**Appendix for**
**"Cost Implications of Improving Blood Glucose Management among U.S. Adults"**

The objective of this study was to estimate the cost and cost-effectiveness *from the healthcare payer perspective* of consistently providing the basic recommended elements of blood glucose management to U.S. adults with type 2 diabetes mellitus. As explained in the Methods section, we compared the annual costs and proportions of diabetic individuals attaining treatment goals between a "status quo" scenario (baseline quality) and an "improved care" scenario (100% of recommended care processes).

The analysis involved the following steps:

1. Selecting quality-of-care criteria (process-of-care criteria and HbA1c outcomes);
2. Developing a probability model;
3. Using the model to characterize care in the Community Quality Index (CQI) study ("status quo scenario");
4. Using the model to characterize care involving 100% adherence to the process-of-care criteria ("improved care scenario"), and estimating the effects of improved care on HbA1c outcomes;
5. Estimating utilization and costs under both scenarios;
6. Calculating annual per-patient costs and incremental cost-effectiveness per patient achieving goals; and
7. Performing sensitivity analyses.

Costs are represented in 2009 U.S. dollars; because we focused on recurring annual costs, we did not discount costs in the main analysis.

PubMed searches provided several parameters for the improved care scenario, ranges for sensitivity analyses, and variables pertaining to secondary analyses that focused on longer-term outcomes and costs. Search terms included diabetes mellitus, glucose/glycemic/intensive control, and cost. PubMed searches identified 551 articles. We identified relevant articles by sequentially reviewing titles, abstracts, and article texts. For each relevant article, we examined references and the first 20 related articles listed by PubMed. We also accessed nationally recognized treatment guidelines and quality measures.

1) Quality-of-Care Criteria

Our objective was to select process-of-care criteria and HbA1c outcomes that reflect the current standard of care, acknowledging that this standard is evolving. We drew from current American Diabetes Association (ADA) guidelines, current HEDIS measures, measures used in the CQI study, and other sources.

Glucose management includes two basic care processes: HbA1c monitoring and medication initiation or adjustment when HbA1c is above goal. Because it is widely recommended that HbA1c be assessed at least every six months, we used this as the process-of-care criterion for HbA1c monitoring.[1, 2]

Selecting HbA1c levels that warrant medication initiation or adjustment was more complex. One recently published set of process measures recommends medication initiation or adjustment for HbA1c >7%.[3] Although this goal had previously been widely accepted as appropriate for most patients based on historical trials, studies published in 2008 have called it into question due to increases in mortality and hypoglycemic events among some patients.[4-6] The ADA continues to recommend a goal of <7% for most patients but recommends that providers should set individualized goals.[2] The 2010 HEDIS measures consider HbA1c <8% to represent "control" and <7% to represent "good control;" HEDIS identified these as "first-year indicators" in 2009. The latter measure (<7%) applies to a restricted population that excludes individuals aged 65-75 or with ischemic vascular disease (with or without prior myocardial infarction), chronic renal insufficiency, heart failure, dementia, history of amputation, or blindness. HEDIS considers HbA1c >9% to represent "poor control."[7]

Based on the above information, we selected medication initiation/adjustment criteria for the model that represented a minimum standard of care applicable to most patients: within 3 months of having a HbA1c value >=8%, patients who are already taking antihyperglycemic medications should have a medication adjustment, and patients who are not should be started on them. The tree structure of the model cannot accommodate "individualized goals." Further, setting individualized goals would involve considering factors that were not assessed in the CQI study, such as patient preferences and adherence to medication therapy.

Although the model required a single HbA1c threshold for determining when medication therapy was adequate, it did permit consideration of multiple outcome criteria. We based these on the 2010 HEDIS measures, which are similar to thresholds that have been used by other quality-of-care researchers.[7, 8]

2) Probability Model

Based on the quality-of-care criteria above, we developed a probability model that depicts the management of blood glucose across a single cycle of recommended testing, medication adjustment, and retesting. Such a cycle can last up to one year, which we call the "modeling period."

Sequential branch points in the probability model included: (1) taking antihyperglycemic medications before the modeling period (yes or no), (2) receipt of an initial HbA1c test within the recommended interval (<180 days, >180 days, no tests), (3) first HbA1c test result >= 8% (yes or no), (4) if that result was >=8%, medications initiated or adjusted within the recommended interval (yes or no), (5) receipt of a follow-up HbA1c test within the recommended interval (<180 days, >180 days, no tests), and (6) HbA1c outcome at the end of the modeling period (3 iterations: <7% vs. >=7%, <8% vs. >=8%, and <=9% vs. >9%). Figure A-1 depicts a portion of the probability tree for the HbA1c outcome threshold of <8% in graphical format. Figure A-2 includes the same but complete tree in a tabular format that includes the probabilities for each branch in the status quo and improved care scenarios.

Figure A-1 only includes the subset of patients with established type 2 diabetes mellitus who were on medications upon entry to the modeling period. The complete model contains analogous branches for patients who were not on medications upon study entry, indicated by "A". As explained in the manuscript and the next section, patients were then stratified by their average HbA1c testing frequency over their two-year wave period. The figure depicts only patients who had HbA1c tests at less than 180-day intervals; the branches are analogous for patients who had more frequent tests, indicated by "B". Patients who received HbA1c tests were stratified by whether their first result was >= 8%, in which case they had medications initiated or adjusted, or not. We based the timing of the second HbA1c test on the average HbA1c testing frequency as well (i.e., patients with a predicted mean time between tests of < 180 days were assumed to have all tests within 180 days).

