998). We assumed that Mexican-Americans were representative of all Hispanic-Americans and used them as a proxy throughout these calculations. In addition, these data tables did not provide specific information about Native-Americans or Asian-Americans. Instead, we used the categories for "women" and "men."

In addition, the specificity of the data varied by race/ethnicity group. The smoking and hypertension estimates provided information on Caucasians, African-Americans, and Mexican-Americans that was dependent on race/ethnicity, sex, age, and diabetes status. The estimates for Asian-Americans or Native-Americans were dependent only on sex and age. The estimates for cholesterol provided information for the entire cohort that was age dependent.

The tables also used age categories that were slightly different from ours. Generally, the information was provided for 18–44 years, 45–64 years, and 65 years and older. Our age categories range from 25–34 through 85–94. Therefore, we used the same probabilities for some of our distinct age groups. For example, our probabilities for both 25–34 years and 35–44 years came from the 18–44 years estimate.

3.2 Distribution in the Current Version

The default values in the current version of the model are based on data on the distribution of prevalent cases of diabetes in NHANES. Users can create their own distribution using diabetes prevalence data from one or more waves of NHANES or focus on newly diagnosed cases by using incidence data from NHIS. As in the early version of the model, age, race, and sex groups should be weighted by their share of the population; it may be necessary to pool the probability of high blood pressure, high cholesterol, or smoking across age, sex, or race or ethnic categories.

Cohort data may be entered either as number of persons or as percentage of the population to be studied; the software normalizes the shares so that they add up to 100%. Normalization also occurs if the user chooses to analyze only some of the cohorts. For example, if the input data includes all age cohorts from 25–94 years old, but the user selects analysis for the 45–54 cohort, the software will normalize the 45–54 cohort distribution to sum to 100%.

4. RACE/ETHNICITY ADJUSTMENTS

Race/ethnicity has three effects in the model. First, age and sex differences in the incidence of diabetes across race/ethnicity groups are reflected in the initial distribution of individuals across model cohorts. Race/ethnicity differences in the prevalence of high cholesterol, hypertension, and smoking are also reflected in the initial distribution.

Second, mean race/ethnicity differences in glycemic levels are incorporated in patients' glycemic levels and consequently affect the hazard rates for neuropathy, nephropathy, and retinopathy. Following Eastman et al. (1999) the effect of these differences in glycemic levels is described in the equation

$$h^*_{i,j}(t) = h_{i,j}(t) \times [g(t)/G(t)]^{\beta i,j} \times [RGL]^{\beta i,j}$$

where RGL is the relative glycemic level for the race/ethnicity group, and the other variables are as in the equation in Section 2.1. The baseline hazard rates are assumed to be based on the average for all Americans. The average glycemic level for non-Hispanic Whites is 98 percent of the American average. Average glycemic levels for other race/ethnicity groups, relative to levels for non-Hispanic Whites, are shown in Table 4-1.

Third, race/ethnicity affects mortality rates from ESRD and other causes (see Section 1.3).

Table 4-1. Race/Ethnicity Differences in Glycemic Levels, Relative to Non-Hispanic Whites

	Males	Females	Source
Non-Hispanic White	1.00	1.00	Harris et al. (1999)
African-American[a]	1.04	1.09	Harris et al. (1999)
Hispanic	1.09	1.04	Harris et al. (1999)
Native-American	1.19	1.19	Eastman et al. (1999)
Asian	0.95	0.95	Eastman et al. (1999)

[a]Non-Hispanic.

5. COSTS OF INTERVENTIONS

5.1 Conventional and Intensive Diabetes Control

The costs of regular diabetes care are costs that are incurred in the absence of complications. These costs can be divided into four components:

- Drugs
- Physician office visits
- Self-testing
- Case management

We calculate the cost of diabetes care under two scenarios. The main analysis, which we call the U.S. cost scenario, includes costs of drug utilization based on the UKPDS experience and outpatient visits, self-testing, and case management that reflect U.S. clinical practice. The U.S. cost scenario includes more resources than are specifically identified in the UKPDS cost study. For example, no case management costs are identified in the UKPDS report, and the annual number of home blood glucose tests listed is substantially lower than in the U.S. cost scenario. In addition, the number of physician visits identified in the UKPDS study is slightly lower than in the U.S. cost scenario. For a sensitivity analysis, we use only those resources specifically identified in the UKPDS cost study to calculate a UKPDS cost scenario. For both the U.S. and UKPDS cost scenarios, U.S. unit costs are used to convert the resource use into costs. Below, we explain how costs are calculated for intensive and conventional control under each cost scenario.

5.1.1 Drug Costs

Drug costs are the same in the U.S. and UKPDS cost scenarios. Costs are based on drug use patterns in the conventional and intensive control arms of the UKPDS multiplied by U.S. prices. The drug use patterns account for the fact that although patients in the conventional treatment arm start with diet alone, many later begin to receive sulphonylurea drugs or insulin. Similarly, patients in the intensive control arm start with either sulphonylurea drugs or insulin but may later switch to alternative therapies.

Drug Use. Model assumptions about the percentage of patients receiving each drug, based on treatment arms, are shown in Table 5-1. Various UKPDS publications serve as the source for these assumptions. The assumptions were selected to reproduce the cumulative patient years on each drug, by original treatment arm, shown in UKPDS 33, Table 3 (1998), while incorporating data on specific drug distributions from individual years in other publications. To do this, we assume drug rates by year, multiply by the number of patients participating

in each year of the trial (UKPDS 33, Figure 3), and compare to the cumulative patient years in UKPDS 33, Table 3.

Below, we describe the specific assumptions for each treatment arm.

Conventional Glycemic Control. The percentage on diet alone is taken from Slide 17 in the UKPDS Barcelona slide show (Turner & Holman, 1998). We assume that 100 percent of the patients in the arm receive diet alone in year 0. Twelve year values are used in years 12+. This distribution yields a cumulative rate of 57 percent on diet alone, just under the 58 percent reported in UKPDS 33, Table 3, Column 6. Numbers at 3 and 6 years (72 percent and 46 percent) are very close to the 71 percent and 45 percent numbers published in UKPDS 16 (1995).

For the percentages on sulphonylureas and insulin, we assumed that patients who failed diet (100 percent minus the percentage on diet alone) were randomly assigned to sulphonylureas and insulin according to the UKPDS trial protocol proportions of 4/7 and 3/7, respectively. Percentages were rounded to the nearest integer. This yields estimated cumulative percentages of 25 percent on sulphonylureas and 18 percent on insulin, reasonably close to the 25 percent and 16 percent figures in UKPDS 33, Table 3, Column 6. This approach does not directly account for patients who are started on sulphonylureas and are then switched to insulin.

The percentage on metformin (assumed to be taken in addition to sulphonylurea) is based on data for patients who fail on diet and are assigned to sulphonylureas in UKPDS 24 (1998). At year 0 after assignment, about 25 percent need additional therapy (1-year need for additional therapy from UKPDS 24, Table 2, p. 169). By year 6, approximately half of the patients taking sulphonylureas are also taking other oral hypoglycemic agents (UKPDS 24, Figure 3). Therefore, 25 percent of patients who start taking sulphonylureas are assumed to take metformin in year 0, and the percent taking metformin increases by 5 percent each year up to the fifth year after starting. Percentages are rounded to the nearest integer. This yields a cumulative rate of 9.8 percent on metformin, close to the 10 percent in UKPDS 33, Table 3, Column 6.

Intensive Glycemic Control: Chlorpropamide. The percentage on diet alone is assumed constant at 6 percent (except 0 percent in year 0) to yield 6 percent in UKPDS 33, Table 3. The percentage on insulin is 5 percent at year 3 and 10 percent at year 6 (UKPDS 16, 1995, p. 1253). The same rate of increase is assumed through year 12, with no increase thereafter. These assumptions yield 9 percent cumulative years on insulin, consistent with the 9 percent rate in UKPDS 33, Table 3, Column 3.

The percentage on chlorpropamide is calculated as 100 percent minus the percentage on diet minus the percentage on insulin. This yields an 85 percent cumulative rate, as implied by UKPDS 33, Table 3, Column 3 if the small (2 percent) group on multiple sulphonylureas is ignored.

The percentage on metformin (assumed to be taken in addition to sulphonylurea) is based on UKPDS 16 (1995, p. 1253), which reports that 7 percent and 20 percent of sulphonylurea patients take additional metformin at years 3 and 6, respectively. We interpolate between years 0 and 3 and between years 3 and 6. We assume that the percentage increases at a rate of 1 percent per year until year 9 and then remains constant. By construction, this yields a cumulative rate of 14 percent, the same as in UKPDS 33, Table 3, Column 3.

Intensive Glycemic Control: Glibenclamide. The percentage on diet alone was assumed constant at 7 percent (except 0 percent in year 0) to yield the 7 percent cumulative percentage in UKPDS 33, Table 3.

For the percentage on insulin, we initially assumed 5 percent at year 3 and 10 percent at year 6 from UKPDS 16 (1995, p. 1253). We assumed the same rate of increase through year 15. In order to yield 10 percent cumulative years on insulin, consistent with the 10 percent rate in UKPDS 33 (Table 33, Column 4), we had to increase the rate by 1 percent per year from year 5 onward.

The percentage on glibenclamide was set at 100 percent minus the percentage on diet minus the percentage on insulin. This yields an 84 percent cumulative rate, very close to the 83 percent on glibenclamide or 85 percent on any sulphonylurea in UKPDS 33, Table 33, Column 4.

The percentage on metformin (assumed to be taken in addition to sulphonylurea) was based on UKPDS 16 (1995, p. 1253), which reported that 7 percent and 20 percent of sulphonylurea patients take additional metformin at years 3 and 6. We interpolated between years 0 and 3 and between years 3 and 6 and assumed that the percentage increases at a similar rate through year 12. This yields a cumulative rate of 19 percent, close to the 20 percent reported in UKPDS 33, Table 3, Column 4.

Intensive Glycemic Control: Sulphonylureas Combined. We took an average of the rates for chlorpropamide and glibenclamide (patients were equally likely to receive the two sulphonylureas in the UKPDS). This leads to an average of 85 percent of years on sulphonylureas, 5.5 percent of years on diet, 9.3 percent of years on insulin, and 17 percent of years on metformin for patients in the intensive treatment arm who began treatment

with sulphonylureas. These results are very similar to the average of sulphonylurea and glibenclamide from UKPDS 33, Table 3, Columns 3 and 4.

