

# Clinical Outcomes and Cost-Effectiveness of Strategies for Managing People at High Risk for Diabetes

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**Background:** Lifestyle modification can forestall diabetes in high-risk people, but the long-term cost-effectiveness is uncertain.

**Objective:** To estimate the effects of the lifestyle modification program used in the Diabetes Prevention Program (DPP) on health and economic outcomes.

**Design:** Cost-effectiveness analysis using the Archimedes model.

**Data Sources:** Published basic and epidemiologic studies, clinical trials, and Kaiser Permanente administrative data.

**Target Population:** Adults at high risk for diabetes (body mass index  $>24$  kg/m<sup>2</sup>, fasting plasma glucose level of 5.2725 to 6.9375 mmol/L [95 to 125 mg/dL], 2-hour glucose tolerance test result of 7.77 to 11.0445 mmol/L [140 to 199 mg/dL]).

**Time Horizon:** 5 to 30 years.

**Perspective:** Patient, health plan, and societal.

**Interventions:** No prevention, DPP's lifestyle modification program, lifestyle modification begun after a person develops diabetes, and metformin.

**Measurements:** Diagnosis and complications of diabetes.

**Results of Base-Case Analysis:** Compared with no prevention program, the DPP lifestyle program would reduce a high-risk person's 30-year chances of getting diabetes from about 72% to 61%, the chances of a serious complication from about 38% to 30%, and the chances of dying of a complication of diabetes from about 13.5% to 11.2%. Metformin would deliver about one third the long-term health benefits achievable by immediate lifestyle modification. Compared with not implementing any prevention program, the expected 30-year cost/quality-adjusted life-year

(QALY) of the DPP lifestyle intervention from the health plan's perspective would be about \$143 000. From a societal perspective, the cost/QALY of the lifestyle intervention compared with doing nothing would be about \$62 600. Either using metformin or delaying the lifestyle intervention until after a person develops diabetes would be more cost-effective, costing about \$35 400 or \$24 500 per QALY gained, respectively, compared with no program. Compared with delaying the lifestyle program until after diabetes is diagnosed, the marginal cost-effectiveness of beginning the DPP lifestyle program immediately would be about \$201 800.

**Results of Sensitivity Analysis:** Variability and uncertainty deriving from the structure of the model were tested by comparing the model's results with the results of real clinical trials of diabetes and its complications. The most critical element of uncertainty is the effectiveness of the lifestyle program, as expressed by the 95% CI of the DPP study. The most important potentially controllable factor is the cost of the lifestyle program. Compared with no program, lifestyle modification for high-risk people can be made cost-saving over 30 years if the annual cost of the intervention can be reduced to about \$100.

**Limitations:** Results depend on the accuracy of the model.

**Conclusions:** Lifestyle modification is likely to have important effects on the morbidity and mortality of diabetes and should be recommended to all high-risk people. The program used in the DPP study may be too expensive for health plans or a national program to implement. Less expensive methods are needed to achieve the degree of weight loss seen in the DPP.

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Recent randomized, controlled studies have shown that diabetes can be prevented or delayed in high-risk individuals by intensive lifestyle modification programs (1, 2) or glucose-lowering drugs (2–4). For example, in the Diabetes Prevention Program (DPP), the relative reductions in the 2.8-year incidence of diabetes were 58% in the lifestyle modification group and 31% in the metformin group (2). This raises hopes of substantially reducing the morbidity, mortality, and cost of this important disease. However, the trial was too short to observe the effects on microvascular or macrovascular outcomes, and the programs cost several hundred dollars a year (5). These findings generate obvious questions: What are the long-term effects of trying to prevent diabetes in high-risk people? Does lifestyle modification truly prevent or just postpone diabetes? Is such a prevention program “cost-effective”? What is the best strategy? A previous analysis has suggested that lifestyle modification would be cost-effective over 75 years from a societal perspective (6). We used a more thorough, clinically

realistic, and independently validated model to estimate the short- and intermediate-term health and economic effects of different prevention programs for high-risk individuals and health plans, as well as for society.

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**Context**

A previous Markov model–based analysis estimated that use of the Diabetes Prevention Program diet and exercise intervention to forestall diabetes in high-risk people would be cost-effective from a societal perspective.

**Contribution**

Using a validated model designed to be more complete and realistic than previous models, the authors estimated that the intervention would cost society about \$62 600 per quality-adjusted life-year saved. It would be cost-saving if the annual cost of the intervention decreased from \$672 to \$100.

**Implications**

This model suggests that the Diabetes Prevention Program intervention costs more per quality-adjusted life-year saved than previously estimated, and health plans and insurers may consider it too expensive to cover.

—The Editors

**METHODS**

We conducted the analysis by using the Archimedes model, which has been described elsewhere (7–9). Briefly, it is a simulation model written at a relatively high level of anatomic, physiologic, clinical, and administrative detail. It uses object-oriented programming to create in the model objects that correspond to objects in reality, one-to-one. Among the hundreds of objects are people, pancreases,  $\beta$  cells, plasma glucose levels, coronary arteries, plaque, chest pain, emergency departments, electrocardiograms, aspirin, and angioplasties. Helpful analogies might be a flight simulator (in which the objects include the plane and its wings, airports, runways, buildings, and the wind), or the SimCity computer game. In the Archimedes model, each individual is simulated down to the level of hepatic glucose production, insulin resistance,  $\beta$ -cell fatigue, and similar biological variables. The core of the model is a set of differential equations that represent the anatomy and physiology pertinent to diseases and their complications. Currently, the model includes diabetes, congestive heart failure, coronary artery disease, stroke, hypertension, and asthma in a single integrated model. The structure and equations of the model pertinent to diabetes and its complications are described elsewhere (8, 9). The Appendix (available at [www.annals.org](http://www.annals.org)) and a technical report available through our Web site (10) describe additional aspects of the model and its validations that are pertinent to this analysis. Calculations are performed by using a distributed computing network.

**Clinical Events**

The model includes the biological variables and outcomes relevant to diabetes and its complications. Examples are basal hepatic glucose production; insulin amount; in-

sulin resistance; fasting plasma glucose; hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>); 2-hour oral glucose tolerance; high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol; triglycerides; systolic and diastolic blood pressures and their determinants (for example, cardiac output, arterial compliance, peripheral resistance); weight and body mass index (BMI); stenosis of coronary arteries; retinopathy (assessed by the Early Treatment of Diabetic Retinopathy scale); urine protein; creatinine; peripheral neuropathy; foot ulcers of varying degrees of severity; and amputations. The use of differential equations preserves the continuous nature of biological variables as well as the interactions between them. Clinical outcomes are defined in terms of the underlying variables, as occurs in reality. For example, a person is said to have diabetes if his or her fasting plasma glucose level exceeds 6.9375 mmol/L (125 mg/dL) or results on a 2-hour oral glucose tolerance test exceed 11.0445 mmol/L (199 mg/dL). This enables the model to incorporate different definitions and changes in definitions. The model is continuous: Biological variables are changing and interacting continuously, the natural histories and severity of conditions progress smoothly, any clinical event can occur at any time, and the timing of events is as condensed or drawn out as occurs in reality. The model also includes a detailed representation of the processes and logistics of clinical care and their related costs.