3) Status Quo Scenario

*Study Subjects*

To determine branch probabilities for the status quo scenario, we applied the probability model to subjects with type 2 diabetes from the CQI study. The CQI study is a collateral study of the Community Tracking Study, which includes a random sample of the U.S. population. Random-digit-dial telephone surveys identified 6,712 adults from 12 metropolitan areas (round 1) and a national sample of 7,598 adults (round 2). In both rounds, trained nurses collected data from medical records in up to two two-year waves per patient from 1996 to 2002. Data from outpatient physician visits included blood pressures, medication changes, and lifestyle counseling. We restricted the current analysis to 821 adults with pre-existing type 2 diabetes at the start of one of their two-year follow-up periods. We used the first available two-year wave of data for each subject (herein, "wave period"), and applied the probability model to the first of these years (herein, "modeling period"). Table A-1 lists subjects' demographic and clinical characteristics.(3) As noted above, Figure A-2 includes the branch probabilities for this scenario.

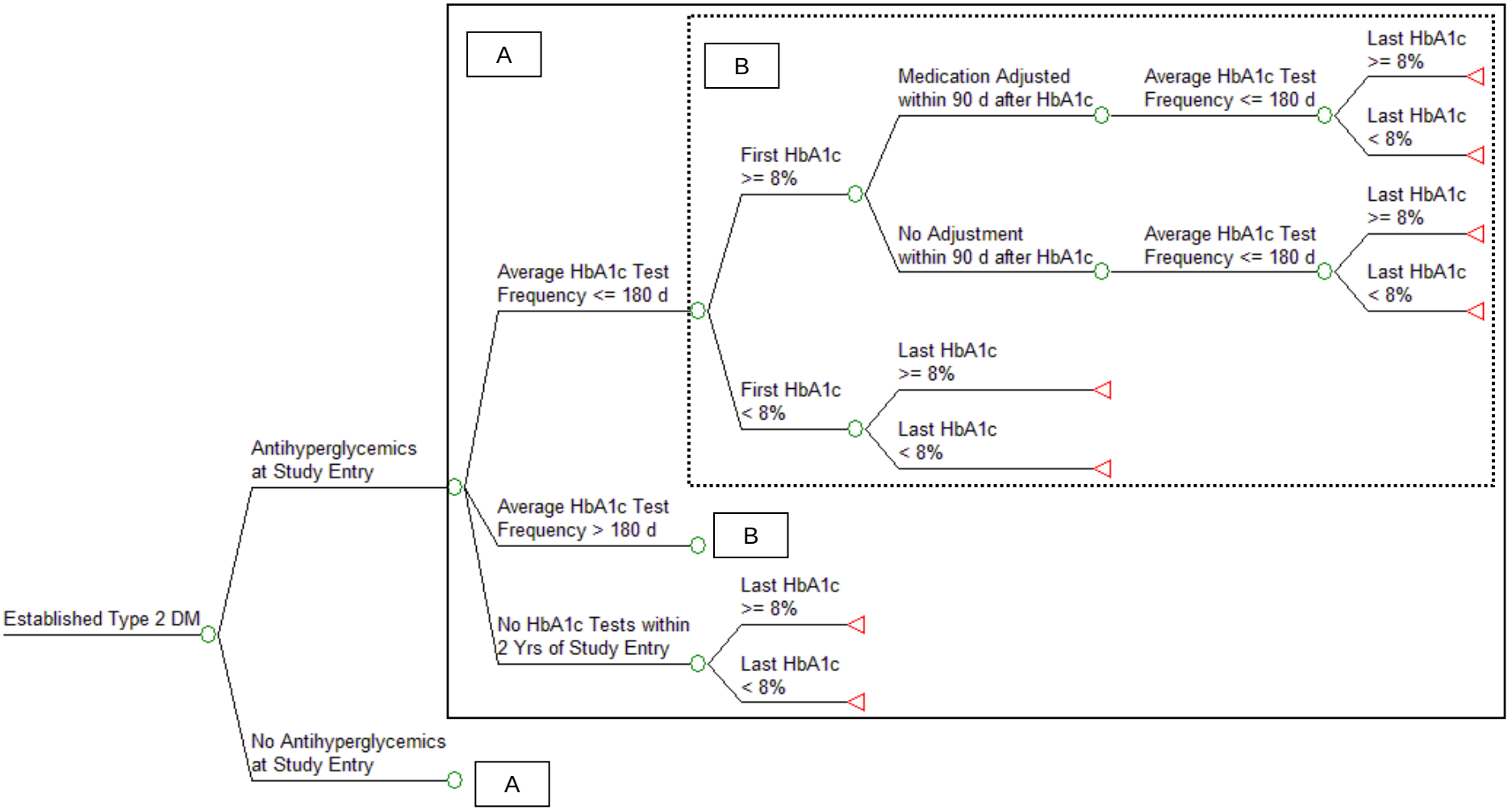


**Figure A-1: The Status Quo Glucose Management Model for HbA1c Threshold < 8%**

**Table A-1: Demographic and Clinical Characteristics of Adults with Established Type 2 Diabetes Mellitus in the CQI Study**

| Number of Adults with Type 2 Diabetes Mellitus | N = 821 (100%) |
|---|---|
| Demographic Characteristics | |
| Age at Enrollment, Mean (Standard Deviation) | 60.2 (13.2) |
| Female, N (%) | 418 (51%) |
| Race, N (%)* | |
| White | 582 (72%) |
| African American | 126 (16%) |
| Hispanic | 77 (9.5%) |
| Other | 22 (2.7%) |
| Education, N (%)* | |
| Less than High School | 168 (21%) |
| High School | 309 (38%) |
| College | 254 (31% |
| Graduate School | 76 (9%) |
| Household Income, Median* | $32,000 |
| Have Health Insurance, N (%)* | 769 (95%) |
| If Insured, Type of Insurance, N (%)*† | |
| Health Maintenance Organization | 332 (43%) |
| Medicare | 394 (51%) |
| Medicaid | 68 (9%) |
| Private Insurance | 547 (71%) |
| General Clinical Characteristics | |
| Hypertension, N (%) | 550 (67%) |
| Hyperlipidemia, N (%) | 364 (44%) |
| Coronary artery disease, N (%) | 217 (26%) |
| >= 1 Chronic Condition Other Than Diabetes, N (%)‡ | 708 (86%) |
| Current Smoker, N (%) | 117 (14%) |