Intensive Glycemic Control: Insulin. The percentage on insulin was assumed to be 100 percent in year 0 and 69 percent in year 1 , Table 2, value at year 1 for main randomization to insulin). At years 3 and 6, 74 percent and 77 percent of patients were taking insulin, respectively (UKPDS 16, 1995, p. 1253). We applied straight-line interpolation between years 1 and 3 and between years 3 and 6, rounded to the nearest integer, and carried the 77 percent figure forward to year 6 onward. This yields a cumulative percentage of 77 percent taking insulin, slightly higher than the 74 percent reported in UKPDS, Table 3, Column 5.

The percentage on sulphonylureas was assumed to be 7 percent except in year 0 to match UKPDS 33, Table 3, Column 5 (100 percent minus 74 percent on insulin minus 19 percent on diet). This yields a 6.4 percent cumulative percentage on sulphonylureas.

The percentage on diet was calculated as 100 percent minus the percentage on insulin minus the percentage on sulphonylureas as calculated above. This calculation yields a diet alone rate of 16 percent, slightly less than the 19 percent reported in UKPDS 33, Table 3, Column 5.

The percentage on metformin (assumed to be taken in addition to sulphonylurea) was assumed to be 3 percent for year 1 onward to yield a cumulative rate of 2.7 percent, approximately equal to the 3 percent rate in UKPDS 33, Table 3, Column 5.

Table 5-1. Treatment Shares by Year[a]

	Distribution Among Treatments (UKPDS 16)														
	Initially (Year 0)	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**	**Year 11**	**Year 12**	**Year 13**	**Year 14**	**Year 15**
Intensive Control																
Insulin	1	0.69	0.72	0.74	0.75	0.76	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77
Sulphonylurea	0	0.07	0.07	0.07	0.07	0.07	0.062	0.062	0.062	0.062	0.062	0.062	0.062	0.062	0.062	0.062
Metformin	0	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
No Drugs (Diet)	0	0.24	0.21	0.19	0.18	0.17	0.168	0.168	0.168	0.168	0.168	0.168	0.168	0.168	0.168	0.168
Sulphonylurea	1	0.92	0.91	0.89	0.87	0.86	0.84	0.82	0.81	0.79	0.77	0.76	0.74	0.73	0.72	0.70
Insulin	0	0.02	0.03	0.05	0.07	0.08	0.10	0.12	0.13	0.15	0.17	0.18	0.2	0.21	0.22	0.24
Metformin	0	0.02	0.05	0.07	0.11	0.16	0.20	0.22	0.26	0.28	0.30	0.33	0.35	0.35	0.35	0.35
No Drugs (Diet)	0	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Conventional Control																
Diet	1	0.90	0.80	0.72	0.62	0.53	0.44	0.39	0.34	0.31	0.28	0.24	0.20	0.20	0.20	0.20
Suphonylurea	0	0.06	0.12	0.16	0.22	0.27	0.32	0.35	0.38	0.39	0.41	0.43	0.46	0.46	0.46	0.46
Insulin	0	0.04	0.08	0.12	0.16	0.20	0.24	0.26	0.28	0.30	0.31	0.33	0.34	0.34	0.34	0.34
Metformin	0	0.02	0.03	0.05	0.07	0.10	0.12	0.14	0.16	0.17	0.19	0.20	0.21	0.22	0.22	0.22

[a]Metformin is assumed to be taken as an adjunct therapy.

Drug Doses and Prices. Drug doses for glibenclamide, chloropropamide, and metformin equal the maximum dose allowed in the UKPDS trial (Table 5-2). Median insulin doses are reported in UKPDS 33 as 22U, 28U, 34U, and 36U for years 3, 6, 9 and 12, respectively; we interpolate for the years in between. Following UKPDS protocol, we assume that patients receive ultralente insulin for the first 14U/day; isophane insulin accounts for any additional units (Table 5-3).

Table 5-2. Drug Doses and Prices

	Dose per Day	Price[a]	Price per Day
Glibenclamide	40 mg	$0.1163/10 mg	$0.465
Chlorpropamide	500/mg	$0.0306/100 mg	$0.153
Metformin	2,550/mg	$0.85/850 mg	$2.55
Insulin			
Ultralente	Varies by year	$0.01946/U	Varies by year
Isophane	Varies by year	$0.02888/U	Varies by year

[a]Drug prices are based on the 1997 *Red Book*(1997).

Table 5-3. Insulin Doses and Costs, by Year

Year	Ultralente (U)	Isophane (U)	Total Units	Total Cost per Day[a]
0	10	0	10	$0.396
1	14	0	14	$0.473
2	14	4	18	$0.939
3	14	8	22	$1.133
4	14	11	25	$1.278
5	14	13	27	$1.374
6	14	16	30	$1.519
7	14	17	31	$1.568
8	14	19	33	$1.664
9	14	20	34	$1.713
10	14	21	35	$1.761
11	14	21	35	$1.761
12 and later	14	22	36	$1.809

[a]Includes $0.201/day for cost of syringes and alcohol swabs.

Drug Costs for Conventional and Intensive Glycemic Control. Annual drug costs for conventional care are calculated by multiplying the share of conventional care patients using each drug by the corresponding cost per day, summing across drugs, and multiplying by 365 days in a year.

Drug costs for intensive control are calculated in a similar way, with the additional consideration that 4/7 of intensive control patients start treatment with sulphonylureas and 3/7 start with insulin. These fractions are taken from the UKPDS protocol.

Drug costs by year for conventional and intensive control are shown in Table 5-4.

5.1.2 Physician Office Visits

U.S. Cost Scenario. Following Dong, Orians, and Manninen (1997), we assume that noninsulin users make four office visits per year under conventional control and seven office visits per year under intensive control (Table 5-5). Insulin users make five office visits per year under conventional control and eight office visits per year under intensive control. Visit costs range from $40 to $102, depending on the length of visits and the types of laboratory tests performed during each visit. Costs are based on the Medicare fee schedule.

Table 5-4. Drug Costs for Conventional and Intensive Control, by Year

	Conventional		Intensive	
Drug Costs	Cost per Day	Cost per Year	Cost per Day	Cost per Year
Initially (Year 0)	0.000	$0.00	0.346	$126.35
Year 1	0.088	$32.30	0.379	$138.38
Year 2	0.158	$57.68	0.457	$166.65
Year 3	0.255	$92.90	0.525	$191.53
Year 4	0.361	$131.74	0.614	$224.29
Year 5	0.491	$179.15	0.710	$259.18
Year 6	0.601	$219.53	0.803	$293.02
Year 7	0.689	$251.45	0.849	$310.01
Year 8	0.781	$285.09	0.932	$340.18
Year 9	0.838	$305.80	0.982	$358.33
Year 10	0.912	$332.79	1.028	$375.30
Year 11	1.086	$396.56	1.076	$392.64
Year 12	1.139	$415.72	1.123	$409.86
Year 13	1.164	$425.03	1.127	$411.29
Year 14	1.164	$425.03	1.131	$412.71
Year 15	1.164	$425.03	1.139	$415.56

The total cost for physician office visits for noninsulin users is $318 per year for conventional control and $439 per year for intensive control. For insulin users, total visit costs are $359 per year for conventional control and $479 per year for intensive control. The difference in annual visit costs between conventional and intensive control is about $120 for both noninsulin and insulin users.

UKPDS Cost Scenario. Office visits for the UKPDS cost scenario are derived from Table 2 in UKPDS 41; the numbers of visits listed in the table are based on study clinicians' opinions about standard UK clinical practice for conventional and intensive control. To determine U.S. payments, we have attempted to match descriptions for the UKPDS visits with corresponding HCFA Common Procedural Coding System (HCPCS) codes (Table 5-5); we have assumed that the visits would be supervised by a physician.

Table 5-5. Physician Office Visits and Costs for Conventional and Intensive Control, U.S. Cost Scenario

U.S. Scenario Clinic Visits	HCPCS Code	Cost/ Visit (1997$)	Number of Annual Visits				Costs (1997$)			
			Conventional		Intensive		Conventional		Intensive	
			Non-insulin	Insulin	Non-insulin	Insulin	Non-insulin	Insulin	Non-insulin	Insulin
Annual visit										
25 minutes	99214	58.66	1	1	1	1	58.66	58.66	58.66	58.66
Urinalysis	81000	4.37	1	1	1	1	4.37	4.37	4.37	4.37
Albumin and creatinine	80002	7.2	1	1	1	1	7.2	7.2	7.2	7.2
HbA_{1c}	83036	13.42	1	1	1	1	13.42	13.42	13.42	13.42
Lipid panel	80061	18.51	1	1	1	1	18.51	18.51	18.51	18.51
Semi-annual visit										
25 minutes	99214	58.66	1	1	1	1	58.66	58.66	58.66	58.66
HbA_{1c}	83036	13.42	1	1	1	1	13.42	13.42	13.42	13.42
Quarterly visit										
25 minutes	99214	58.66	2	2	2	2	117.32	117.32	117.32	117.32
HbA_{1c}	83036	13.42	2	2	2	2	26.84	26.84	26.84	26.84
Additional visit										
10 minutes	99212	26.82	0	1	3	4	0	26.82	80.46	107.28
HbA_{1c}		13.42	0	1	3	4	0	13.42	40.26	53.68
Total Annual Cost of Visits							318.40	358.64	439.12	479.36

Table 5-6. Physician Office Visits and Costs for Conventional and Intensive Control, UKPDS Cost Scenario

UKPDS Clinic Visits	HCPCS Code	Cost / Visit (1997$)	Number of Annual Visits				Costs (1997$)			
			Conventional		Intensive		Conventional		Intensive	
			Non-insulin	Insulin	Non-insulin	Insulin	Non-insulin	Insulin	Non-insulin	Insulin
General Practice Nurse	99212	26.83	3	3	2	0	80.49	80.49	53.66	0
Specialist Nurse	99213	38.63	0	1	2	4	0	38.63	77.26	154.52
General Practice Clinic	99214	58.66	1	1	2	2	58.66	58.66	117.32	117.32
Doctor at Hospital Diabetes Clinic	99215	92.99	0	0.5	0.5	1	0	46.495	46.495	92.99
Total Annual Cost of Visits							139.15	224.275	294.735	364.83

Under the UKPDS scenario, the total cost for physician office visits for noninsulin users is $139 per year for conventional control and $295 per year for intensive control. For insulin users, total visit costs are $224 per year for conventional control and $365 per year for intensive control. Although each of these costs is lower than the corresponding cost in the U.S. cost scenario, the difference in cost between conventional and intensive care is about the same for the U.S. ($120) and UKPDS ($155 for noninsulin users and $141 for insulin users) scenarios.