Interventions, both to prevent diabetes and to manage it when it occurs, are modeled at the level of the underlying biology. Pertinent to this analysis is that in the model, diet and exercise reduce weight (2); reduce blood pressure (11); improve LDL cholesterol, HDL cholesterol, and total cholesterol levels (12); and decrease fasting plasma glucose levels (2). The effects of metformin in the model are to reduce fasting plasma glucose and 2-hour oral glucose tolerance test results (2) (by reducing basal hepatic glucose production), decrease LDL cholesterol and triglyceride levels (13), and retard weight gain.

Data used to build the model were derived from basic physiologic studies, surveys, epidemiologic studies, and clinical trials using methods described in the technical report (10). Every variable in the model is estimated from at least 1 empirical source; no variables are simply assumed. We identified specific sources by searching MEDLINE from 1970 to 28 February 2005 and by consulting textbooks and clinical experts. Because the model includes scores of continuously valued, interacting variables, it does not have simplified “states,” transitions, or events at discrete time intervals that can be tabulated, as is commonly done for a Markov-type model. The equations themselves are in the technical report (10). For nonmathematical readers, we have calculated annualized rates of change of representative biological variables and annualized rates of occurrence of representative clinical events, and compared them with rates for comparable events observed in epi-

miologic studies and clinical trials. The Appendix (available at [www.annals.org](http://www.annals.org)) reports those results.

### Costs

The DPP measured the direct medical costs of delivering the lifestyle and metformin interventions (for example, personnel, health education materials, medications, and laboratory tests). Compared with the placebo group's costs, costs in the lifestyle group were \$1356 more per person in the first year, with approximately \$672 in annual costs thereafter; for the metformin group, costs were \$977 in the first year and averaged \$742 per year thereafter (5). Following the completion of the DPP, metformin became generic. When this is considered, the cost of the metformin program is reduced to about \$780 for 3 years, or about \$260 a year. In the DPP study, costs apply to the year 2000.

To calculate the routine costs of providing health care to high-risk people before they develop diabetes, as well as to people with diabetes and its complications, the model includes a detailed mathematical representation of a health care system, including such elements as facilities, personnel, tests and treatments, protocols, and provider behaviors. For the base-case analysis, we obtained itemized costs from Kaiser Permanente, a nonprofit, group-practice, integrated managed care organization that provides comprehensive care (with no deductibles or copayments). The facilities, personnel, protocols, and costs in the model are based on that organization's records, at the level of detail at which actual accounts are kept (for example, 37 different kinds of office visits). The model calculates costs by keeping track of the occurrence of every event that has cost implications and adding them up. The costs assigned to any event or item were calculated by Kaiser Permanente's cost-accounting department using "micro-costing" methods (14), and they represent the real costs to the organization, not charges, reimbursements, or diagnosis-related groups. Because costs vary from setting to setting, the implications of different cost structures are examined in the sensitivity analysis. Calculation of costs applies to the year 2000. Indirect costs, such as lost time from work and decreased productivity, are included in the cost-effectiveness analysis through the Quality of Well-Being Index (14).

We calculated the effects of lifestyle and metformin interventions on quality of life. For people who do not yet have diabetes, we used utility weights reported for the participants of the DPP study (15). For people who have diabetes and its complications, we used the results of a published survey by Coffey and colleagues (16). Both surveys used the Quality of Well-Being Index. The decrements in quality of life were assumed to be additive for people who have 2 or more complications, with a limit that quality of life could not be less than 0. Use of an additive rule biases the calculation of cost/quality-adjusted life-year (QALY) in favor of a prevention program, making the program appear more cost-effective than would occur if a

multiplicative model were used. We discuss the potential effects of lifestyle modification itself (for example, exercise and weight loss) in the sensitivity analysis section.

### Definitions

We use the term *high risk* to describe people who meet the eligibility requirements of the DPP study, which include all of the following: BMI greater than 24 kg/m<sup>2</sup>, fasting plasma glucose level of 5.2725 to 6.9375 mmol/L (95 to 125 mg/dL), and 2-hour oral glucose tolerance test result of 7.77 to 11.0445 mmol/L (140 to 199 mg/dL). *Diabetes* is considered to be present if the fasting plasma glucose level was greater than 6.9375 mmol/L (>125 mg/dL) or the 2-hour oral glucose tolerance test result was greater than 11.0445 mmol/L (>199 mg/dL) (17).

### Validation of the Model

#### Internal Testing

We tested the model for internal consistency and bugs by a variety of methods, including face validity, use of inputs with known outputs, independent duplicate programming of parts, and simulation of studies and trials that have empirically known results.

#### Calibration

Each equation in the model was estimated by fitting functions to data. We confirmed the fits by comparing the resulting functions with the data from which they were fitted. To prevent overfitting of curves, we chose functional forms with the smallest higher-order derivatives (the smoothest curves), and we confirmed each fit visually. We also prevented overfitting of curves by conducting simulations that involved dozens of equations or spanned long durations of time and by conducting independent validations that involved data points never used to fit any equation.

#### Clinical Outcomes

The Archimedes diabetes model has been validated by simulating real epidemiologic studies and clinical trials at a high level of detail and by comparing the model's results with the results actually observed in the trials (9). Thus far, the model has been validated against 19 clinical trials that are pertinent to this application (2, 12, 18–34). An independent committee appointed by the American Diabetes Association chose 18 of the trials on the basis of their quality and ability to collectively span the full spectrum of the natural history of the disease, its complications, and its treatments. When the individual arms and outcomes of the different trials are counted, a total of 74 validation exercises have been published (9). Overall, the correlation between the model's results and the trials' results was 0.993. Ten of the 18 trials were not used to help build the model and thus provide independent validations. The correlation of the model's results and the trials' results for these independent validations was 0.99. The 19th trial (34) was the

subject of a publicly announced, prospective, blinded prediction by the Archimedes model. Because more than half of the validations involve trials that were never used to help build the model, there was no “fitting” of any of the model’s parameters to the results of these trials, and therefore no possibility of “overfitting” of the model to their results. The Appendix (available at [www.annals.org](http://www.annals.org)) summarizes the methods and results.

The validations cover whatever outcomes were observed in the trials, including the incidence of diabetes, myocardial infarctions, strokes, retinopathy, and end-stage renal disease. The validations also cover whatever follow-up times were observed in the trials, ranging from about 3 years (2) to 15 years (18). Finally, the validations span several decades in the progression of the disease: from normal to high risk to newly diagnosed diabetes (which itself spans more than a decade, from the time a person first meets the biological definition at a fasting plasma glucose level  $> 6.9375$  mmol/L [ $>125$  mg/dL]) to the occurrence of symptoms at fasting plasma glucose levels of about 9.99 mmol/L [180 mg/dL]), to late complications, such as myocardial infarctions and end-stage renal disease.

### Costs

The direct and nondirect medical costs of the management strategies were obtained from the DPP study and are assumed to be valid. To validate the model’s method for calculating the net costs associated with managing people with diabetes and their complications, we compared costs calculated by the model to the actual costs measured in an independently conducted study of patients with diabetes in Kaiser Permanente Northern California. The annual diabetes-related cost of an average patient with diabetes in this health care plan was \$4241; the cost calculated by the model was \$4683. For people with prediabetes, costs calculated by the model were compared with costs estimated for the people in the DPP study (5). In the trial, the average annual direct medical cost for the placebo group was

about \$1670. The comparable cost calculated by the model was \$1552.