*Data are missing for 14 of 821 patients (1.7%).
†Some patients have more than one type of insurance.
‡Chronic conditions: asthma, atrial fibrillation, benign prostatic hyperplasia, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, depression, congestive heart failure, hyperlipidemia, hypertension, arthritis, prostate cancer.

*Timing of HbA1c Tests and Medication Changes*

When applying early versions of the probability model to the CQI data, we observed substantial inter- and intra-patient variability in HbA1c testing intervals within the wave periods. Failing to account for such variability could produce inaccurate cost estimates. Many patients whose average testing frequency in the two-year wave period is greater than 180 days would by chance have a test during the first 180 days of the one-year modeling period. This could bias estimates of adherence to recommended testing and baseline costs upward. Analogous timing issues occur at the end of each modeling period. Consequently, we modified the probability

models to include average HbA1c testing frequency rather than the actual time between the start of the modeling period and the first HbA1c test.

To predict the average testing frequency for each patient, we performed a time-to-event analysis using data from his or her entire two-year wave period. For patients with two or more HbA1c tests within the wave period, we predicted the testing frequency by fitting an exponential survival time model. Covariates included gender, age, hyperlipedemia, CAD, hypertension, result of first HbA1c test, and patient-level fixed effects.

Next, we classified all subjects' average HbA1c testing frequency as: (1) $\leq$180 days; (2) >180 days; and (3) no tests. For subjects with two or more HbA1c tests, we classified them based on their predicted test frequency based on the models directly above. Patients with one test were assumed to have an average testing frequency of >180 days.

Our data support the usefulness of this approach. We observed that only 17% of subjects had an average HbA1c testing frequency of 180 days or less, 55% received tests less frequently than every 180 days, and 28% received no tests during their two-year wave periods. In contrast, 32% of subjects received their first HbA1c test within the first 180 days of the one-year modeling period. This suggests that 15% of all subjects (32% minus 17%) had an HbA1c test during that 180-day period by chance rather than because they were generally receiving tests with the recommended frequency. Thus, using the actual time to the first test would bias the adherence and cost estimates, as we had suspected.

Variability in timing of medication initiation and adjustment had less potential to bias adherence cost estimates because these events usually occur in response to HbA1c results. Therefore, the branch points in the probability tree for medication initiation and adjustment classified subjects by whether recommended medication changes actually occurred within three months of an elevated HbA1c test, or not.

The probability tree depicts a follow-up HbA1c test after recommended medication changes. To be consistent in how we determine test frequency, we used the average HbA1c testing frequency for this branch as well. Consequently, the probability tree depicts only one branch at this point rather than several options. For example, for subjects with an average testing frequency of $\leq$ 180 days, it would not make sense for the probability tree to include a branch representing a testing frequency of >180 days.

*Clinical Outcome*

The clinical outcome for this analysis was based on the HbA1c result at the end of the one-year modeling period, which is represented by the tips of the probability tree. Specifically, we used the HbA1c test results closest to the end of the modeling period, which is the midpoint of the two-year wave period (the last result in the modeling period, which is the first year of the wave period, or the first result in the second year of the wave period). For patients without a second test, we used the result of their first test to impute their outcome.

For patients with no HbA1c tests in the status quo scenario, we imputed improved outcomes as follows. We obtained HbA1c results for the population tested less often than every 180 days and assumed that those with no HbA1c tests would have the same distribution of results. We estimated a weighted mean HbA1c for the entire population for the status quo scenario as follows. We counted the number of people who were tested at less than 180-day intervals and the number with no tests. We then created a new dataset that listed each person tested at least every 180 days once and those tested at less than 180-day intervals twice; all entries were assigned a weight of 1 except for the duplicate entries, which were assigned a weight = (# with no tests)/(# tested at <180-day intervals). We then multiplied each subjects' last HbA1c by their weight to create a weighted mean HbA1c for the entire population, including those with no HbA1c tests.

Next, we determined the number of subjects whose last HbA1cs were below each of the three HbA1c goal thresholds. For subjects tested at less than 180-day intervals, we determined the percentages below each of the thresholds. Next, for those with no tests, we determined the number below each threshold by multiplying the number of people with no tests by the percentage of patients tested at less than 180-day intervals falling into each outcome category. We then used these results to determine the total number and percentage of subjects in each outcome category, including both actual and imputed values.

4) Improved Care Scenario

We used the same probability model to represent the improved care scenario but made two additional assumptions. First, we assumed that adherence to the process-of-care criteria was increased to 100% throughout the model. Second, we assumed that HbA1c outcomes at the end of the first year of the modeling period improved due to the increased provision of recommended care.