5.1.3 Self-Testing

U.S. Cost Scenario. Based on data from the 1989 National Health Interview Survey (NHIS) Diabetes Supplement, we assume that, for conventional care, noninsulin and insulin users use an average of 43 and 193 glucose testing strips, respectively (Table 5-7).

Table 5-7. Self-Testing Costs for Conventional Control, U.S. Cost Scenario

	Events/Year			Annual Cost ($)	
Resource	Insulin	Non-insulin	1997 Cost/Unit	Insulin	Non-insulin
Glucose Test Strips	193	43	76/100	146.68	32.68
Lancet	193	43	2.6/100	5.02	1.12
Glucose Meter	0.171	0.0787	162.50/3 years	27.79	12.79
Battery for Glucose Meter	3.084	1.42	5.15	15.88	7.31
Glucagon	1	0	30.81	30.81	0
Total				**226.18**	**53.90**

In U.S. practice, self-testing is an important component of intensive glycemic control. However, specific guidelines for frequency of testing have not been issued. For example, current American Diabetes Association (ADA) recommendations on self-monitoring of blood glucose (SMBG) state that “the optimal frequency of SMBG for patients with type 2 diabetes is not known, but should be sufficient to facilitate reaching glucose goals. The role of SMBG in stable diet-treated patients with type 2 diabetes is not known” (ADA, 2000, pp. S33-S34), p. S33-S34. Later the recommendations note that “SMBG is recommended for all insulin-treated patients with diabetes. SMBG may be desirable in patients treated with sulfonylureas and in all patients not achieving glycemic goals” (p. S80). This statement may support the use of different rates for SMBG for insulin and noninsulin users.

We assume that insulin users will conduct self-testing 3 times daily under intensive control, while noninsulin users will average 1 self-test daily (Table 5-8). These assumptions are roughly consistent with Medicare coverage policy for persons with diabetes: Medicare currently provides reimbursement for up to 100 blood glucose test strips and lancets per month for persons with diabetes who use insulin (additional test strips and lancets can be covered if the physician documents medical need). Medicare provides reimbursement for up to 50 test strips and lancets every 2 months for persons with diabetes who do not use insulin (HCFA, 1998).

Table 5-8. Self-Testing Costs for Intensive Control, U.S. Cost Scenario

	Events/Year			Annual Cost ($)	
Resource	**Insulin**	**Noninsulin**	**1997 Cost/Unit**	**Insulin**	**Noninsulin**
Glucose Test Strips	1095	365	76/100	832.20	277.44
Lancet	1095	365	2.6/100	28.47	9.49
Glucose Meter	0.33	0.33	162.50/3 years	53.63	53.63
Battery for Glucose Meter	3.084	1.42	5.15	15.88	7.31
Glucagon	1	0	30.81	30.81	0
Total				**960.99**	**347.83**

UKPDS Cost Scenario. Self-testing costs for the UKPDS cost scenario are derived from Table 2 in UKPDS 41; the numbers of tests listed in the table are based on study clinicians' opinions about standard U.K. clinical practice for conventional and intensive control. The clinicians estimated that self-testing would be more common among insulin users than among noninsulin users, but they did not distinguish between patients receiving conventional and intensive control. For the purposes of the UKPDS scenario, we have also assumed no distinction between conventional and intensive control, except to the extent that insulin use is more likely among intensive control patients (Table 5-9). Because self-testing is assumed to occur less frequently in the United Kingdom, self-testing costs are much lower in the UKPDS cost scenario than in the U.S. cost scenario; the difference in self-testing costs between conventional and intensive care is also much smaller in the UKPDS scenario.

Table 5-9. Self-Testing Costs for Conventional and Intensive Control, UKPDS Cost Scenario

	Events/Year			Annual Cost ($)	
Resource	Insulin	Noninsulin	1997 Cost/Unit	Insulin	Noninsulin
Glucose Test Strips	121	12	76/100	91.96	9.12
Lancet	121	12	2.6/100	3.15	0.31
Glucose Meter	0.33	0.33	162.50/3 years	53.63	53.63
Battery for Glucose Meter	3.084	1.42	5.15	15.88	7.31
Glucagon	1	0	30.81	30.81	0
Glycated Hemoglobin Tests (HCPCS 83036)	1	1	13.42	13.42	13.42
Total				**208.84**	**83.79**

5.1.4 Case Management

U.S. Cost Scenario. Case management plays a significant role in some intensive control strategies. For example, in the DCCT, case management consisted of four telephone calls, two letters, treatment team conferences worth $60, and $8 worth of other time per year for a total cost of $129 in 1997 dollars. For intensive care, case management consisted of 32 telephone calls, 5 letters, treatment team conferences worth $183, and $61 worth of other time per year, for a total cost of $616 (Diabetes Control and Complications Trial Research Group, 1995b) updated for inflation.

We base our estimate of case management under intensive care on Aubert et al. (1998). In this study, a nurse case manager saw patients for a 45-minute initial assessment and met with the patient for a 2-week follow-up visit. The nurse case manager followed a specified algorithm for management of type 2 diabetes. Patients taking insulin received weekly follow-up telephone calls (52 calls per year), and patients treated with oral agents or drugs received telephone calls every 2 weeks (26 calls per year). In-person follow-up visits occurred quarterly. The nurse met at least biweekly with the family medicine physician and endocrinologist to review patient progress. We assume that the initial assessment and follow-up visit are included in the office visit costs considered earlier and that the rates for outpatient visits are sufficient to cover any nonvisit consultation time spent by the physician and staff. The telephone calls are priced at $8 per call, based on data from the DCCT. Case management costs for intensive control patients are shown in Table 5-10. We assume that no case management calls will be made to patients receiving conventional control.

Table 5-10. Case Management Costs for Intensive Control,[a] U.S. Cost Scenario

Resource	Events/Year		1997 Cost/Call	Annual Cost ($)	
	Insulin	Noninsulin		Insulin	Noninsulin
Telephone calls	52	26	8.00	416	208

[a]We assume that 0 case management calls are made under conventional control.

UKPDS Cost Scenario. No costs for case management are included in the UKPDS cost analysis (UKPDS 41). Therefore, our UKPDS cost scenario sets case management costs equal to zero.

5.1.5 Total Diabetes Care Costs of Conventional and Intensive Glycemic Control

Diabetes care costs for conventional control are calculated by multiplying the share of patients in the conventional treatment arm who receive each possible therapy (Table 5-1, based on the UKPDS) by the drug, office visit, self-testing, and case management costs associated with the therapy, and then summing across therapies. Treatment costs for intensive care are calculated in a similar manner.

The annual diabetes care costs for conventional and intensive control under the U.S. and UKPDS treatment scenarios are shown in Table 5-11. Costs for a treatment arm vary by year as the distribution of patients across therapies changes over time within the treatment arm. For example, costs rise over time in the conventional treatment arm as patients who initially receive diet alone are switched to drug therapies. The difference in costs between conventional and intensive control generally declines over time. The difference plays a key role in the calculation of the incremental cost-effectiveness ratio associated with intensive control.

Both conventional and intensive control costs are higher in the U.S. cost scenario than in the UKPDS cost scenario; the differences in costs between conventional and intensive control are also larger in the U.S. cost scenario. The higher costs in the U.S. cost scenario are driven by higher office visit, self-testing, and case management costs, while the U.S. scenario's larger difference between conventional and intensive care is driven primarily by larger differences in the self-testing and case management cost components.

Table 5-11. Costs of Conventional and Intensive Diabetes Control, U.S. and UKPDS Cost Scenarios

Diabetes Care Costs	U.S. Scenario			UKPDS Scenario		
Year	Conven-tional	Intensive	Difference	Conven-tional	Intensive	Difference
0	$372	$1,490	$1,118	$223	$589	$366
1	$413	$1,398	$985	$264	$577	$313
2	$447	$1,442	$995	$297	$609	$311
3	$490	$1,484	$994	$341	$638	$296
4	$538	$1,531	$993	$388	$673	$285
5	$594	$1,574	$980	$444	$710	$266
6	$642	$1,621	$979	$493	$747	$254
7	$679	$1,648	$969	$529	$766	$237
8	$717	$1,683	$966	$567	$798	$231
9	$741	$1,711	$970	$592	$818	$226
10	$771	$1,738	$967	$621	$837	$216
11	$839	$1,760	$921	$689	$856	$167
12	$860	$1,788	$927	$710	$875	$165
13	$870	$1,794	$924	$719	$878	$158
14	$870	$1,800	$930	$719	$880	$161
15+	$870	$1,813	$943	$719	$924	$166

5.2 Hypertension Control

The costs of moderate and intensive blood pressure control were estimated using dosage data from the UKPDS (UKPDS 39, 1998). The UKPDS provided a graph displaying the average number of drugs used per year as well as the average dose given per drug and the order in which the drugs were dispensed. The average number of drugs taken per year for moderate control and intensive control are presented in Tables 5-12 and 5-13, respectively.

Table 5-12. Distribution of the Number of Drugs Taken Under Moderate Control, by Year

Year	P (no drugs)	P (one drug)	P (two drugs)	P (three drugs)
1	0.53	0.32	0.10	0.05
2	0.53	0.26	0.14	0.07
3	0.51	0.28	0.12	0.09
4	0.44	0.35	0.13	0.08
5	0.40	0.38	0.14	0.08
6	0.38	0.40	0.14	0.08
7	0.30	0.42	0.18	0.10
8	0.30	0.42	0.18	0.10
9 and up	0.26	0.36	0.27	0.11

Source: UKPDS 39 (1998).

Table 5-13. Distribution of the Number of Drugs Taken Under Intensive Control, by Year

Year	P (no drugs)	P (one drug)	P (two drugs)	P (three drugs)
1	0.07	0.53	0.30	0.10
2	0.07	0.43	0.35	0.15
3	0.08	0.32	0.40	0.20
4	0.08	0.32	0.38	0.22
5	0.10	0.29	0.36	0.25
6	0.08	0.32	0.35	0.25
7	0.06	0.33	0.35	0.26
8	0.09	0.28	0.35	0.28
9 and up	0.06	0.31	0.34	0.29

Source: UKPDS 39 (1998).

We assumed that under moderate control, patients would first be given furosemide, then nifedipine, and finally methyldopa. This is the order that is reported in UKPDS 39 (1998). Drugs were added when the patient's hypertension was not controlled. Under intensive control, we assumed that patients would first be given either atenolol or captopril (the cost of treatment with these was equal). We assumed that the maximum number of drugs that would be taken at one time was three.