### This Analysis

To analyze the effects of different management strategies, we used the Archimedes model to simulate what would happen if 10 000 people who met the entry criteria of the DPP trial were exposed to 4 different management strategies and were followed for 30 years. In the first strategy, called the “DPP lifestyle program,” people were immediately (while still high risk, before a diagnosis of diabetes) exposed to lifestyle modification such as that described for the lifestyle arm of the DPP study (35). Those who developed diabetes were maintained on the intensive lifestyle modification and followed for disease progression. Persons whose HbA<sub>1c</sub> level exceeded 7% were entered into an intensive diabetes treatment protocol designed to reduce their HbA<sub>1c</sub> level to below 7%. This treatment protocol was modeled after the intensive policy group of the United Kingdom Prospective Diabetes Study (UKPDS) (18) and reduced HbA<sub>1c</sub> levels to an average of 6.6%. The goal of 7% corresponds to the recommendations of the American Diabetes Association.

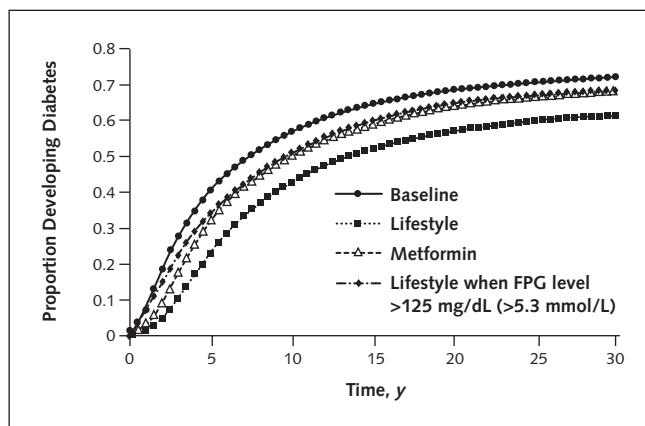
In the second strategy, called “baseline,” no lifestyle or other intervention was given initially. If these people developed diabetes, they were given dietary advice (but were not entered into an intensive lifestyle program) and monitored for progression of the disease. If their HbA<sub>1c</sub> level exceeded 7%, they were entered into an intensive management program with a goal of controlling HbA<sub>1c</sub> level to below 7%, based on recommendations of the American Diabetes Association.

In a third strategy, called “lifestyle when FPG  $> 125$ ” (that is, when fasting plasma glucose level  $> 125$  mg/dL [ $>6.9375$  mmol/L]), no lifestyle or other intervention was given initially. If these people developed diabetes, they were entered into the intensive DPP lifestyle program and monitored. If their HbA<sub>1c</sub> level increased to greater than 7%, they began receiving intensive treatment to control their HbA<sub>1c</sub> levels to a goal of less than 7%, as recommended by the American Diabetes Association.

The last strategy, called “metformin,” corresponded to the metformin arm of the DPP trial and involved putting patients on metformin as soon as they were determined to be at high risk. If diabetes was diagnosed in these patients, they continued receiving metformin, were given dietary advice, and continued to be monitored. If their HbA<sub>1c</sub> level exceeded 7%, their drug treatment was intensified to control the HbA<sub>1c</sub> level to less than 7%.

We assumed that both the effectiveness and the costs observed at the end of the DPP would persist as long as a person was receiving lifestyle intervention (2, 5). Specifically, after an initial weight loss of about 7%, the simulated persons’ weights gradually increased to a 4% weight-loss level after 3 years, as occurred in the DPP trial, and that degree of weight loss persisted as long as they were receiv-

Figure 1. Effects of 4 programs on progression to diabetes.



FPG = fasting plasma glucose.

**Table 1. Expected Outcomes over Various Time Horizons for a Typical Person with Diabetes Prevention Program Characteristics\***

Variable	Without Lifestyle Program (Baseline)			Absolute Difference Made by Lifestyle Program†		
	Length of Follow-up			Length of Follow-up		
	10 y	20 y	30 y	10 y	20 y	30 y
<b>Diabetes, %</b>	56.91	68.55	72.18	-14.26	-11.58	-10.84
<b>Coronary artery disease or CHF, %</b>						
Myocardial infarction	3.98	8.53	12.02	-0.39	-1.07	-1.65
CHF (systolic or diastolic)	0.23	0.67	1.19	-0.07	-0.07	-0.08
<b>Retinopathy, %</b>						
Blindness (legal)	0.71	2.16	3.02	-0.39	-1.04	-1.44
Proliferative diabetic retinopathy	1.38	3.15	4.33	-0.68	-1.36	-1.40
Retinopathy	1.11	2.57	3.39	-0.53	-1.15	-1.21
Total serious eye complication	3.20	7.89	10.74	-1.60	-3.55	-4.05
<b>Stroke (ischemic or hemorrhagic), %</b>	2.89	6.99	11.61	-0.46	-0.97	-1.42
<b>Nephropathy, %</b>						
ESRD	0.00	0.00	0.07	0.00	0.00	-0.04
Dialysis	0.00	0.00	0.05	0.00	0.00	-0.03
Kidney transplantation	0.00	0.00	0.02	0.00	0.00	-0.01
Total serious kidney complication	0.00	0.00	0.15	0.00	0.00	-0.08
<b>Neuropathy (symptomatic), %</b>						
Foot ulcers	0.68	1.43	1.78	-0.38	-0.65	-0.74
Partial foot amputation	0.17	0.58	0.74	-0.04	-0.31	-0.37
Amputation of any part of lower limb	0.00	0.00	0.03	0.01	0.02	-0.01
Total serious foot complication	0.84	2.01	2.55	-0.41	-0.94	-1.12
Total for all serious complications	11.15	26.08	38.24	-2.94	-6.60	-8.40
<b>Deaths, %</b>						
From coronary heart disease	2.22	6.65	11.90	-0.61	-1.07	-2.01
From stroke	0.37	0.94	1.48	-0.08	-0.25	-0.26
From renal disease	0.00	0.02	0.09	0.00	-0.01	-0.04
Total for death from any complication	2.59	7.61	13.47	-0.70	-1.32	-2.31
<b>Life-year data</b>						
Life-years			24.032			0.288
Undiscounted QALYs			16.125			0.276
QALYs discounted 3%			11.319			0.159

\* For each time horizon, the entries are the chance of having a complication or the decrease in chance of a complication up to the end of that time horizon. The columns labeled "baseline" give the chances that would apply with the baseline program; "difference" gives the absolute increase or decrease in the chance of a complication caused by the Diabetes Prevention Program lifestyle program. The chances that would apply with this lifestyle program can be determined from the table by subtracting the "difference" from the "baseline" values. CHF = congestive heart failure; ESRD = end-stage renal disease; QALY = quality-adjusted life-year.

† Differences between percentages are expressed as percentage points.

ing the lifestyle intervention. When a person's fasting plasma glucose level reached 9.99 mmol/L (180 mg/dL) or their HbA<sub>1c</sub> level reached 7%, the person was switched from the DPP lifestyle program to the intensive diet and exercise treatment protocol described above. Throughout the entire program, every individual in every group was at risk for other clinical events, such as angina, stroke, and heart attack.