To determine the magnitude of the decline in HbA1c with improved care, we conducted literature searches for articles on diabetes quality improvement programs and on randomized controlled trials on blood glucose control. We based our estimated declines on a recent systematic review of diabetes quality improvement programs and the UKPDS. We did not include the ACCORD, ADVANCE, or Veterans Association trials due to their use of more intensive control targets and mixed results. We assumed that patients with higher HbA1c levels would experience greater improvements in outcomes than patients with lower values. Specifically, we assumed that patients with an HbA1c outcome >=10% in the status quo scenario would have a 1% decline with improved care (0.5-2.5% in sensitivity analyses), patients with an HbA1c outcome 8 -<10% in the status quo scenario would have a 1% decline (0.5-1.0% in sensitivity analyses), and those with an HbA1c outcome of 7-<8% in the status quo scenario would have a 0.5% decline (0-0.5% in sensitivity analyses).

Our methods for estimating outcomes for those with no HbA1c tests were analogous to those for the status quo care scenario described above. First, we used the new dataset that listed those tested at less than 180-days twice but down-weighted the duplicate entry, thereby reflect results for the population with no HbA1c tests. Then we applied the assumptions immediately above to estimate the effects of improved care on HbA1c for three scenarios, which included a base case, high, and low estimate. We then recalculated the weighted mean HbA1c values for each of the three scenarios, and determined the number and percentage in each outcome category for each of the three scenarios.

5) Utilization and Costs

*Laboratory Tests*

In the status quo scenario, we assumed that the number of HbA1c tests equaled 365 divided by the average HbA1c testing frequency. In the improved care scenario, the number of tests was the higher of two values: the minimum that would be adherent to the testing criterion (2 tests per year), or the number of tests in the status quo scenario (365 divided by the average HbA1c testing frequency). Cost per test was based on the Medicare Clinical Laboratory Fee Schedule for 2009: $14.17.[9]

*Physician Visits*

As discussed in the manuscript, we assumed that each HbA1c test and each medication initiation/adjustment involved one physician visit. Although in practice physicians handle some

tests and medication changes by telephone or during visits for other conditions, we counted these as diabetes visits on the assumption that compensation would be an incentive for physician adherence.

In the status quo scenario, we assumed that patients with HbA1c >=8% had zero to 1 medication-related visits during the modeling period, and that patients with HbA1c <8% had no medication-related visits. In the improved care scenario, we assumed that all patients with HbA1c >=8% had one medication-related visit and that patients with HbA1c <8% had none.

We assigned Current Procedural Terminology codes to the HbA1c-testing and medication-related visits based on the complexity of the care. HbA1c-testing visits were considered level 2 physician visits (CPT 99212) while medication-related visits were considered level 4 visits (CPT 99214). Costs per visit were based on the Medicare Physician Fee Schedule for 2009: HbA1c-testing visits cost $37.15 each and medication-related visits cost $92.33.[10]

*Medications*

The CQI data did not include sufficiently detailed information on medication utilization to estimate costs. While it included information on when physicians adjusted medications or initiated them, it did not track when patients took medications or when they refilled prescriptions. Consequently, to estimate medication expenditures per patient per year, we obtained an additional data set. We used pharmacy claims data for 1.1 million non-elderly adults continuously enrolled in four health plans in Massachusetts from 2004-2006. We derived costs from actual health plan expenditures (i.e., excluding patient co-payments, rebates, etc). The health plan claims file included the National Drug Codes for each prescription, actual expenditures for each prescription, days supply for each prescription, prescription fill dates, and the type of episode associated with the prescription (see below).

First, we identified individuals treated for diabetes. We used a commercial software episode-treatment grouper program (Symmetry Episode Treatment Groups) to identify episodes of diabetes care and selected patients with one or more episodes of diabetes care, resulting in 40,000 individuals.[10] Second, we identified antihyperglycemic medications prescribed for these individuals. Pharmacy claims related to diabetes episodes were identified using Episode Treatment Grouper. We then created a list of all National Drug Codes (NDC) and generic medication names associated with these claims. An internal medicine physician reviewed the list and identified antihyperglycemic medications (including insulin and oral medications as well as supplies like syringes).

Third, we calculated average expenditures per patient per day; this involved several steps. To reduce variations in costs of drugs across and within the four health plans related to contracts with individual pharmacies, we calculated average expenditures per filled prescription for each NDC code (i.e., the total expenditures per NDC code divided by the total number of prescriptions for each NDC code) across the population of hypertensive individuals. Thus, we have an estimate of the average cost of an individual prescription for each medication.

Next, for each patient, we determined the total cost of his or her prescriptions for antihyperglycemic medications over the two year period, which we call the standardized drug costs. For each medication obtained (i.e., NDC code), we determined the total expenditures over the two year period by multiplying the number of prescriptions they filled by the average cost for that NDC code (as derived above). We then summed the total costs for each patient for all their antihyperglycemic medications over the two years. For example, if one patient filled five prescriptions for generic glyburide and the medication had a hypothetical cost per prescription of $2.15, the total cost of glyburide for that patient would be $10.75. If this patient also took metformin, with a hypothetical cost of $5.75, and filled four prescriptions, the total cost for metformin would be $23. The standardized drug costs for this patient would be $33.75.

Next, for each patient, we calculated their total time on antihyperglycemic medication therapy. By adding a prescription start date to the days supply for the prescription, we were able to estimate the time the patient was on the medication. We added up all the time periods for all prescriptions for the entire time that we see the patient in our claims file to determine the total number of days on antihyperglycemic medications. If any prescriptions had days supplies that overlapped, we counted each day only once. For the patient in the example above, if the five prescriptions for glyburide each had a 30 days supply, the total duration of glyburide would be 150 days. If the four prescriptions for metformin each had a 60 days supply, the total duration of metformin would be 240 days. If the glyburide and metformin overlapped for 100 days, the total duration of antihyperglycemic therapy would be (150+240-100) 290 days for that patient.