We used the 1997 *Red Book* to determine the cost per dose of each drug. To determine the total annual cost, we added the weighted average of one drug, two drugs, and three drugs; the cost of two physician visits; and the cost of three chemistry panels. We did this for both moderate and intensive control. Costs are presented by year in Table 5-14.

Table 5-14. Costs of Hypertension Treatment, by Year

Year	Moderate Control ($)	Intensive Control ($)
1	241.43	599.06
2	277.14	629.87
3	287.08	656.19
4	291.67	663.74
5	301.14	667.28
6	303.53	675.06
7	348.79	689.01
8	348.79	685.48
9 and up	404.28	702.72

Source: See text.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in its sixth report (Joint National Committee on Prevention, 1997) emphasized the importance of lifestyle modifications such as diet and physical activity. While we recognize that some patients do not need drug therapy after they make these lifestyle changes, about half of the 50 million people in the United States who have elevated blood pressure are treated with antihypertensive drugs (Manolio et al., 1995). Lifestyle changes were not included in the model because cost estimates were not available in the literature for dietary changes, sodium reduction, or aerobic exercise.

5.3 Cholesterol Reduction

Costs were determined using the 1997 *Red Book*. The cost of the first year of treatment with pravastatin was determined based on a daily dose of 40 mg, plus physician visits and lab work as shown in Table 5-15. The cost of gemfibrozil was determined based on a daily dosage of 1,200 mg, in addition to physician visits and lab costs.

Table 5-15. Cholesterol Treatment Costs (1997$)

Intervention	Total Cost per Year	Nondrug Costs
Fibrate (gemfibrozil)	Year 1: $349.68 Subsequent Years: $240.54	In initial year: four physician visits, four blood test sample collections, four lipid profiles, and four biochemical profiles. Subsequent years included two physician visits, two blood test sample collections, two lipid profiles, and two biochemical profiles. The cost of year 1 tests is $218.28. The cost of testing for subsequent years is $109.14.
Statin (pravastatin)	Year 1: $1,397.60 Subsequent Years: $1,288.46	See above for additional costs.

Source: See text

5.4 Smoking Cessation

Costs of the smoking interventions were taken from journal articles and then updated to 1997 dollars (Table 2-9). The cost for these programs ranged from $40 for self care to $525 for nicotine gum.

6. MEDICAL COSTS

6.1 Cost of Complications

Costs for care for diabetes complications were updated in 2017 using a variety of sources and were reported in 2016 dollars. We conducted a literature review and meta-analysis of diabetes-related event-year costs and annual state costs. Event-year costs are those associated with resource use specific to the defining clinical event. This includes acute care (initial management in an inpatient or outpatient setting) and subsequent event-related health care delivered in the first year of a diabetes complication. Annual state costs present the annual management costs for years after the event year and reflect the typical utilization of health care services for the ongoing management of a given health state. To find the most-recent publications on costs associated with diabetes complications, we first searched literature published on all models presented at the 2016 Mount Hood meeting. We also obtained sources by searching PubMed and RTI's e-journals library with the search terms "Cost" AND "Complications" AND "Diabetes," limiting the results to papers published in the year 2000 or later. We excluded all articles that did not report on the medical cost of diabetes complications or that reported non-U.S. costs.

In addition to reviewing sources used by other models (Brandle et al., 2003; Liao et al., 2006; Nichols et al., 2011; O'Brien et al., 2003; U.S. Renal Data System, 2013; Ward et al., 2014) and sources obtained by our literature search strategy (Johnson et al., 2016; Kind et al., 2008; Lin et al., 2016; Pelletier et al., 2012; Qureshi et al., 2007; Sloss et al., 2004; United States Renal Data System, 2016; Wittenborn & Rein, 2013), we also reviewed the latest guidelines regarding treatment of diabetes-related conditions. In reviewing the American Diabetes Association's (ADA's) 2017 Standards of Care, we confirmed that our model was capturing the correct set of medical costs associated with management and treatment of the major diabetes-related conditions.

Costs in 2016 USD are shown in Table 6-1. Meta-analyses for angina, CA/MI, CHF, LEA, and stroke, and CA/MI used the following data sources, all updated to 2016 dollars.

- Health Care and Utilization Project (HCUP) data from 2013: all event costs
- Pelletier et al. (2012): all event and annual costs
- O'Brien et al. (2003): all event and annual costs except CHF
- Bonafede et al. (2015): all event costs except CHF
- Ward et al. (2014): event and annual costs for CA/MI, CHF, and stroke, and LEA event costs
- Brandle et al. (2003): event and annual costs for CA/MI and stroke and angina annual costs

- Johnson et al. (2016): stroke event and annual costs
- Liao et al. (2006): CHF annual costs

Table 6-1. Costs of Diabetes Complications

	One Time Cost (2016 USD)	Annual Cost (2016 USD)	Source
Nephropathy			
Normoalbuminuria	0	0	
Microalbuminuria	490	490	Nichols et al. (2011)
Clinical Nephropathy	839	839	Nichols et al. (2011)
ESRD	89,362	89.362	USRDS (2016)
Death from ESRD	Normal death cost (see below)	0	
Neuropathy			
No Neuropathy	0	0	
Peripheral Neuropathy	245	0	Ward et al. (2014)
Diabetic Foot Ulcer	2,405	0	Ward et al. (2014)
Initial Lower Extremity Amputation	Nonfatal: 22,175 Fatal: 67,635	Nonfatal: 1,695 Fatal: 0	Meta-analysis
Subsequent Lower Extremity Amputation	Nonfatal: 22,175 Fatal: 67,635	Nonfatal: 1,695 Fatal: 0	Meta-analysis
Retinopathy			
No Retinopathy	0	0	
Photocoagulation	3,982	0	Wittenborn and Rein (2013)
Blind	7,307	7,307	Wittenborn and Rein (2013)
Coronary Heart Disease			
Normal	0	0	
Angina	10,004	1,687	Meta-analysis
CA Death Without Hospitalization	1,504	0	Russell et al. (1998)
CA/MI Death Within 30 Days With Hospitalization	30,957	0	Russel et al. (1998)
CA/MI Survivors	50,271	(go to History of CA/MI)	Meta-analysis
History of CA/MI	0	2,132	Ward et al. (2014)
CHF	26,285	4,289	Meta-analysis
Death Given History of MI	Normal death cost (see below)	0	
Death Given Angina	Normal death cost (see below)	0	

(continued)

Table 6-1. Costs of Diabetes Complications (continued)

	One Time Cost (1997 dollars)	Annual Cost (1997 dollars)	Source
Stroke			
Normal	0	0	
History of Stroke	Age < 65: 32,737 65–74: 32,737 75–84: 32,737 ≥ 85: 32,737	Age < 45: 7,615 45–54: 7,615 55–64: 7,615 65–74: 7,615 75–84: 7,615 ≥ 85: 7,615	Meta-analysis
Immediate Death from Stroke	Age All ages: Normal death cost (see below)	0	
Death Given History of Stroke	Normal death cost (see below)	0	
Normal Death Cost	Age < 65: 24,735 65–74: 24,735 75–84: 21,545 ≥ 85: 14,623	0	Riley and Lubitz (2010)

Note: All disease stages except ESRD and death also may have an annual cost of regular diabetes care. These costs are shown in Table 6-3.

Note that all disease stages except ESRD and death also have an annual cost of regular diabetes care. The annual ESRD cost includes all costs associated with a patient's care.

The CHD- and stroke-related costs were found through a literature search. The CHD event costs were taken from the sources listed above Table 6-1, while we followed the method of Weinstein et al. (1987) to calculate the total costs per period. Cost equations for CHD are as follows:

- The one time total cost of Angina = P_1* P_2* one-time cost of Angina * population in Normal
- The total first-year yearly cost (for months 2–12 of year 1) for people who start in Normal and end up in B at the end of year 1 = P_1* P_2* P_8*yearly cost of Angina* (11/12) * population in Normal
- The total yearly cost of angina for people who start in B (and remain in B) = P_9 * yearly cost * population in Angina

- Combining the previous three entries, the total cost of angina in a year = P_1* P_2* one-time cost of angina * population in Normal + P_1* P_2* P_8 * yearly cost of angina* (11/12) * population in Normal + P_9 * yearly cost * population in Angina
- The total one-time cost of CA death prior to admission = [(P_1* P_2* P_6 + P_1* P_3 + P_1* P_3* P_{13}* P_{15}) * population in Normal + P_7 * population in Angina + P_{19} * population in History of CA/MI] * [(1 – Prob(Survival to Admission | CA)] * P(CA | CA/MI)] * one-time cost of CA death before admission where P(Survival to Admission | CA) is given in Table 1-12, and the one-time cost of CA death before admission = $759.
- The total one-time cost of CA/MI death with hospitalization = ({[(P_1* P_2* P_6 + P_1* P_3 + P_1* P_3* P_{13}* P_{15}) * population in Normal + P_7 * population in Angina + P_{19} * population in History of CA/MI] * P(Survival to Admission | CA) [1 – P(Survival to Discharge | CA)] * P(CA | CA/MI)} + {[(P_1 * P_2* P_6 + P_1 * P_3) * population in Normal + P_7 * population in Angina] * P(Death | 1st MI) + [P_1 * P_3 * P_{13} * P_{15} * population in Normal + P_{19} * population in History of CA/MI] * P(Death | Recurrent MI)] * P(MI | CA/MI)]}) * cost of CA/MI death with hospitalization where P(Survival to Admission | CA) and P(Survival to Discharge | CA) are given in Table 1-12.
- The total one-time cost of CA/MI survival = [(P_1* P_2* P_6 * P_{11} + P_1* P_3* P_{13} + P_1* P_3* P_{13}* P_{15} * P_{18})* population in Normal + (P_7 * P_{21}) * population in Angina +(P_{19} * P_{25}) * population in History of CA/MI] * one-time cost CA/MI survival
- The total yearly cost of History of CA/MI = (1 – P_{19} – P_{22})* yearly cost of History of CA/MI * population in History of CA/MI
- The total yearly cost of death from chronic MI = [($P_1 \times P_3 \times P_{13} \times P_{14}$) * population in Normal + P_{22} * population in History of CA/MI] * cost of Normal death
- The total yearly cost of death from Angina (without CA or MI) = [($P_1 \times P_2 \times P_4$ * population in Normal) + (P_5 * population in Angina] * cost of Normal death

6.2 Cost of Normal Death

Estimates of the cost of death are scarce. Due to the scarcity of information on the cost of death, we used cost estimates from Riley and Lubitz (2010) who estimated the costs from the Medicare program. Although Medicare only covers those who are over 65 years of age or disabled, these were the most accurate estimates available. Lubitz and Riley calculated Medicare expenditures for beneficiaries in their last year of life. They found that 40 percent of the expenditures for people in their last year of life were spent in the last month of life. We used this information to estimate the cost of death by multiplying Medicare expenditures for the last year of life by 40 percent. This provided an approximation of the cost of normal death, as shown in Table 6-2. The estimated cost of death for those ages 65 to 69 was applied to individuals less than 65 when they died. We used this age group because it was the youngest group for which there were data available.