### Perspectives

We examined each management strategy from 3 different points of view: a high-risk person, a 100 000-member health plan (approximately twice the average size of managed care organizations), and a societal perspective. For the health plan and societal perspectives, we included the entire distribution of people with DPP characteristics,

in the proportions seen in the DPP trial (2). The health plan point of view differs from the more traditional "health system perspective" in that it takes into account the size of the plan, the need to consider shorter time horizons, and member turnover. The societal perspective corresponds to the recommendations of the Panel on Cost-effectiveness Analysis (14). Specifically, we calculated the logistic events and clinical outcomes for each person in the population over a 30-year horizon, noting when each event and outcome occurred. We then assigned costs to each logistic event (for example, each test, visit, admission, and treatment) and assigned quality-of-life weights to each clinical outcome (for example, each heart attack, stroke, and amputation) to calculate the time stream of costs and quality-adjusted life-years (QALYs) for each person. We added all

Table 2. Expected Number of Cases of Diabetes and Complications in a Health Plan of 100 000 Members\*

Variable	Without Lifestyle Program (Baseline)				Absolute Difference Made by Lifestyle Program			
	Length of Follow-up				Length of Follow-up			
	5 y	10 y	20 y	30 y	5 y	10 y	20 y	30 y
<b>Diabetes, n</b>	1626	2276	2742	2887	-696	-570	-463	-434
<b>Coronary artery disease or CHF, n</b>								
Myocardial infarction	82	183	442	659	-9	-20	-44	-60
CHF (systolic or diastolic)	2	9	27	47	0	-3	-3	-3
<b>Retinopathy, n</b>								
Blindness (legal)	6	28	87	121	-5	-16	-42	-57
Proliferative diabetic retinopathy	19	55	126	173	-11	-27	-54	-56
Retinopathy	19	45	103	136	-12	-21	-46	-49
Total serious eye complication	44	128	315	429	-29	-64	-142	-162
<b>Stroke (ischemic or hemorrhagic), n</b>	47	116	280	464	-4	-19	-39	-57
<b>Nephropathy, n</b>								
ESRD	0	0	0	3	0	0	0	-2
Dialysis	0	0	0	2	0	0	0	-1
Kidney transplantation	0	0	0	1	0	0	0	0
Total serious kidney complication	0	0	0	6	0	0	0	-3
<b>Neuropathy (symptomatic), n</b>								
Foot ulcers	8	27	57	71	-6	-15	-26	-30
Partial foot amputations	2	7	23	30	0	-2	-12	-15
Amputation	0	0	0	1	0	0	0	0
Total serious foot complication	10	34	80	102	-7	-17	-38	-45
Total for all serious complications	186	470	1144	1708	-48	-122	-266	-330
<b>Deaths, n</b>								
From coronary heart disease	32	89	266	476	-8	-25	-43	-80
From stroke	6	15	37	59	-1	-3	-10	-11
From renal disease	0	0	1	4	0	0	0	-2
Total for death from any complication	38	104	304	539	-9	-28	-53	-92

\* For each time horizon, the entries are the cumulative number of cases or differences in number of cases up to the end of that time horizon. The columns labeled "baseline" give the cases that would occur with the baseline program; "difference" gives the absolute increase or decrease in cases caused by the Diabetes Prevention Program lifestyle program. The number of cases that would occur with this lifestyle program can be determined from the table by subtracting the "difference" from the "baseline" values. CHF = congestive heart failure; ESRD = end-stage renal disease.

the costs and the QALYs for the entire population to obtain time streams of the aggregated costs and QALYs. We used standard methods (14) to convert the time streams of events and outcomes into their present values, and divided the former by the latter to determine the cost per QALY. Because the cost per QALY is a ratio, it is not necessary to do this for the millions of people in the United States who are at high risk but only for a statistically meaningful sample—in this case, 10 000 such people. Logistic costs experienced by individuals (for example, out-of-pocket medical costs, nonmedical costs such as travel time, or social costs such as lost productivity) were included in the denominator through the use of the Quality of Well-Being Index.

### Calculations

For the main comparison, the DPP lifestyle program was compared with the baseline program. We also calculated its incremental cost-effectiveness compared with the "lifestyle when FPG > 125" program and the metformin program. Results for each program were calculated for 10 000 people. All calculations were performed with full precision; results were rounded for presentation. For all

calculations of cost per QALY in the base case, both costs and QALYs were discounted at an annual rate of 3%. For the reference comparison, the DPP lifestyle program was compared with the baseline program. We also calculated the incremental cost-effectiveness of the lifestyle program compared with the other programs.

### Role of the Funding Sources

The funding sources did not influence the decision to analyze this topic; the design, conduct, or reporting of the study; or the decision to publish the manuscript.

## RESULTS

### Individual High-Risk Person Perspective

Figure 1 shows the effect of lifestyle modification and metformin on development of diabetes for different lengths of follow-up. The 30-year probability that a person with DPP characteristics will develop diabetes is about 72%. Lifestyle modification, if persistent, would reduce that risk by a relative 15%, to about 61%. This indicates that over 30 years, the disease would be prevented in about

11% of cases and postponed in about 61%. In absolute terms, the risk reduction would be 11 percentage points and the long-term number needed to treat for benefit would be about 9. For metformin, about 4% of cases of diabetes would be prevented over a 30-year period, a relative reduction of about 5.5%.

**Table 1** shows the effects of a DPP lifestyle program on clinical outcomes for various periods of time for a typical high-risk person. For example, intensive lifestyle modification would decrease the chance that a high-risk person would have a myocardial infarction over the next 30 years by an absolute 1.7 percentage points (from 12% to 10.3%). The chance of having any severe complication would be decreased by an absolute 8.4 percentage points (from 38.2% to 29.8%).

### Health Plan Perspective

The health and economic outcomes that health plans can expect from implementing a DPP-like lifestyle program depend on the size of the plan, the planning horizon, and the turnover rate. A health plan with 100 000 members can expect to have approximately 4% of its membership, or 4000 people, at high risk for diabetes (36). **Table 2** shows the expected number of events for that cohort of people, for various lengths of follow-up, assuming no turnover.

**Table 3** shows the effects of the DPP lifestyle program on a health plan's costs for several time horizons. For most events, they are multiples of the probabilities in **Table 2**. For myocardial infarction, however, the numbers for health plans include second and further events. To help health plans anticipate how the costs and savings will be distributed across different departments, **Table 3** also shows the financial effects for the main components of a plan's budget. The last 2 rows of the table show the net cost translated into a per member per month cost for high-risk people and for the entire membership, averaged over the applicable time horizon.

For calculating the cost-effectiveness of the DPP lifestyle program from the plan's perspective, we assumed a turnover rate of 10% per year. The expected value of the cost/QALY is about \$143 000. The expected cost of gaining a QALY is higher for shorter time horizons. Over periods of 5, 10, or 20 years after the start of the program, the expected costs of gaining a QALY would be about \$2.7 million, \$1.2 million, and \$180 000, respectively. The much higher costs required to gain a QALY in the earlier years of follow-up are due to the fact that in the first few years after the introduction of the program, the costs are high and the clinical benefits, with their related cost-savings, are relatively small.

### Societal Perspective

**Figure 2** and **Table 4** show the cost-effectiveness of the DPP lifestyle program from a societal perspective. Compared with the baseline program, providing a nationwide DPP lifestyle program to all high-risk people would gain a QALY at a cost of about \$62 600 (**Table 4**, average cost/QALY). As for health plans, the cost/QALY at the societal level depends on the time horizon: The cost/QALY after 5, 10, and 20 years would be about \$492 000, \$222 000, and \$88 000, respectively (not shown in the table). Calculation of the expected cost/QALY of the DPP lifestyle program from the societal perspective differs from the cost/QALY calculated for the health plan because of the lack of turnover and because the recommended methods for calculating cost/QALY from a societal perspective do not include the size of a population.