To determine each patient's average cost of all antihyperglycemic medications per day, we then divided his or her standardized drug costs by his or her total time on drug therapy. For the hypothetical patient above, standardized costs of $33.75 divided by 290 total days of therapy yields an average cost per day of $0.1164.

Because some patients might have unusually high or low average costs per day, we Winsorized those in the top and bottom 2.5 percentiles, meaning we lowered their average costs of medications per day to the 97.5 percentile or raised it to the 2.5 percentile, respectively. Finally, we calculated a mean cost per patient per day by averaging all the patients' costs per day. The average expenditure per patient per day was $3.18 in 2005 dollars. We then applied the prescription drug component of the consumer price index (multiplier 391.055/ 349.0) to inflate costs to 2009 dollars, which yielded $3.56 per patient per day.[11]

Lastly, we conducted literature searches to identify the costs of medications used to treat diabetes per patient per day. We identified a range of estimates from several prior studies; converted to daily costs; inflated to 2009; and used those in the sensitivity analysis ($1.42-$9.13).[12-17]

*Hyper- and hypoglycemia*

Severe alterations in blood glucose sometimes result in emergency department visits or hospitalization. Because the CQI data did not include data on hospitalizations for diabetes, we considered the potential effect of the costs of severe hyper- and hypoglycemia in the following sensitivity analysis. Based on recent literature (including systematic reviews and data from national samples), we estimated rates of severe hypoglycemia, uncontrolled diabetes (hyperglycemia without complications), and short-term complications of diabetes (including diabetic ketoacidosis and hyperosmolar non-ketotic conditions).

For hypoglycemic events, we focused on severe events that would generally require medical assistance, such as physician visits or emergency department visits. We did not include milder events that might require consumption of glucose-containing substances or injection with glucagon at home, or the very unusual hypoglycemic events that might require hospitalization (since hypoglycemia is usually rapidly reversible). For the status quo scenario, the minimum event rate was calculated by multiplying the percentage of patients on antihyperglycemics upon entry to the CQI study (32%) by the annual risk of severe hypoglycemia while on such medications (60-110 per 100,000 patients per year), according to a recent systematic review.[18] The maximum rate was based on patients in the control arms of randomized controlled trials.[19] Rates reported in the UKPDS were within this range.[20] For the improved care scenario, we estimated the relative risk of hypoglycemic events based on a recent systematic review of randomized controlled trials[19] and a recent VA trial.[6] To estimate the cost per event, we assumed that each event would require one level 5 physician visit, either in the clinic (CPT 99215) or in the emergency department (CPT 99285).

For hyperglycemic events, we used data on hospitalizations reported by Wang (2009), who described rates of hospitalization due to diabetes in the absence of complications as well as rates for short-term complications (uncontrolled diabetes with ketoacidosis, hyperosmolality, and coma).[21] The authors did not distinguish type 1 and type 2 diabetes, and some studies have found that about a third of diabetic ketoacidosis occurs among patients with type 2 diabetes.[22] Consequently, to estimate the rate of such events per patient per year, we drew from the rates reported for age strata above age 44. The annual rate of hyperglycemic events is substantially lower in this older population, which is consistent with the notion that type 1 diabetes tends to be a disease of younger adults.[21] Our search of the literature did not identify data on the relative risk or change in rate of hospitalizations for severe hyperglycemia with improved care. However, between 1999 and 2002, mean HbA1c declined from 7.6 to 7.1% and rates of hospitalizations for hyperglycemic events were lower in 2006 than in 1998. Consequently, we calculated a range of relative risks of hospitalizations for hyperglycemia by comparing the event rates in 1998 and 2006.[21]

To estimate costs associated with severe hyperglycemic events, we used data from Kim et al., who estimated the total number of admissions and total costs across all admissions for these same types of hospitalizations. We calculated averages per admission. For uncontrolled diabetes with complications, we used data reported by Kim to calculate a weighted average cost across admissions for uncontrolled diabetes with ketoacidosis, hyperosmolality, and coma.[23]

6) Incremental Cost and Cost per Patient Achieving Goal

For each scenario, we summed the costs associated with care processes pertaining to glucose management, including costs associated with HbA1c testing, physician visits associated with such testing as well as recommended medication adjustments, and the expenditures associated with antihyperglycemic medications. Next, we determined the proportion of patients in each scenario who attained the outcome of interest (HbA1c <7%, <8%, or <=9%). Finally, we calculated cost-effectiveness ratios as described in the manuscript. Although we examined three different HbA1c outcomes, the costs associated with improved care did not vary according to the outcome we selected. We did not include the costs associated with severe hyper- and hypoglycemia in the base cases analysis.