Table 6-2. Death Costs

Age	Cost of Death (2016 USD)
<65	$24,735
65–74	$24,735
75–84	$21,545
>85	$14,623

Source: See text.

6.3 Normal Medical Costs

Normal medical costs include costs for direct medical care outside of standard diabetes treatments, interventions or care for diabetes complications. These costs represent how much the individual would pay if they did not have diabetes. Their inclusion in an analysis is optional and can be used to compute total costs for persons with diabetes (i.e., normal medical costs + diabetes-related costs).

Annual normal medical costs based on age, race/ethnicity, and sex, as specified in Table 6-3. The values in Table 6-3 are assumed.

Table 6-3. Annual normal medical costs of patients with diabetes.

Age (years)	Race / Ethnicity	Male	Female
0 -94	White	$1500	$1500
0 -94	Black	$1500	$1500
0 -94	Hispanic	$1500	$1500
0 -94	Asian	$1500	$1500
0 -94	Native American	$1500	$1500

Source: Assumption

6.4 Updating Costs for Inflation

Costs in the model come from various sources and base years. Costs can be updated to reflect any year using the Consumer Price Index for All Urban Consumers (CPI-U), U.S. city average for medical care services (Table 6-4).

Table 6-4. Cost Update Factors

Year	Index (1982-1984 = 100)
1990	162.8
1991	177
1992	190.1
1993	201.4
1994	211
1995	220.5
1996	228.2
1997	234.6
1998	242.1
1999	250.6
2000	260.8
2001	272.8
2002	285.6
2003	297.1
2004	310.1
2005	323.2
2006	336.2
2007	351.1
2008	364.1
2009	375.6
2010	388.4
2011	400.3
2012	414.9
2013	425.1
2014	435.3
2015	446.8
2016	463.7
2017 (May)	473.5

Source: Bureau of Labor Statistics, Consumer Price Index for All Urban Consumers (CPI-U): U.S. city average for Medical care services, annual rate (except for 2017). Series ID: CUUR0000SAM, not seasonally adjusted.

7. MULTIPLICATIVE COST CALCULATION MODEL (HERMAN)

The costs presented thus far are combined additively. The Herman Multiplicative Model is an alternative cost calculation method. It calculates the annual normal medical cost for each year of life as either a one-time cost associated with an acute event or a base value x the product of several multipliers associated with demographic variables, diabetes-related complications, and diabetes-related treatments (Brandle et al., 2003) so that direct medical costs = baseline cost * demographic multiplier * complications multiplier * treatment multiplier.

7.1 Acute event costs

Brandle and co-authors separately calculate costs associated with acute events of myocardial infarction ($24,500), stroke ($26,600) and amputation ($37,600). When these events occur, we apply the corresponding cost as the total complication costs that year instead of using the multiplicative equation. When more than one of these events occurs in a year, the maximum cost between those events is applied to the year.

Because the costs of photocoagulation and blindness are not otherwise considered in the model, we also allow users to add one-time costs for these complications to the costs calculated using the multiplicative formula. The default values for these costs are $2,943 and $0, respectively, both of which were applied in the normal additive cost portion of the model (Table 7-1). The cost for amputations is also included as an acute event cost.

7.2 Multiplicative cost calculations

The base cost listed in Table 7-1 represents the costs for a non-African-American male with diabetes who has a BMI $\leq$ 30 kg/m^2, is not taking oral anti-diabetic agents or insulin and does not have microalbuminuria, nephropathy, ESRD with dialysis, history of stroke, angina, history of CA/MI, peripheral vascular disease, or treated hypertension. If the individual has any characteristics other than the “base” individual and does not experience any major acute events, his or her cost is equal to the base cost multiplied by the values associated with those characteristics, as listed in Table 7-1. For example, the cost for a white female with type 2 diabetes, microalbuminuria, and angina who receives oral anti-diabetic agents and treatment for hypertension = 1,684 * 1.00 * 1.25 * 1.17 * 1.73 * 1.10 * 1.24 = $5,812.

Demographics Multiplier. The model cohort determines whether the female and race multipliers are used to estimate costs. In the Herman cost model, only African-American status has a significant effect.

The Herman cost model also allows cost to depend on obesity. Our model does not include an obesity cohort. Instead, our default assumption is that individuals have a BMI level of 30 or lower; in this case, the obesity "multiplier" is 1. However, we allow users to select BMI levels greater than 30 for the entire cohort.

Complications Multiplier. The model complications depend on the disease state. Within disease paths, only the multiplier associated with the most severe complication is applied. Thus, if a person has ESRD, the ESRD multiplier is applied, but the multipliers for nephropathy or microalbuminuria are not. Similarly, if a person has a history of CA/MI, the corresponding multiplier is applied but the multiplier for angina is not.

It should be noted that none of the coefficients for retinopathy or neuropathy states were significant in the Herman cost equation, so the default values for these parameters are set equal to one. However, these states are important in our model. To account for this, we allowed one-time costs for photocoagulation and blindness.

The Herman cost model also allows cost to depend on peripheral vascular disease. Our model does not include a specific peripheral vascular state. We assume that 39% of the population has peripheral vascular disease (Table 1, Brandle, et al., 2003), therefore the peripheral vascular disease multiplier is applied to 39% of the population in each state.

Treatment Multiplier. Treatment in the Herman model is defined as glycemic and hypertension control. The glycemic control multiplier is the weighted average of the oral anti-diabetic agents multiplier and the insulin multiplier, weighted according to the percentages of individuals receiving each type of treatment in the Herman diabetes treatment model for that year (see "Glycemic Control" below). The treatment multiplier also includes the hypertension (treated) factor for hypertensive cohorts. Note that in the additive cost calculation model, costs associated with these treatments are included in the costs of standard care or the costs of the intensive glycemic control intervention.

Allocating costs under the multiplicative model. The total costs for a given year under the multiplicative model, when acute event costs are not incurred, are equal to the cost of complications plus the cost of treatment.

The cost of complications is calculated using the following formula:

Complications cost = baseline cost * demographics multiplier * treatment multiplier * (complications multipler – 1)

The treatment cost is then calculated using the following formula:

Treatment cost = baseline cost * demographics multiplier * treatment multiplier

The multiplicative model includes all glycemic and hypertension control costs as treatment costs. The costs of other interventions, screening, and death are added in to their appropriate categories separately.

7.3 Glycemic Control

The multiplicative cost model allows different fractions of people to receive diabetes treatments depending on whether standard or intensive care is selected. The model has separate diabetes treatment parameters for oral diabetic agents and insulin, including the percentage of patients receiving diet only, oral only, insulin only, and oral and insulin by year for patients receiving standard or intensive glycemic control. Individuals in the first 10 years after diabetes onset receive standard glycemic control only, under which they receive either oral diabetic agents only or diet only. During that time 6.03% of patients transition from diet to orals each year; this rate is based on the average of the rates of development of hyperglycemia among the three DPP intervention arms (8.5% in placebo, 5.5% in metformin, 4.1% in lifestyle) (Source: Unpublished DPP data). The distribution of treatments for intensive glycemic control is based on UKPDS patients and is the same distribution upon which the additive cost model costs is based.

Table 7-1. Base Values and Multipliers Associated with Individual-Specific Factors Used in the Herman Multiplicative Model for Individuals with Diabetes

	Category	Diabetes
Base	**n/a**	**$1684**
Multipliers		
Female	demographic	1.25
White	demographic	1.00
Black	demographic	0.82
Hispanic	demographic	1.00
Asian	demographic	1.00
Native American	demographic	1.00
BMI excess over 30 kg/m^2	demographic	1.01
Oral anti-diabetic agents	treatment	1.10
Insulin	treatment	1.59
Microalbuminuria	complication	1.17
Nephropathy	complication	1.30
ESRD with dialysis	complication	10.53
History of stroke	complication	1.30
Angina	complication	1.73
History of CA/MI	complication	1.90
Peripheral vascular disease	complication	1.31
Hypertension (treated)	treatment	1.24

8. HEALTH UTILITY AND QUALITY OF LIFE ADJUSTMENTS

Health utility values between 0 and 1 are used to calculate quality-adjusted life years (QALYs) for patients who are alive. Three different methods can be used to calculate the number of QALYs assigned to a patient each year of life. The first two methods, described in 8.1, are based on the same quality-of-life values assigned to each complication state, but use different strategies to determine the value to assign to an individual when several complications apply at the same time. Section 8.2 describes the Herman Additive QOL Calculation Method.

8.1 Minimum and Product QOL Calculation Methods

Health utility values for diabetes' complications were updated in 2017 after a literature review and meta-analysis of values used in diabetes cost-effectiveness models.

We used all searchable references on quality of life (QoL) for type 2 diabetes–related complications used in the cost-effectiveness models presented at the 2016 Mount Hood meeting in St. Gallen, Switzerland. Nine models were presented in Mount Hood, and two of these have not been published in peer-reviewed journals: MMUs Diabetes Model (Mount Hood, 2016) and the Reference Model (Barhak, 2015). Three of the published models did not include QoL valuation: MICADO (van der Heijden et al., 2015), MDM-TTM (Smolen et al., 2014), and ECHO-T2DM (Willis et al., 2013). We also included QoL estimates from the original CORE Diabetes Model (Palmer et al., 2004); an updated version of this model was presented at the Mount Hood conference, but with less documentation than the original model). This gave us five published cost-effectiveness models and their corresponding published sources.

To find the most-recent publications on utility values associated with diabetes complications, we also searched PubMed and RTI's e-journals library with the following search terms: "quality of life" and "diabetes" or "diabetes complications." We limited our search to articles published after 2000 and excluded articles that were not relevant to type 2 diabetes (i.e., sources that did not provide specific utility values or utility decrements for any of the key diabetes complications, such as blindness, end-stage renal disease [ESRD], lower-extremity amputation [LEA], angina, cardiac arrest/myocardial infarction [CA/MI], congestive heart failure [CHF], or stroke). We also examined all sources presented in Beaudet et al.'s (2014) review of utility values used in economic modeling of type 2 diabetes.