### Incremental Cost-Effectiveness

**Table 4** and **Figure 2** also show the overall effects of the other programs on the discounted 30-year costs and QALYs from the societal perspective. The "lifestyle when FPG > 125" program delivers the greatest increase in QALYs for the cost. Compared with the baseline program, this program would deliver a 30-year cost/QALY of ap-

**Table 3. Effect of Lifestyle Program on Expected Costs in a Health Plan with 100 000 Members for 4 Time Horizons\***

Variable	Costs without Lifestyle Program (Baseline), \$				Cost Difference Made by Lifestyle Program, \$			
	Length of Follow-up				Length of Follow-up			
	5 y	10 y	20 y	30 y	5 y	10 y	20 y	30 y
Hospital admissions†	10.03	23.11	57.66	96.12	0.83	0.67	1.53	2.23
Office visits‡	8.26	16.14	33.00	47.78	-0.36	-1.01	-1.66	-2.02
Procedures§	7.40	15.93	37.63	57.07	-0.82	-2.03	-4.21	-5.46
Medications and ongoing programs	3.38	6.64	15.61	26.14	14.09	26.36	48.18	64.13
Total	29.07	61.82	143.9	227.11	13.73	24.00	43.84	58.88
Increase in PMPM for high-risk people					57.22	49.99	45.67	40.89
Increase in PMPM for entire membership					2.29	2.00	1.83	1.64

\* For each time horizon, the entries are the cumulative costs or cost differences up to the end of that time horizon, expressed in millions of U.S. dollars. The columns labeled "baseline" give the costs under the baseline program; "difference" gives the increase or decrease in costs caused by the Diabetes Prevention Program lifestyle program. The costs under this lifestyle program can be calculated from the table by adding the "difference" to the "baseline" values. The per member per month (PMPM) charges are the averages over the applicable time horizons.

† All costs associated with hospital admissions and emergency department visits, including physician hospital visits.

‡ All costs associated with office and clinic visits.

§ All tests and discrete procedures, such as electrocardiography, coronary artery bypasses, and photocoagulation surgery.

|| For example, case management and lifestyle modification.

**Table 4. 30-Year Costs, Quality-Adjusted Life-Years, and Incremental Costs/Quality-Adjusted Life-Years for 4 Programs from Societal Perspective (Discounted 3%)\***

Program	Cost per Person, \$	QALY per Person	Average Cost/QALY, \$	Incremental Increase in Cost, \$	Incremental Increase in QALYs	Cost/QALY, \$
Baseline	37 171	11.319				
Lifestyle when FPG level >125 mg/dL†	40 237	11.444	24 523	3066	0.125	24 523
DPP lifestyle‡	47 140	11.478	62 602	6903	0.034	201 818
Metformin	41 189	11.432	35 523	Dominated	Dominated	Dominated

\* DPP = Diabetes Prevention Program; FPG = fasting plasma glucose; QALY = quality-adjusted life-year.

† Incremental values are compared with those of the baseline program.

‡ Incremental values are compared with those of the “lifestyle when FPG level >125 mg/dL [ $>6.9375$  mmol/L]” program.

proximately \$24 500. If this strategy were made the reference point for calculating the cost-effectiveness of the DPP lifestyle program, then the incremental cost-effectiveness of that program would be about \$202 000 per QALY gained, over a 30-year horizon.

### Sensitivity Analysis

There are 2 main types of uncertainty about the results of any model. One is the structure of the model—the equations it uses. The other is the accuracy of the values that are assigned to the variables in the equations. Traditional sensitivity analysis addresses the second source of variability and uncertainty, and the results of our sensitivity analyses are described in this section. However, traditional sensitivity analysis does not address uncertainty about the structure of a model because it uses the very model about which the uncertainty exists and merely shows the effects of changing some variables within that structure. It does not make any comparisons with actual, empirically observed results. Far from exploring uncertainty about a model’s structure, traditional sensitivity analysis assumes that the structure is correct. The best way to explore variability and uncertainty about the entire model—both its structure and its variables—is to compare the model’s results with real-world results. The ability to

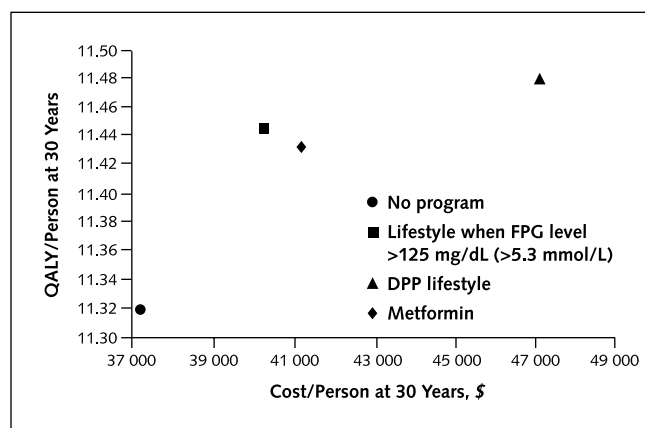
do this depends on the available empirical evidence. The fact that the Archimedes model independently and prospectively predicted the results of the DPP provides a test of the parts of the model that address prediabetes, early diabetes, and the effects of metformin and lifestyle. The model’s success in matching or predicting the results of 18 other clinical trials relating to diabetes and its complications tests the structure of those other parts of the model.

Several sources of variation and randomness affect the results. Individuals vary widely with respect to such factors as their chances of developing diabetes, when they will develop it, the rate at which it will progress, and their chances and timing of complications. In addition to these individual variations are random factors that affect such things as test results and response to treatments. To address these factors, the Archimedes model represents them as random variables (10). Each simulated individual is created by simultaneously drawing a value for each variable from its respective distribution. The calculated results are subject to a range of uncertainty determined by the number of individuals in the simulation. In this case, the number of simulated individuals is so large that the effect is negligible. For example, the 95% CI for the 30-year chance of developing diabetes is 71.28% to 73.08%. The 95% CI for the decrease in chances of developing diabetes caused by the lifestyle program is 10.83% to 10.85%.

A much more important factor is the uncertainty in the results of the DPP itself. The observed relative reduction in incidence of diabetes after an average follow-up of 2.8 years was 58%, but the 95% CI for this relative reduction was 48% to 66% (2). This has a large effect on the estimated health benefits of the program. For example, incorporating this source of uncertainty in the model increases the 95% CI for the 30-year chance that a high-risk person will develop diabetes to 69.4% to 75%, and increases the 95% CI for the absolute decrease in the chance of developing diabetes caused by the lifestyle program to 7.3 to 14.4 percentage points. The 95% CIs for the chance of any complication and the effect of the lifestyle program on that chance are 35.2% to 41.3% and 4.9 to 12 percentage points, respectively.

An important factor affecting the expected clinical effects of the DPP for a health plan is its size. This is con-

**Figure 2. Quality-adjusted life-years (QALYs) versus cost for 4 programs.**



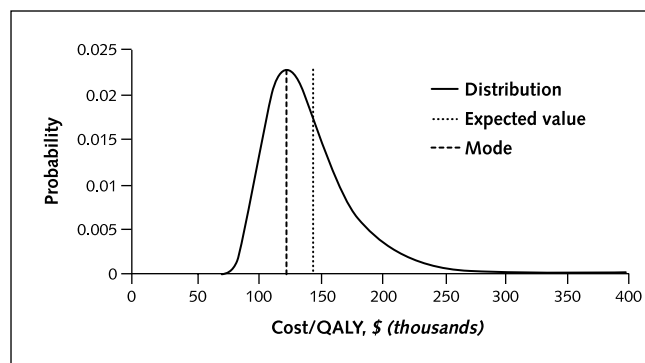
DPP = Diabetes Prevention Program; FPG = fasting plasma glucose.

ceptually similar to the sampling variation that affects the outcomes of clinical trials. For example, with the baseline program, the number of myocardial infarctions (including repeated myocardial infarctions) that can be expected to occur over a 30-year period is 659 (Table 2), but the 95% CI for the number of myocardial infarctions ranges from 612 to 706, or a range of  $\pm 7\%$  from the expected value given in Table 2. The 95% CI for the difference in myocardial infarctions caused by the lifestyle program is  $\pm 9.5\%$ . The CIs are smaller for more frequent outcomes, such as the occurrence of diabetes ( $\pm 2\%$ ), or for aggregated outcomes, such as “total for all complications” ( $\pm 4.3\%$ ), but are larger for less frequent outcomes, such as those relating to nephropathy and neuropathy ( $> \pm 50\%$ ).