**Table A-2: Rates and Cost of Severe Hyper- and Hypoglycemia**

| | Rate, Status Quo Scenario | Relative Risk, Improved Care Scenario | Cost per Event (2009) | Cost per Patient per Year, Status Quo Scenario | Cost per Patient per Year, Improved Care Scenario | Incremental Cost per Patient per Year | References |
|---|---|---|---|---|---|---|---|
| **Hypoglycemic Events:** Hypoglycemia described as severe, requiring medical care, or involving impairment of consciousness | 0.2 – 7.8 per 1000 patients per year | RR 2-3 | $124.79-170.23 | $0.02-1.33 | $0.05-3.98 | $0.02 to $2.66 | 6, 18, 19, 24 |
| **Hyperglycemic Events** | | | | | | | 21, 23, 25 |
| Hospitalizations for uncontrolled diabetes (without complications) | 5-7.7 per 1000 patients per year | RR 0.41-0.89 (2.1-6.9 per 1000) | $14,501-$18,786 | $72.51-144.65 | $59.31-64.53 | -$7.98 to -$85.34 | |
| Hospitalizations for short-term complications of hyperglycemia (hyperosmolar coma, etc.) | 3.1-5.7 per 1000 patients per year | RR 0.35-0.5 (1.6-2.0 per 1000) | $16,449-$21,775 | $50.99-124.12 | $25.50-43.44 | -$25.50 to -$80.68 | |
| **Total** | | | | **$124.82 to 268.79** | **$94.01 to 102.80** | **-$30.82 to -$166.00** | |

7) Sensitivity and Additional Analyses

The specific parameters examined in sensitivity analyses are discussed in the sections where they are relevant (above). To review, these included several parameters reflecting the fact that blood glucose control has improved since the time of the CQI study (including percentage of diabetics on medications at study entry and adherence to recommended HbA1c testing and medication adjustments). We also examined a range of possible effects of improved care on HbA1c at the end of the modeling period. For cost parameters, sensitivity analyses examined a wide range of possible per-patient medication expenditures and considered the effect of including the costs of severe hyper- and hypoglycemia.

As noted in the paper, we used available literature to determine a range of plausible values for the model parameters, and then performed a Monte Carlo sensitivity analysis. For each variable, we randomly sampled from the range of values and assumed a uniform distribution because some alternatives, such as a normal distribution, could underestimate the uncertainty in our model parameters.

*Supplemental Analysis of Long-Term Costs and Outcomes*

As discussed in the manuscript, we did not include long term effects and costs in our main analysis for several reasons. Our principal objective was to estimate the recurring annual costs and changes in a short-term intermediate outcome (i.e., HbA1c levels) associated with adherence to recommended care and estimate cost-effectiveness from the payer perspective. The CQI study was cross-sectional, not longitudinal; therefore, including long-term clinical effects and costs in our analysis requires extrapolating from prior studies, which increases uncertainty in our estimates. Finally, multiple groups of investigators have developed sophisticated models to estimate the long-term effects and costs associated with tight blood glucose control and it would be challenging to do a better job than they have already done.

Consequently, the current section focuses on estimating the long-term clinical effects of improved care and long-term cost offsets by drawing from existing studies. We focus on one recent study by Kahn et al., for several reasons. First, this study was based on a well-validated diabetes model, the Archimedes model. Second, the investigators used data on baseline conditions from the same period as the CQI study. Third, they examined a change in the percentage of patients attaining an HbA1c goal of <7% that was virtually identical to the one we obtained in our analysis. Finally, our investigation complements the Kahn study because the investigators did not appear to have any empirical information on the cost of improving blood glucose management but rather made assumptions about what those costs are. We, therefore, made several assumptions that enabled us to recalculate Kahn's cost-effectiveness estimates using our more accurate estimates of the potential cost of improving glucose management.

*Summary of the Study by Kahn et al.*

According to Kahn et al., the Archimedes model is "…a person-by-person, object-by-object, large-scale simulation model of physiology, disease, and health care systems written at a high level of detail using object-oriented programming and run on a distributed computing network. The core of the model is a set of ordinary and differential equations that represent the physiological pathways pertinent to diseases and their complications. Currently, the model includes coronary artery disease (CAD), stroke, diabetes and its complications, congestive heart failure, obesity, smoking, asthma, and the metabolic syndrome in a single integrated model."

Kahn et al. analyzed 11 prevention activities pertaining to cardiovascular disease, basing model parameters for baseline conditions on NHANES data for 1998–2004. One of the prevention activity was achieving HbA1c <7%. For each of the prevention activities, the

investigators estimated the clinical effects and cost-effectiveness of attaining 100% performance (all diabetics with HbA1c <7%) and, alternatively, of attaining "more feasible" levels of performance based on rates from other studies (60% of diabetics with HbA1c <7%). Essentially, the study entailed setting HbA1c levels in the Archimedes model to 6.8%, making rough assumptions about the costs of the glucose management required to attain those levels, and then using the Archimedes model to estimate 30-year costs, changes in clinical outcomes (such as myocardial infarction), and quality-adjusted life-years (QALYs). Data were scaled to the U.S. population as of 2005. Future costs and clinical outcomes were discounted at a rate of 3%. Although the authors only reported changes in selected clinical outcomes (e.g., myocardial infarction and QALYs), the model included the effects of HbA1c <7% on a wide range of relevant conditions (e.g., retinopathy, nephropathy) and excluded unrelated conditions (e.g., osteoporosis).

Kahn et al. do not appear to report the baseline HbA1c for the NHANES data set during the 1998-2004 time period.[12] However, Saaddine et al. report that the percentage of adults with HbA1c <7% was 42.3% in the 1999 to 2002 time period, based on NHANES and another survey.[26] Based on the CQI data set, which is from 1996 to 2002, 37.3% of the population attained HbA1c <7%, a fairly similar baseline. Whereas Kahn et al. assumed that maximum possible adherence to HbA1c <7% was 60%, our assumptions about the effect of improving care processes led to 61.4% of the population attaining this HbA1c goal.

As noted above, Kahn et al. did not cite data on the cost of attaining these improvements in HbA1c. Rather, they made assumptions about the recurring annual costs. They assumed that diabetic patients would have four physician visits for blood glucose management per year at $74 each, two HbA1c tests at $59 each, and expenditures for antihyperglycemic medications would be $3,150 per year (2005 dollars). Thus, they assumed that total incremental annual costs would be $3,564 per patient per year; inflating to 2009 yields a total annual cost of $4,142.