The literature search provided us with five cost-effectiveness models to compare with the CDC-RTI model—UKPDS (Hayes et al., 2013), Michigan (Ye et al., 2015), Cardiff (McEwan et al., 2006), SPHR (Breeze et al., 2015) and CORE (Palmer et al., 2004)—and eight original

studies (Bagust & Beale, 2005; Glasziou et al., 2007; Lloyd et al., 2008; O'Reilly et al., 2011; Ragnarson Tennvall & Apelqvist, 2000; Smith et al., 2008; Solli et al., 2010; Zhang et al., 2012). Table 8-1 shows the references used by the CDC-RTI model and the other five most-well-known cost-effectiveness models.

Table 8-2 presents summary results of all the included studies looking at QoL decrements attributable to diabetes. The table includes the eight additional studies, not included in the cost-effectiveness studies reported in Table 8-1, representing new estimates of diabetes-related complications on QoL. No study provides estimates for all diabetes-related complications present in our model (i.e., blindness, ESRD, LEA, angina, CA/MI, CHF, and stroke).

Table 8-1. Sources of QoL Decrements Attributable to Diabetes Used in Cost-Effectiveness Models

CE Model	Sources Used for QoL Decrements
CDC-RTI	Coffey et al. (2002)
Cardiff Stochastic Simulation Cost-Utility Model	McEwan et al. (2006)
CORE	Coffey et al. (2002); Tengs & Wallace (2000)
Michigan (2015)	Coffey et al. (2002)
UKPDS Outcomes Model V1	Clarke et al. (2002)
UKPDS Outcomes Model V2	Alva et al. (2014)
SPHR	Alva et al. (2014); Coffey et al. (2002)

All studies but one used the EQ–5D as their health-related QoL instrument. The EQ-5D covers five dimensions (mobility, self-care, usual activity, pain or discomfort, and anxiety and depression) each of which has three levels (no problem, some problems, and extreme problems). Reference values for each of the possible 243 health states are combined into a single utility score with weightings derived from country-specific population studies where preference values are elicited using the time-trade-off (TTO) method. The algorithms produce tariffs ranging from 1 (for full health) to less than zero (for a severe problem). As zero represents death, negative values of the index indicate states that are deemed to be "worse than death."

Out of the 11 studies that used the EQ-5D, one study used the Health Utilities Index 3 (HUI3) (Lloyd et al., 2008), one study used the Quality of Well-Being Scale Self-Administered (QWB-SA) (Coffey et al., 2002), and one study compared different versions of

the Standard Form (SF) questionnaire (i.e., SF-36, SF-12, SF-6D). Lloyd et al. (2008) and Glasziou et al. (2007) used two or more instruments.

The SF-36 and SF-12 are not directly translatable into utility scores, but patients who complete these questionnaires can be classified according to the SF-6D. SF-6D is a classification for describing health derived from a selection of items. The SF-6D comes with a set of preference weights obtained from a sample of the general population using the standard gamble (SG) as the valuation mechanism. The choice of the most appropriate elicitation mechanism is as controversial as the choice of QoL instrument (Glasziou et al., 2007). Both the SG and TTO methods share a common theoretical foundation in utility theory; they both require people to sacrifice something they value (certainty and life expectancy, respectively) to gain another (QoL). In a comparison between these two methods, Dolan et al. (1996) showed that TTO performed slightly better in terms of the internal consistency of the answers given by respondents, the sensitivity of valuations to parameters known to influence respondents, and the reliability of responses when the valuation task was repeated by the same respondents.

Table 8-2. Additional Sources of QoL Decrements Attributable to Diabetes

Additional Sources	Sample Size	Number of Chronic Conditions	Type of Chronic Condition	Valuation Instrument	Country	Baseline Utility
New Studies						
Ragnarson Tennvall & Apelqvist (2000)	310	1	LEA	EQ-5D	SWE	0.702
Bagust & Beale (2005)	4,641	5	Blindness, ESRD, LEA, CA/MI, Stroke	EQ-5D	Europe	1.027
Glasziou et al. (2007)	975	5	Blindness, LEA, Angina, CA/MI, Stroke	SF-6D SF-12/ SF-6D SF-36/EQ-5 D UK/ EQ-5D US	AUS	
Smith (2008)	2,074	1	Blindness	EQ-5D	US	0.94
Lloyd et al. (2008)	321	1	Blindness	EQ-5D/HUI	UK	0.83/0.81
Solli et al. (2010)	356	1	Stroke	EQ-5D	NOR	0.85
O'Reilly et al. (2011)	1,143	4	ESRD, LEA, CA/MI, Stroke	EQ-5D	CAN (US weights)	0.76

(continued)

Table 8-2. Additional Sources of QoL Decrements Attributable to Diabetes (continued)

Additional Sources	Sample Size	Number of Chronic Conditions	Type of Chronic Condition	Valuation Instrument	Country	Baseline Utility
Zhang et al. (2012)	7,327	6	ESRD, LEA, Angina, CA/MI, Stroke, CHF	EQ-5D	US	0.92
Studies Used in Major Models						
Coffey at al. (2002)	1,257	5	Blindness, ESRD, LEA, Stroke, CHF	QWB-SA	US	0.689
Clarke et al. (2002)	3,129	5	Blindness, LEA, CA/MI, Stroke, CHF	EQ-5D	UK	0.785
McEwan et al. (2006)	20,664	5	Blindness, ESRD, LEA, CA/MI, Stroke	EQ-5D	UK	0.71
Alva et al. (2014)	3,380	5	Blindness, LEA, CA/MI, Stroke, CHF	EQ-5D	UK	0.807

Note: We excluded Tengs and Wallace (2000), used in the CORE model, because they only provide utility decrements and no population, standard error, or baseline values.

The HUI-3 classification system consists of eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each attribute has five or six levels of health states. The utility values are determined using TTO methods that determine preferences for particular health states. In HUI-3, utility values range from −0.36 to 1, where 1 indicates perfect health, and 0 indicates death.

QWB-SA has 4 domain scores (physical activities, social activities, mobility, and symptom or problem complexes) and 71 questions, which are combined into a total score that ranges from 0 to 1.0, with 1.0 representing optimum function and 0 representing death (Kaplan et al., 1997).

From an economic perspective, questionnaires with descriptive system of QoL that can be translated into index values using preference weights from the general population are preferred. This means that the index value can be regarded as a societal valuation of health states rather than the patient's own assessment of his or her health state.

Differences across studies are amplified by the fact that the same valuation instrument is paired with different sources of tariffs depending on the country in which the study was performed. For example, the Dolan (1997) tariff was used in U.K.-based studies using the EQ-5D and in the Australian study conducted by Glasziou et al. (2007). Zhang et al. (2012)

and O'Reilly et al. (2011) used U.S. weights provided by Johnson et al. (1998), and Smith et al. (2008) used U.S. weights provided by Shaw et al. (2005). For comparisons across weights, see Appendix B.1.

When analyzing the marginal impact of type 2 diabetes complications, it is important to note that the utility decrements need to be anchored to a baseline of "no complication." The baseline utility also provides information on the underlying health state of the population sampled. Baseline utilities in the sample range from 1.027 in Bagust and Beale (2005) to 0.702 in Ragnarson Tennvall and Apelqvist (2000). Bagust and Beale (2005) chose to transform the 0–1 tariff by rescaling values so that all values would be greater than zero.

For each of the seven complications used in our model, we pooled results from the literature using meta-analyses. In meta-analysis, an important decision is how to assign weights to each study and how to select the appropriate model (fixed versus random effects). Results from studies can be pooled by fitting either a fixed-effects or a random-effects model. Under the fixed-effects model, we assume that the true effect is the same in all studies. By contrast, under the random-effects model, the underlying assumption is that true effect may vary from one study to the next. Under fixed effects, the weights are the reciprocals of the squared standard error, and under random effects, the weights follow the DerSimonian and Laird method (Egger et al., 2007). To undertake the random effects meta-analysis, the standard errors of the study-specific estimates are adjusted to incorporate a measure of the extent of variation, or heterogeneity, among the intervention effects observed in different studies. The amount of variation, and hence the adjustment, is estimated from the intervention effects and standard errors of the studies included in the meta-analysis.

Heterogeneity tests conducted suggest that studies should be pooled using the random-effects method. It is important to note that smaller studies are given relatively more weight with the random-effects analysis than with the fixed-effects model.

Results of the meta-analysis are shown in Table 8-3. The model inputs are in the form of QoL levels for each complication. These can be calculated by subtracting the utility decrement from the baseline utility. The default baseline utility is set as 1, so the utility level for someone with blindness would be 1 – 0.161 = 0.839.

Table 8-3. Quality of Life Decrements

Health State	Utility Decrement from Meta-Analysis
Blindness	−0.161 (95% CI: −0.222, −0.1)
ESRD	−0.130 (95% CI: −0.21, −0.05)
LEA	−0.170 (95% CI: −0.240, −0.1)
Angina	−0.050 (95% CI: −0.100, 0.01)
History of CA/MI	−0.040 (95% CI: −0.05, −0.03)
Stroke	−0.110 (95% CI: −0.19, −0.04)
CHF	−0.060 (95% CI: −0.08, −0.04)

8.2 Additive QOL Calculation Method for Diabetes (Herman)

The Herman Additive QOL Calculation Model, described in Coffey, et. al. (2002), uses a regression equation to calculate the number of QALYs to assign to an individual for each year of life. Table 8-4 lists the equation's intercept and coefficients associated with each relevant factor. The variables in the equation equal 1 if the factor is true of the individual and 0 otherwise. The intercept represents the QALYs for a diabetic male with a BMI < 30 who does not have hypertension, blindness, nephropathy, ESRD, peripheral neuropathy, foot ulcer, lower extremity amputation, or history of CA/MI or stroke. If the individual has any characteristics other than the "base" individual, the value of the coefficient associated with that characteristic is added to the intercept.

Table 8-4. Intercept and coefficients associated with individual-specific factors used in the Herman Additive Model for calculating QALYs for individuals with diabetes

Intercept	**0.6890**
Coefficients	
Female	-0.0380
Hypertension	-0.0110
Blind	-0.1700
Nephropathy	-0.0110
End Stage Renal Disease (ESRD)	-0.0780
Peripheral Neuropathy	-0.0650
Foot Ulcer	-0.0990
Lower Extremity Amputation	-0.1050
History of CA/MI	-0.0520
Stroke	-0.0720
BMI ≥ 30.0	-0.0210

Source: Coffey et al. (2002).