The size of the health plan has a much smaller effect on the costs shown in Table 3. For example, the 95% CI for the increase in cost at 30 years (\$58.88 million in Table 2) is about \$56.8 million to \$60.8 million. However, because of the wide range of uncertainty about the clinical benefits in a plan of this size, uncertainty about the cost of gaining a QALY is considerable. Figure 3 shows a probability distribution for the cost/QALY for the DPP lifestyle program versus the baseline program. The most likely value (mode) is about \$121 000 per QALY gained, but the expected value of the cost/QALY, which considers the uncertainty about the magnitudes of the clinical benefits, is about \$143 000. It is exceedingly unlikely ( $< 0.1\%$  chance) that the cost/QALY for a health plan of 100 000 members would be less than the arbitrary threshold of \$50 000.

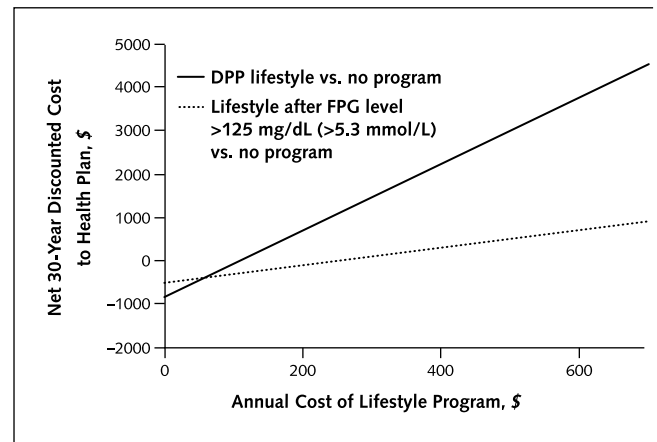
Several other factors that are typically known to a health plan but that can vary across plans affect the estimates of quality of life and cost/QALY. Table 5 summarizes these, including turnover (0%, 5%, 10% [reference], and 15%); discount rate (0%, 3% [reference], and 5%); cost of diabetes care (across-the-board 20% increase and 20% decrease); size of the health plan (50 000, 100 000

**Figure 3. Probability distribution for cost/quality-adjusted life-year (QALY) for Diabetes Prevention Program lifestyle program versus no program.**



Analysis is from the health plan perspective and incorporates size of plan and turnover.

**Figure 4. Net cost to health plan (discounted) of 2 programs, as function of annual cost of lifestyle program.**



DPP = Diabetes Prevention Program; FPG = fasting plasma glucose.

[reference], 200 000, and 500 000); and the cost of the lifestyle intervention (20% increase, 20% decrease). Table 5 also shows the effects of uncertainty or variability about utility weights (across-the-board 20% increase and 20% decrease) and includes several time horizons.

Uncertainty in the results of the DPP itself also has a large effect on the cost/QALY calculated from the societal perspective. When this is considered, the uncertainty about the increase in QALYs (approximately  $\pm 0.2$  year) is greater than the increase in QALYs itself (0.125 year). This large range of uncertainty about the gain in QALYs renders the cost/QALY almost meaningless for practical planning.

The most important factor that is potentially controllable is the cost of the lifestyle intervention. Of particular interest is the possibility that fundamentally different, less expensive ways of modifying lifestyles to lose weight may be found. For example, the DPP Research Group has suggested that group-based programs might be just as effective in achieving sustained weight loss as the individual-based program used in the DPP study (15). According to their methods and assumptions, the annual cost of a lifestyle program would be reduced to about \$650 over 3 years, or about \$217 a year. Table 5 shows the cost implications of such a program, assuming the same degree of effectiveness on weight, blood pressure, and cholesterol levels, in the row labeled “Group (\$217/y).”

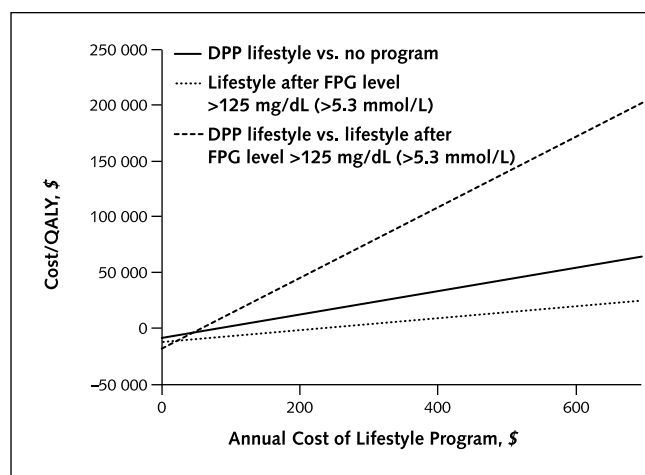
Figure 4 shows the relationship between the annual per person cost of a lifestyle intervention and the 30-year per person increase in net cost of the DPP lifestyle program compared with no program (solid line) and the “lifestyle when FPG  $> 125$ ” program compared with no program (dotted line). Figure 5 shows the effect of the annual per person cost of a lifestyle intervention on the 30-year cost/QALY for the following comparisons: DPP lifestyle versus baseline (solid line), “lifestyle when FPG  $> 125$ ” versus baseline (dotted line), and DPP lifestyle versus “lifestyle when FPG  $> 125$ ” (dashed line).

Table 5. Sensitivity Analysis: Cost/Quality-Adjusted Life-Year\*

Variable	Cost/QALY, \$							
	Health Plan Perspective				Societal Perspective			
	Time Horizon				Time Horizon			
	5 y	10 y	20 y	30 y	5 y	10 y	20 y	30 y
Reference case	2757	1238	180	143	492	222	88	63
<b>Turnover in membership (reference, 10%)</b>								
0%	2502	1060	224	121				
5%	2627	1158	163	107				
15%	2890	1280	218	195				
<b>Discount rate for cost and quality of life (reference, 3%)</b>								
0%	2679	1193	166	119	477	206	77	52
5%	2810	1261	194	163	502	233	97	71
<b>Cost of diabetes care (reference, costs at Kaiser Permanente)</b>								
-20%	2826	1276	185	147	504	229	91	64
20%	2688	1200	176	139	480	215	85	61
<b>Cost of lifestyle intervention (reference, \$1365 first year, \$672 thereafter)</b>								
-20%	2114	943	143	110	378	169	67	48
20%	3400	1533	215	176	606	275	109	77
Group (\$217/y)	459	201	39	27	86	37	16	12
<b>Size of plan (reference, 100 000)</b>								
50 000	2820	1367	228	170				
200 000	2604	685	159	130				
500 000	2074	349	148	125				
<b>QALY scores†</b>								
-20%	3446	1548	217	178	615	277	110	78
20%	2298	1032	154	120	410	185	73	52

\* Costs are expressed in thousands of U.S. dollars. QALY = quality-adjusted life-year.  
 † Weights applied to events that affect quality of life.