For a population of approximately 200 million U.S. adults, which includes 5,739,000 diabetics, Kahn et al. estimate that reducing HbA1c to <7% for 100% of diabetics would prevent 1,086,000 myocardial infarctions, increase total years lived by 25,282,000, and increase QALYs by 38,389,000 over 30 years. The direct cost of preventive care would be $1,780 billion over that period, with a net cost of medical care of $1,548 billion. The cost per QALY was estimated at $48,759 (2005 dollars); or $56,666/ QALY inflated to 2009.[11]

Attaining "maximum feasible performance"—i.e., 60% of diabetics with HbA1c <7%--would prevent 652,000 myocardial infarctions, add 15 million years of life, increase QALYs by 23 million, involve direct costs of $1,068 billion, reduce other medical care expenditures by $139 billion, and involve net costs of $929 billion across the U.S. adult population over 30 years; the cost per QALY would be the same as for 100% performance $48,759 (2005 dollars); or $56,666/ QALY inflated to 2009.[12]

*Assumptions We Used In Re-calculating Cost per QALY*

First, we assumed that our analysis and Kahn's would involve equal long-term clinical effects on myocardial infarctions and QALYs. This is a reasonable assumption because both the baseline rate and improved rate of attaining HbA1c <7% are virtually identical in Kahn's "maximum feasible performance" analysis and ours.

Second, we estimated the average per-person costs of improving glucose management in the Kahn analysis, and compared those with our estimates. Presumably Kahn et al. applied their cost assumptions to the 58% of diabetic patients with HbA1c >= 7%, since those with HbA1c <7% would not need to incur those costs. Consequently, Kahn's estimate of average per capita costs can be assumed to be $2,402 ($4,142 times 58%). Our estimate is much lower, $327.01 per patient per year. Thus, the cost of improving blood glucose management may be only 14% of what Kahn et al. assumed.

Third, we calculated the difference between the expenditures on improved quality of care in Kahn's analysis and ours. To do so, we determined the present value of the incremental medical care expenses associated with improving glucose management, assuming a 3% discounting rate and 30-year time horizon. Using a cost of improved glucose management of $2,402 per person with diabetes per year, the present value of 30 years of care is $47,080 per person with diabetes. Using a cost of improved glucose management of $327.01 per person with diabetes per year, the present value of 30 years of such care is $6,410 per person with diabetes. Thus, the difference in the present values is $40,671 per person with diabetes. Applying the difference in these present value estimates to the size of the population with diabetes in Kahn's study ($40,671 times 5,739,000 individuals) indicates that the nationwide costs of improving blood glucose management may be $233 billion lower than Kahn et al. estimated.

Fourth, we estimated the total (medical plus non-medical costs) that Kahn et al. appeared to use but did not report in the paper. They reported that the cost per QALY for HbA1c <7% was reported as $48,759 and that this would lead to 23 million additional QALYs among U.S. adults. This implies that the total direct and indirect (i.e., medical and non-medical) costs over 30 years would have been $1,121 billion as of 2005 ($48,759 times 23 million).

Finally, we recalculated the new cost per QALY using our assumptions about how much improving quality of care would cost. As noted in two paragraphs immediately above, the cost of improving quality of care over 30 years would be $233 billion lower nationwide than Kahn et al. estimated, and they estimate that total costs over thirty years would be $1,121. Thus, a revised estimate of the total lifetime costs would be $888 billion. Dividing by 23 million QALYs yields a cost per QALY of $38,609 (as of 2005); inflating to 2009 changes this to $44,869.[11]