The utility decrements shown in Table 8-3 in Section 8.1 could be substituted into the Herman Additive Model. This would, however, negate the Herman Additive Model's advantage of being computed from a single data source.

9. MODEL COMPUTATIONS

The global state transition matrix ($S_{nurcs + death}$) is computed from the transition matrices for each of the five disease paths. Each of the five indices on the S matrix indicates a specific disease state in each of the five disease paths (nephropathy, neuropathy, retinopathy, CHD, and stroke). In this manner, S_{42321} represents the state where individuals have ESRD (n_4), peripheral neuropathy (u_2), blindness (r_3), history of CHD (c_2), and no history of stroke (s_1). The single "death" state is a global death state and encompasses all of the individual deaths from each disease path as well as deaths from other causes. The matrix is large with 217 states ($4 \times 3 \times 3 \times 3 \times 2 + 1$).

We use a global state transition matrix instead of the matrices for the five individual disease paths separately due to the

- interaction between the CHD and nephropathy disease paths,
- ability to include other dependency relationships in the future,
- different causes of death and the appropriate accounting techniques necessary to avoid double counting deaths, and
- computational issues.

Presently, the model contains one major interdependency between disease paths. Once patients reach microalbuminuria on the nephropathy disease path, they are assumed to have high blood pressure. Because hypertensives have higher risk of CHD and stroke and hazard rates for hypertensives are higher on the nephropathy and retinopathy paths, this assumption leads to faster progression on each of these paths.

To compute the transition probability for going from S_{nurcs} to $S_{n'u'r'c's'}$, the computer program looks up the transition probability of going from n to n', the transition probability of going from u to u', the transition probability of going from r to r', the transition probability of going from c to c', and the transition probability of going from s to s', and multiplies all of the probabilities to obtain the global transition probability. The multiplicative approach is appropriate because the transition probabilities are independent across disease states, conditional on hypertension status. The model updates the patient's hypertension status once microalbuminuria is reached.

Deaths caused by disease progression in one of the five disease paths are incorporated into the model formulation. To account for deaths from other causes, a few additional calculations are necessary. We assume deaths from other causes are equally likely to occur to individuals in any state. Let the age-specific probability of death = p_d. Once the global state transition matrix has been calculated and implemented for the specific time period, we

multiply all of the alive states in the resulting state vector by $(1 - p_d)$. In this manner, $newS_{nurcs} = S_{nurcs}*(1 - p_d)$. We then add $newS_{death} = S_{nurcs}*(p_d)$ individuals from each state to the death state.

To avoid double counting deaths from the different diabetic disease paths, the model only contains one death state. Recall that in this model a cohort is simultaneously in a nephropathy, neuropathy, retinopathy, CHD, and stroke state. The probability of being in a given state is the product of the probability of transitioning to each state in the individual disease paths. The probability of transitioning to the global death state equals 1 minus the sum of the probabilities of transitioning to all the other possible states. The death rates from the individual disease paths are used to calculate the transition probability of remaining in a disease state within the individual disease path. For example, the probability of staying in ESRD is 1 minus the probability of dying due to ESRD. At the end of each 1-year time interval, the entire cohort is diminished by the death from other causes, each state being equally affected.

We now describe how to use the transition probabilities defined in the previous sections to compute the lifetime costs and effectiveness for a cohort of diabetes patients.

$P_j(t+1)$, the probability of being in state j (where j represents one $S_{nurcs + death}$ combination) at time t+1, is given by

$$P_j(t+1) = \Sigma_i P_i(t) \times p_{i,j}(t)$$

If $\mathbf{P}(t)$ is the vector of state probabilities at time t and $\mathbf{p}(t)$ is the transition probability matrix at time t, then

$$\mathbf{P}(t+1) = \mathbf{P}(t) \times \mathbf{p}(t)$$

Hence,

$$\mathbf{P}(t+1) = \mathbf{P}(0) \times \mathbf{p}(1) \times \mathbf{p}(2) \ldots \mathbf{p}(t)$$

Thus, if we know the initial distribution of patients among the different disease states [$\mathbf{P}(0)$] and the transition probability matrix at every given point in time, we can compute the distribution of patients among the disease states at any given point in time.

We can use the transition probability matrix to compute the total cost of treating the given patient population as well as their quality-adjusted life years (QALYs). Let **C** be the vector corresponding to the average cost of treating a patient in the different disease states for one time period. Now the average treatment cost for the patient population at time t is given by

$\mathbf{C}(t) = \mathbf{P}(t) \times \mathbf{C}$

The total cost over the lifetime of the cohort, discounted using a discount rate r, is

$\text{Total cost} = \Sigma_t \mathbf{C}(t) / (1+r)^t$

Similarly, if **Q** is the vector of health utility weights for the different disease states, the average QALY at time t is given by

$\mathbf{Q}(t) = \mathbf{P}(t) \times \mathbf{Q}$

The total QALY over the lifetime of the cohort, discounted using a discount rate r, is

$\text{Total QALY} = \Sigma_t \mathbf{Q}(t) / (1+r)^t$

To estimate the cost-effectiveness of an intervention, the model is first run under the baseline parameters and then run under the intervention assumptions. The difference in costs ($\Delta\mathbf{C}$) and QALYs ($\Delta\mathbf{Q}$) between the intervention and baseline estimates can then be combined to form the incremental CE ratio, using the following formula:

$\text{Incremental CE ratio} = \Delta\mathbf{C} / \Delta\mathbf{Q}$

The intervention's effects on outcomes will generally be transmitted by changing transition probabilities. For example, intensive glycemic control affects many of the transition probabilities through a multiplier. As a cohort's progress through the successively worsening states of diabetes complications is slowed, patient quality of life will improve and the costs associated with the later, more, serious disease stages will occur farther in the future. Interventions will also incur immediate costs associated with their implementation.

10. IMPAIRED GLUCOSE TOLERANCE (IGT), EARLY DIABETES AND THE DIABETES PREVENTION PROGRAM (DPP)

This section describes the other two major modules covered in the model – the IGT/DPP Module and the Early Diabetes Progression Module. We first discuss the two components of the IGT/DPP Module, the disease state of IGT and the DPP intervention. In the final portion of section 10, we will describe the disease progression of patients with early diabetes.

10.1 Distribution of IGT Population

In order to run the model for a cohort of DPP patients with IGT, it was necessary to determine the distribution of the population among the different population groups as defined by age, sex, race/ethnicity, hypertension status, cholesterol status, and smoking status. We estimated the population distribution using published data on the baseline characteristics of the randomized DPP cohort (Diabetes Prevention Program Research Group, 2000). The distribution of persons with IGT by age, race, sex, and smoking, hypertension and cholesterol status was determined using the following formula:

> (% in age group by sex, race) * (% in race group by sex) * (% in sex group) * (% w/ smoking status by sex) * (% w/ hypertension status by race) * (% w/ cholesterol status by sex, race).

10.2 IGT Disease Progression

Patients with IGT are followed in the model from the time of diagnosis of IGT to diagnosis of diabetes, or death, whichever comes first.

10.2.1 IGT complications

Persons with IGT may already have some complications at IGT diagnosis. The distribution among disease states at IGT diagnosis is outlined in Table 10-1. The values populating this table are based on initial complication levels of patients in the DPP study. Small portions of the population were non-normal on all disease paths except for retinopathy. Some complications, including angina, made individuals ineligible for participation in the study and were therefore not present in the population.

Table 10-1. Initial disease distribution at diagnosis of IGT

Disease	Disease state	Percentage	Source
Nephropathy	Normal	94.00	Unpublished DPP study data
	Microalbuminuria	5.60	
	Nephropathy	0.40	
	ESRD	0.00	
Neuropathy	Normal	91.50	Egypt study by Herman, et al. 1998
	Peripheral Neuropathy	8.50	
	LEA	0.00	
Retinopathy (3-state)	Normal	100.00	
	Photocoagulation	0.00	
	Blind	0.00	
CHD	Normal	98.00	Table 6, DPP Research Group, 2000 (ECG results for MN code MI)
	Angina	0.00	
	History of CA/MI	2.00	
Stroke	Normal	98.90	Table 6 in DPP Research Group, 2000
	Stroke	1.10	

Patients with IGT may also develop CHD, stroke, early stages of nephropathy and neuropathy, or death. Table 10-2 includes hazard rates associated with the development of microalbuminuria and peripheral neuropathy while an individual has IGT. We assume that both are 0. The table also lists risk factors to apply multiplicatively to the results of the Framingham and UKPDS risk engine for calculating CHD and stroke risk. The Framingham equation is based on individuals without diabetes, therefore the risk factors associated with IGT are greater than 1; the UKPDS risk equation, however, calculates risks for individuals with diabetes, so the risk factors are less than 1, indicating a reduced risk. We assumed Framingham risk factors. UKPDS risk engine risk factors for CHD and stroke are based on odds ratios of adverse event risks for persons with IGT versus persons with diabetes published by Qureshi, et al. (1998). The relative risk of death from causes other than diabetes-related complications for persons with IGT is assumed to be equal to 1.

Table 10-2. Disease progression for an individual with IGT

Hazard rate for IGT Normal	
Microalbuminuria	0.00
Peripheral Neuropathy	0.00
IGT Coronary Heart Disease risk factor	
Framingham equation	1.50
UKPDS risk engine	0.58
IGT Stroke risk factor	
Framingham equation	1.50
UKPDS risk engine	0.56
Relative risk of death from other causes (vs. diabetes)	1.00

10.2.2 IGT blood pressure and cholesterol

Individuals with IGT may also develop high blood pressure or high cholesterol. The values used in the model for both hazard rates, below in Table 10-3, are based on the number of persons with hypertension and hyperlipidemia in the DPP study in each intervention arm over time (Source: Unpublished DPP study data).

Table 10-3. Disease progression for an individual with IGT

Years since diagnosis	Hazard rate, high blood pressure	Hazard rate, high cholesterol
0 – 94	0.0506	0.0375

10.2.3 Diabetes onset

Persons in the model with IGT run the risk each year of developing diabetes. The annual probability of onset of diabetes in a person with IGT is 0.108 (Source: Unpublished DPP study data). This risk value is based on the progression into diabetes of participants in the placebo arm of the DPP study.