Figure 5. Cost/quality-adjusted life-year (QALY) of 3 comparisons as function of cost of lifestyle program.



DPP = Diabetes Prevention Program; FPG = fasting plasma glucose.

## DISCUSSION

Our analysis indicates that the 30-year probability that a person with DPP characteristics will develop diabetes is about 72%, and that lifestyle modification, if persistent, would reduce that risk by a relative 15%, to about 61%. This indicates that over 30 years, the disease would be prevented in 11% of cases (number needed to treat for benefit, 9) and postponed in 61%. This may appear to conflict with the results of the DPP study, in which the authors stated that “the lifestyle intervention reduced the incidence [of diabetes] by 58%” (2). The apparent conflict is explained by the fact that the 58% figure applies to the average follow-up time of the DPP study, which was only 2.8 years. It does not apply to the long-term effect. In fact, the relative effect of the lifestyle program on development of diabetes decreases over time (Figure 1). Two main factors diminish the relative effect. First, the relative effect of lifestyle on progression to diabetes (measured as percentage

reduction) decreases over time. This is seen in the DPP study itself; the relative reduction was 68% at 1 year, 64% at 2 years, 51% at 3 years, and 46% at 4 years (Figure 2 in reference 1). Second, even if the rate of progression to diabetes is decreased by a constant proportion (for example, is assumed to be a constant 58%), as people progress from high risk to diabetes there are fewer people at high risk and therefore fewer people to be affected by the treatment. The simplest case, in which both the transition from high risk to diabetes and the relative effect of lifestyle on that transition are assumed to be constant, is illustrated in an analysis of this problem by the DPP Research Group. Their report illustrates the gradual diminution in relative effect (6). The Archimedes model shows the same phenomenon of a diminishing relative effect, but with greater accuracy because it incorporates the fact that neither the transition rate nor the relative effect of lifestyle is constant.

Even though the long-term effect of the lifestyle program is smaller than that observed in the short duration of the trial, and even though effects always appear smaller when presented in absolute rather than relative terms, the long-term absolute effects of lifestyle modification are still very important clinically. The most important messages for a person with DPP characteristics are the following: 1) Your risk for developing diabetes is about 72%; 2) Your chance of having a serious complication of the disease is almost 40%, and your chance of dying of a complication of the disease is about 13%; 3) If you change your lifestyle and permanently lose just 4% of your weight (about 7 pounds for the typical high-risk person), you can reduce your risk for a serious complication or for dying of diabetes by about 20% (relative risk); and 4) Over the range of weight loss seen in the DPP, every pound you lose and keep off permanently will lower your risk for a serious complication more than 1 percentage point (absolute risk).

From the perspective of a health plan, the clinical benefits of implementing a DPP-like lifestyle modification program are clear. Reductions in cases of diabetes and its complications would be seen within 5 years and would gradually grow over time (Table 2). Over a 30-year horizon, such a program would be expected to prevent about 11% of cases of diabetes, about 22% of its most serious complications, and about 18% of diabetes-related deaths in people who are at high risk for this disease (Table 2).

Unfortunately, a DPP-like lifestyle program would considerably increase costs. Even for the most optimistic picture—a 30-year horizon and assuming no turnover—the net effect on diabetes-related costs would be an increase of about 25% (calculated from Table 3). The proportional increase would be even greater over shorter time horizons. For example, in the first 5 years the increase in diabetes-related costs would be about 50%. Cast in terms of per person costs and the immediate burden a health plan would face, the actual cost increase in the first 5 years would be about \$60 per month per high-risk person, or about \$2.30 per member (any person) per month. To put

this in perspective, it would represent a permanent increase in total costs for all interventions for all conditions of about 1 percentage point. In an era when the United States is struggling to keep annual health care cost increases to single digits, this would represent a heavy burden.

For cost-effectiveness, from the perspective of a health plan of about 100 000 members and with a member turnover of about 10% per year, the expected 30-year cost/QALY of a DPP-like lifestyle intervention compared with no prevention program at all would be in the range of \$143 000. The cost/QALY is higher for shorter time horizons and smaller plans (Table 5). From a societal perspective, the cost/QALY compared with no program would be approximately \$63 000 over a 30-year horizon and would be higher for shorter time horizons (Table 5). From either perspective, and setting aside uncertainty about the effectiveness of the intervention itself, there is a less than 0.1% chance that the 30-year cost/QALY would be below \$50 000.

Two additional factors make the argument for cost-effectiveness even more pessimistic. First, other options are available. The figures just given represent average cost/QALY of the DPP lifestyle intervention, in which the comparison is with no program at all. Another possible strategy is to delay implementing the lifestyle intervention until after a person actually gets diabetes. Compared with no program, this has a 30-year cost/QALY of about \$24 500. If this is used as the reference for calculating the marginal cost/QALY of the DPP lifestyle program (which is begun immediately upon determination that a person is at high risk, instead of waiting until diabetes develops), the expected cost-effectiveness of that program increases to about \$202 000 from a societal perspective (Table 4). It would be even greater for a health plan. Indeed, even the metformin program has a lower average cost/QALY than the DPP lifestyle program.

Second, the cost/QALY is considerably higher in early years than in later years (Table 5). In fact, it is the outcomes in the early years (5 and 10 years) that will actually occur. Calculation of longer-term costs/QALY requires an assumption that the program will be in place for decades without change and that there will be no technological advancements in the management of diabetes, such as new drugs, tests, devices (for example, insulin pumps), or procedures (pancreas transplants). While the long-term cost/QALY is useful as a method of making comparisons across technologies or as a measure for determining the sensitivity of results to various factors, the long-term cost/QALY is an abstraction and does not represent an outcome that health plans or a national program would actually experience.

The results are sensitive to several factors, as described in the section on sensitivity analysis. The most important is uncertainty about the results of the DPP trial itself. On this point, it is encouraging that the Archimedes model independently and prospectively predicted results almost identical to those seen in the DPP. The Archimedes model

has also been validated against a broad range of other clinical trials to help ensure that it accurately represents the best information available to date. The high concordance between the Archimedes prediction of the DPP results and the actual DPP results indicate that the DPP's results are consistent with preexisting information.

Given the high clinical value of improving the lifestyle program, finding ways to deliver it at a lower cost is critical. There are 2 main ways to do this: Delay starting the program until people actually develop diabetes, and find less expensive ways to modify lifestyle and maintain the changes. From the perspective of a health plan, implementing a lifestyle modification program at the time people develop diabetes (after fasting plasma glucose level is  $>9.9375$  mmol/L [ $>125$  mg/dL] or 2-hour oral glucose tolerance test result is  $>11.0445$  mmol/L [ $>199$  mg/dL]) would increase the net cost only 3% in the first 5 years, and 9% over 30 years (data not shown in the tables). This is considerably more feasible than the 50% and 25% 5-year and 30-year increases that occur with the DPP lifestyle program. In absolute terms, the increase in per member per month cost with the "lifestyle when FPG  $> 125$ " program would be about \$0.37 in the first 5 years, and lower thereafter.