**Figure A-2**

| | N | % | | N | % | | N | % | | N | % | | | | | N | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Status Quo Scenario** | | | | | | | | | | | | | | | | | |
| Anti-hyperglycemics | 264 | 32% | HbA1c Testing <180 d | 53 | 20% | HbA1c >=8% | 13 | 25% | Any med adjustments | 7 | 58% | Testing <180 d | 7 | 100% | HbA1c >=8% | 3 | 43% |
| | | | | | | | | | | (1 missing) | | | | | HbA1c <8% | 4 | 58% |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | No med adjustments | 5 | 42% | Testing <180 d | 5 | 100% | HbA1c >=8% | 4 | 80% |
| | | | | | | | | | | | | | | | HbA1c <8% | 1 | 20% |
| | | | | | | HbA1c <8% | 40 | 75% | HbA1c >=8% | 10 | 26% | (1 missing) | | | | | |
| | | | | | | | | | HbA1c <8% | 29 | 74% | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | HbA1c Testing >180 d | 147 | 56% | HbA1c >=8% | 74 | 50% | Any med adjustments | 15 | 29% | Testing >180 d | 15 | 100% | HbA1c >=8% | 10 | 67% |
| | | | | | | | | | | (22 missing) | | | | | HbA1c <8% | 5 | 33% |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | No med adjustments | 37 | 71% | Testing >180 d | 37 | 100% | HbA1c >=8% | 33 | 90% |
| | | | | | | | | | | | | | | | HbA1c <8% | 4 | 10% |
| | | | | | | HbA1c <8% | 73 | 50% | HbA1c >=8% | 6 | 8% | | | | | | |
| | | | | | | | | | HbA1c <8% | 67 | 92% | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | No HbA1c Tests | 64 | 24% | HbA1c >=8% | 32 | 50% | (Imputed) | | | | | | | | |
| | | | | | | HbA1c <8% | 32 | 50% | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| No Anti-hyperglycemics | 557 | 68% | HbA1c Testing <180 d | 85 | 15% | HbA1c >=8% | 19 | 22% | Any med adjustments | 15 | 79% | Testing <180 d | 15 | 100% | HbA1c >=8% | 10 | 67% |
| | | | | | | | | | | | | | | | HbA1c <8% | 5 | 33% |
| | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | No med adjustments | 4 | 21% | Testing <180 d | 4 | 100% | HbA1c >=8% | 2 | 50% |
| | | | | | | | | | | | | | | | HbA1c <8% | 2 | 50% |
| | | | | | | HbA1c <8% | 66 | 78% | HbA1c >=8% | 22 | 33% | | | | | | |
| | | | | | | | | | HbA1c <8% | 44 | 66% | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | HbA1c Testing >180 d | 307 | 55% | HbA1c >=8% | 114 | 37% | Any med adjustments | 27 | 24% | Testing >180 d | 27 | 100% | HbA1c >=8% | 13 | 48% |
| | | | | | | | (2 missing) | | | | | | | | HbA1c <8% | 14 | 52% |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | No med adjustments | 87 | 76% | Testing >180 d | 87 | 100% | HbA1c >=8% | 78 | 90% |
| | | | | | | | | | | | | | | | HbA1c <8% | 9 | 10% |
| | | | | | | HbA1c <8% | 191 | 62% | HbA1c >=8% | 10 | 5% | (1 missing) | | | | | |
| | | | | | | | | | HbA1c <8% | 180 | 95% | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | No HbA1c Tests | 165 | 30% | HbA1c >=8% | 61 | 37% | (Imputed) | | | | | | | | |
| | | | | | | HbA1c <8% | 103 | 63% | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| **Improved Care Scenario** | | | | | | | | | | | | | | | | | |
| Anti-hyperglycemics | 264 | 32% | HbA1c Testing <180 d | 53 | 20% | HbA1c >=8% | 13 | 25% | Any med adjustments | 7 | 58% | Testing <180 d | 7 | 100% | HbA1c >=8% | 3 | 43% |
| | | | | | | | | | | (1 missing) | | | | | HbA1c <8% | 4 | 58% |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | NEW med adjustment | 5 | 42% | Testing <180 d | 5 | 100% | HbA1c >=8% | 1 | 20% |
| | | | | | | | | | | | | | | | HbA1c <8% | 4 | 80% |
| | | | | | | HbA1c <8% | 40 | 75% | HbA1c >=8% | 10 | 26% | (1 missing) | | | | | |
| | | | | | | | | | HbA1c <8% | 29 | 74% | | | | | | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | NEW HbA1c Testing <180 d | 147 | 56% | HbA1c >=8% | 74 | 50% | Any med adjustments | 15 | 29% | Testing <180 d | 15 | 100% | HbA1c >=8% | 6 | 40% |
| | | | | | | | | | | (22 missing) | | | | | HbA1c <8% | 9 | 60% |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | NEW med adjustment | 37 | 71% | Testing <180 d | 37 | 100% | HbA1c >=8% | 25 | 68% |
| | | | | | | | | | | | | | | | HbA1c <8% | 12 | 32% |
| | | | | | | HbA1c <8% | 73 | 50% | HbA1c >=8% | 2 | 3% | | | | | | |
| | | | | | | | | | HbA1c <8% | 71 | 97% | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | NEW HbA1c Testing <180 d | 64 | 24% | HbA1c >=8% | | | NEW med adjustment | | 100% | Testing <180 d | | 100% | HbA1c >=8% | | 33% |
| | | | | | | HbA1c <8% | | | | | | Testing <180 d | | 100% | HbA1c <8% | | 67% |
| | | | | | | | | | | | | | | | | | |
| No Anti-hyperglycemics | 557 | 68% | HbA1c Testing <180 d | 85 | 15% | HbA1c >=8% | 19 | 22% | Any med adjustments | 15 | 79% | Testing <180 d | 15 | 100% | HbA1c >=8% | 10 | 67% |
| | | | | | | | | | | | | | | | HbA1c <8% | 5 | 33% |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | NEW med adjustment | 4 | 21% | Testing <180 d | 4 | 100% | HbA1c >=8% | 0 | 0% |
| | | | | | | | | | | | | | | | HbA1c <8% | 4 | 100% |
| | | | | | | HbA1c <8% | 66 | 78% | HbA1c >=8% | 22 | 33% | | | | | | |
| | | | | | | | | | HbA1c <8% | 44 | 66% | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | NEW HbA1c Testing <180 d | 307 | 55% | HbA1c >=8% | 114 | 37% | Any med adjustments | 27 | 24% | Testing <180 d | 27 | 100% | HbA1c >=8% | 9 | 33% |
| | | | | | | | (2 missing) | | | | | | | | HbA1c <8% | 18 | 66% |
| | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | NEW med adjustment | 87 | 76% | Testing <180 d | 87 | 100% | HbA1c >=8% | 54 | 62% |
| | | | | | | | | | | | | | | | HbA1c <8% | 33 | 38% |
| | | | | | | HbA1c <8% | 191 | 62% | HbA1c >=8% | 1 | 1% | (1 missing) | | | | | |
| | | | | | | | | | HbA1c <8% | 190 | 99% | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | NEW HbA1c Testing <180 d | 165 | 30% | HbA1c >=8% | | | NEW med adjustment | | 100% | Testing <180 d | | 100% | HbA1c >=8% | | 24% |
| | | | | | | HbA1c <8% | | | | | | Testing <180 d | | 100% | HbA1c <8% | | 76% |
| | | | | | | | | | | | | | | | | | |

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