10.3 Medical Costs

10.3.1 Additive Cost Calculation Model for IGT

Like the Additive Model for diabetes described in 6.1.2, the Additive Model for IGT determines annual normal medical costs based on age, race/ethnicity and sex, as specified in Table 10-4. The values in Table 10-4 are assumptions only.

Table 10-4. Annual normal medical costs used in the Additive Model for IGT.

Age (years)	Race / Ethnicity	Male	Female
0 -94	White	$1100	$1100
0 -94	African American	$1100	$1100
0 -94	Hispanic	$1100	$1100
0 -94	Asian	$1100	$1100
0 -94	Native American	$1100	$1100

10.3.2 Multiplicative Cost Calculation Model for IGT

Our model allows for costs for persons with IGT to also be calculated using a multiplicative model with the same structure as that described in Section 6.1.2 for persons with diabetes (Herman model). We have included the same multiplicative equation as for diabetes, but with different coefficients. We note, however, that this equation has not been estimated for IGT, so these coefficients are based on assumptions. The base cost for IGT, $1296, is based on the average direct medical costs for male participants in the DPP study for care outside the DPP (Source: Unpublished breakdown of costs published by the DPP Research Group, 2003). We assume that being female or being African-American will have the same effect on patients with IGT as they have on patients with diabetes. In our model, patients with IGT cannot develop microalbuminuria, nephropathy, or ESRD, nor do they receive oral agents or insulin. Therefore, the multipliers for these variables are set to one, which is equivalent to saying that the variables are not included in the cost equation. Our model allows IGT patients to develop stroke, CA/MI, and angina; we assume that these events have the same multipliers as for patients with diabetes. We also apply the acute costs of stroke and MI. Finally, we allow the user to set obesity levels greater than 30 BMI. Unlike the model's application to persons with diabetes, peripheral vascular disease is not applied to any portion of the IGT cohort.

Table 10-5. Base values and multipliers associated with individual-specific factors used in the Herman Multiplicative Model for individuals with IGT

	Category	IGT
Base	**n/a**	**$1296**
Multipliers		
Female	demographic	1.1420
White	demographic	1.0000
African-American	demographic	0.8200
Hispanic	demographic	1.0000
Asian	demographic	1.0000
Native American	demographic	1.0000
BMI excess over 30 kg/m^2	demographic	1.0100
Oral anti-diabetic agents	treatment	1.0000
Insulin	treatment	1.0000
Microalbuminuria	complication	1.0000

10.4 Health Utility and QOL Adjustments

10.4.1 Minimum and Product QOL Calculation Methods for IGT

The Minimum and Product Methods for calculating QALYs for individuals with IGT are the same as those for persons with diabetes. QOL values associated with the various health states of IGT are also equal to those applied to diabetes.

10.4.2 Additive Cost Calculation Model for IGT

A Herman Additive QOL Calculation Model similar to the one described in 8.2 exists for calculating the number of QALYs to assign for each year of life to an individual with IGT (the model in 8.2 if for persons with diabetes). Table 10-6 lists the intercept value and coefficients associated with each relevant factor. The values of the intercept and DPP intervention coefficients are based on DPP participants (Herman et al., 2005). All others are common to both this model and the diabetes model in 8.2 and have the same coefficient values.

Table 10-6. Intercept and coefficents associated with individual-specific factors used in the Herman Additive Model for calculating QALYs for individuals with IGT

Intercept	**0.7302**
Coefficients	
Female	-0.0380
Hypertension	-0.0110
Blind	-0.1700
Nephropathy	-0.0110
End Stage Renal Disease (ESRD)	-0.0780
Peripheral Neuropathy	-0.0650
Foot Ulcer	-0.0990
Lower Extremity Amputation	-0.1050
History of CA/MI	-0.0520
Stroke	-0.0720
BMI $\geq$ 30.0	-0.0210
DPP Lifestyle Intervention	0.0189
DPP Metformin Intervention	0.0000

10.5 DPP Intervention

Patients with IGT receive either a placebo intervention or one of two DPP interventions – one based on intensive lifestyle changes (Lifestyle) and the other on the antihyperglycemic drug metformin. The model assumes that diagnosis occurs at disease onset because of regular screening of all DPP participants, including the placebo group.

10.5.1 DPP Effects

The primary effect of the DPP intervention is a reduction in the risk of diabetes onset for individuals with IGT. This effect is applied in the model by multiplying the probability of transitioning from IGT to diabetes by (1- the relevant risk reduction factor), which is less than or equal to 1. Risk reduction factors vary by the year of the intervention and the DPP intervention arm. Values used in the model are listed in Table 10-7. Risk reduction values for years 1 through 3 are based on 3-year DPP study findings (Source: Unpublished DPP study data). We assumed a continuation of the same DPP effect for years 4 and on.

Table 10-7. Diabetes onset risk reduction, as compared to the placebo group, by DPP intervention arm and year since intervention start

	Year of Intervention			
Intervention Arm	**1**	**2**	**3**	**4+**
Lifestyle	0.553	0.553	0.553	0.553
Metformin	0.299	0.299	0.299	0.299
No Intervention (placebo)	0	0	0	0

Table 10-3 in Section 10.2.2 lists the baseline hazard rates for development of high blood pressure and high cholesterol for persons with IGT. In our model we allow the DPP to reduce the development of both of these conditions for persons with IGT. The risk reduction values applied in the model (Table 10-8) are based on the prevalence of hypertension and hyperlipidemia at baseline and at 3 years among the DPP study groups (Source: Unpublished DPP study data). From that data, we assume that the Lifestyle intervention reduces the risks of high blood pressure by 100% and high cholesterol by 22.6%. Metformin has no risk reduction effects.

Table 10-8. Hypertension and hyperlipidemia onset risk reduction by DPP intervention arm and year since IGT diagnosis / intervention start

		Risk reduction	
Intervention type	**Years since IGT diagnosis**	**High blood pressure**	**High cholesterol**
Metformin	0 - 94	0.0	0.0
Lifestyle	0 - 94	100.0	22.6
No Intervention (placebo)	0 - 94	0.0	0.0

The DPP also can affect quality of life when applying the additive QOL model, as specified in Section 10.4.

10.5.2 Cost of the DPP

The DPP-related costs included in the model are those for implementation of the interventions, the direct costs of medical care incurred or averted by the interventions outside the DPP, and annual diagnostic tests.

Intervention implementation costs. Intervention implementation costs, listed in Table 10-9, are per-capita averages based on the full DPP cohort. They include personnel time,

health education materials, medications and laboratory tests related to the DPP. Values for years 1 through 3 are based on published numbers by the (Diabetes Prevention Program Research Group, 2000). We assumed the same implementation costs for years 4 and on as were incurred in year 3.

Table 10-9. Per-capita DPP intervention implementation costs, by DPP intervention arm and year since intervention start

Intervention Arm	Format	Year of Intervention			
		1	2	3	4+
Lifestyle	Standard	1399	679	702	702
	Groups of 10	537	299	323	323
Metformin	Standard	1019	772	751	751
	Generic	517	308	306	306
No Intervention (placebo)		43	18	18	18

Source: Diabetes Prevention Program Research Group, 2003

Care outside of DPP. The costs of medical care outside the DPP, listed in Table 10-10, are per-capita averages based on the full DPP cohort. They include all inpatient, outpatient, emergency room, and urgent care visits; telephone calls to health care providers; and prescription medicines incurred by DPP participants outside of DPP intervention implementation. The model considers only the differences from the gender-specific averages, $1,480 for males and $1,296 for females.

Table 10-10. Per-capita costs for medical care outside the DPP, by DPP intervention arm and sex

Intervention Arm	Per-capita annual cost		Difference from gender-specific average cost	
	Males	Females	Males	Females
Lifestyle	1,192	1,447	-105	-33
Metformin	1,380	1,460	83	-20
No Intervention (placebo)	1,320	1,533	23	53
Average	1,480	1,296	0	0

Source: Diabetes Prevention Program Research Group, 2003 (Unpublished cost breakdown)

Annual diagnostic tests. DPP participants in all 3 intervention arms were given annual diagnostic tests to detect diabetes onset. Our model assumes that each test requires an extra 10 minutes of physician time over the usual 15-minute visit ($58.66-$38.63=$20.03)

plus the cost of administering and processing the test itself (Table 10-11). We assumed use of the oral glucose tolerance test (OGTT) and 100% test accuracy. The total cost per test sums to $37.83.

Table 10-11. Costs to conduct annual diagnostic test for onset of diabetes

Cost of 15 minute physician visit (CPT code 99213)	$38.63	*RBRVS*, 1997
Cost of 25 minute physician visit (CPT code 99214)	$58.66	*RBRVS*, 1997
Cost of OGTT test	$17.80	1999 Medicare Clinical Diagnostic Laboratory Fee Schedule

10.6 Early diabetes

Because diagnostic tests are conducted with all patients in the DPP every year, we assume that any that are diagnosed with diabetes are diagnosed immediately after onset. As was specified earlier, however, the model assumes that patients with diabetes who are diagnosed through usual methods have 10 years between onset and diagnosis, upon which the Diabetes Progression module begins. The Early Diabetes Progression module covers the time between onset and the start of the Diabetes Progression for those individuals diagnosed with diabetes before the time of normal clinical diagnosis. The model assumes that disease progression and complication development may be different during this time than after the time of normal clinical diagnosis.

The parameters that determine complication rates during early diabetes, outlined in Table 10-12, are hazard rates that lead to the same complication incidence after 10 years as is set in the model for individuals diagnosed at the time of normal diagnosis. For example, a hazard rate of 0.0064 for developing microalbuminuria from the normal state results in 6.5% incidence of microalbuminuria by 10 years, the same initial percentage of patients newly diagnosed with diabetes 10 years after onset.

Table 10-12. Hazard rates for disease progression from onset of diabetes until normal time of diagnosis (Early Diabetes Progression module)

disease	from disease state	to disease state	hazard rate
Nephropathy	Normal	Microalbuminuria	0.0064
	Microalbuminuria	Nephropathy	0.0
	Nephropathy	ESRD	0.0
	Normal	Peripheral Neuropathy	0.00333
	Peripheral Neuropathy	Lower Extremity Amputation	0.0
Retinopathy (6-state)	Normal	Background Retinopathy	0.0
	Background Retinopathy	Macular Edema	0.0
	Background Retinopathy	Proliferative Retinopathy	0.0
	Macular Edema	Blind	0.0
	Proliferative Retinopathy	Blind	0.0
Retinopathy (3-state)	Normal	Photocoagulation	0.0
	Photocoagulation	Blind	0.0

Source: see text.

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