Finding less expensive ways to modify people's lifestyles and achieve the degrees of weight loss seen in the DPP study could have a more important effect on the desirability and cost-effectiveness of lifestyle modification. Less expensive methods would affect the net costs of both the DPP lifestyle program and the "lifestyle when FPG  $> 125$ " program. The relationship between the annual cost of achieving lifestyle changes and the net 30-year per-person cost of diabetes-related care can be determined from **Figure 4**. For example, lifestyle modification after the diagnosis of diabetes ("lifestyle when FPG  $> 125$ ") would become cost-neutral over 30 years if the annual cost of implementing it could be reduced to about \$220. To make the DPP lifestyle program cost-neutral, the annual cost of implementing the lifestyle changes would have to be approximately \$100. As the cost of implementing the lifestyle program is reduced, the "DPP lifestyle when FPG  $> 125$ " program becomes even more attractive; at an annual implementation cost of \$100, the "DPP lifestyle when FPG  $> 125$ " program is cost-saving.

**Figure 5** shows the cost/QALY that would be achieved with various programs under different assumptions about the annual cost of a lifestyle modification program, for a societal perspective and 30-year horizon. For example, if the annual cost of a lifestyle program could be decreased to \$217, compared with no program (baseline), a lifestyle intervention delivered as soon as a person develops diabetes ("lifestyle when FPG  $> 125$ ") would gain a QALY at a cost of about \$2000. Compared with waiting until the diagnosis of diabetes ("lifestyle when FPG  $> 125$ "), the marginal cost/QALY of starting the lifestyle program immediately (DPP lifestyle) would be about \$49 500. **Figure**

**5** can also be used to work backward to find the annual cost of lifestyle modification needed to make the DPP lifestyle program cost-effective, for any specified threshold for an acceptable cost/QALY. For example, if \$50 000 is determined to be an appropriate threshold for a 30-year cost/QALY, the DPP lifestyle intervention should have an annual cost of about \$210 to justify beginning the program as soon as a person is determined to be at high risk, instead of waiting until after the diagnosis of diabetes (read from **Figure 5**, *solid line*).

It is unlikely that the effects of prevention on specific complications of diabetes will ever be shown in a clinical trial. The DPP study involved approximately 1000 people in each of the 3 groups, and the average follow-up time was only about 3 years. The results in **Table 1** imply that if a trial like the DPP were continued for an average follow-up of 10 years, the power for finding a statistically significant effect on the most frequent complication, myocardial infarction, at a significance level of a *P* value less than 0.05 would be about 7.5% (37). A 20-year follow-up would increase the power to about 14%. The prospects for showing an effect on a compound outcome are better, but still difficult and expensive. For example, if a combined outcome of any serious complication or death were used, extending the trial for 10 years would have a power of about 70%. The cost of the 3-year DPP study was on the order of \$175 million; extending the trial for 10 years would at least double that cost. The implications are that it is unlikely a trial will be conducted to document the effects of prevention on the complications of diabetes. A corollary is that the evidence is unlikely to get any better, and it would be pointless to insist on such documentation before recommending prevention.

Our results differ from those of a recent analysis by Herman and colleagues, which showed a larger effect on the chance of developing diabetes, larger increases in QALYs, lower costs, and a lower cost/QALY (6). Several factors explain the differences. First, the models have very different structures. Herman and colleagues used a Markov model, which represents diseases as a set of discrete clinical "states," represents the progression of a disease as annual transitions between states, and represents the effects of treatments as changes in the chances of transitions between states. The Archimedes model was designed to be considerably more thorough and clinically realistic. **Appendix Table 1** (available at [www.annals.org](http://www.annals.org)) provides additional details and examples from the 2 models. Second, because they had to fit a complex disease such as diabetes and its complications into the Markov structure, and because there are no direct data for many of the transition probabilities, Herman and colleagues had to make many simplifications and assumptions. These are described in their paper (6) and its accompanying technical report (available at [www.annals.org](http://www.annals.org)). These assumptions differ considerably from the way the same issues are addressed in the Archimedes model. Some of the most important differ-

ences are compared in **Appendix Table 2** (available at [www.annals.org](http://www.annals.org)), which readers are encouraged to study. Third, Herman and colleagues' model has not been validated.

Our analysis has several limitations. First, there may be other populations for whom the natural history or response to lifestyle modification is substantially different from that seen in the DPP study or UKPDS. This analysis would not apply to them. To the extent that such populations can be identified, their rates of disease progression determined, and the effects of lifestyle changes determined, separate analyses must be done. Second, what happens in clinical trials might not represent what happens in actual practice, especially in terms of the effectiveness of the interventions. Although the Archimedes model has the ability to include such factors as provider and patient behaviors (for example, adherence to a guideline or treatment recommendation), for this analysis we assumed that the lifestyle and metformin interventions would be as effective as in the DPP study. The effect of this assumption is a bias in favor of the lifestyle intervention (reducing the calculated cost/QALY).

This analysis uses costs from a very large, nonprofit managed care organization that provides comprehensive care to a diverse population. Thus, our costs reflect true resource costs, as recommended for the societal perspective (14), and avoid many of the distortions that can occur because of deductibles, copayments, profits, discounts, or underpayment. However, in settings where charges reflect true costs less accurately, the costs incurred by insurers, individuals, employers, Medicare programs, and others who pay bills may be different. For example, market prices or charges will tend to be higher than true resource costs in for-profit settings and lower in settings where reimbursement rates fall short of true resource costs. Because financial arrangements vary so widely across settings, no single set of costs will reflect every setting or the United States as a whole. Sensitivity analysis is the best way to estimate the cost-effectiveness of the programs for settings where charges differ more widely from true resource costs. The range of values shown in **Table 5** covers a wide variety of health plans. The cost-effectiveness calculated for the societal perspective is less vulnerable to the differences in cost structures seen across real settings because the societal perspective is intentionally designed to be an idealized representation of true resource costs.

Finally, although the Archimedes model has been rigorously validated against the pertinent clinical trials, there is no way to ensure that it is perfectly accurate for predicting events that have never been studied empirically with trials. The purpose of the validations is to confirm that the model faithfully represents the pathophysiology of the disease and the effects of treatments as they are currently understood through existing evidence. This builds confidence but does not guarantee that the model will be accurate for questions for which no evidence exists.

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**Note:** The order of authorship for Drs. Eddy and Schlessinger is alphabetical.

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## References

1. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343-50. [PMID: 11333990]
2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403. [PMID: 11832527]
3. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072-7. [PMID: 12086760]
4. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002;51:2796-803. [PMID: 12196473]
5. Herman WH, Brandle M, Zhang P, Williamson DF, Matulik MJ, Ratner RE, et al. Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. *Diabetes Care*. 2003;26:36-47. [PMID: 12502656]
6. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med*. 2005;142:323-32. [PMID: 15738451]
7. Schlessinger L, Eddy DM. Archimedes: a new model for simulating health care systems—the mathematical formulation. *J Biomed Inform*. 2002;35:37-50. [PMID: 12415725]
8. Eddy DM, Schlessinger L. Archimedes: a trial-validated model of diabetes. *Diabetes Care*. 2003;26:3093-101. [PMID: 14578245]
9. Eddy DM, Schlessinger L. Validation of the Archimedes diabetes model. *Diabetes Care*. 2003;26:3102-10. [PMID: 14578246]
10. Schlessinger L, Eddy DM. Equations for the Archimedes model of diabetes and its complications. Technical Report, Parts A and B. 2004. Accessed at <http://archimedesmodel.com>.
11. Blumenthal JA, Sherwood A, Gullette EC, Babyak M, Waugh R, Georgiades A, et al. Exercise and weight loss reduce blood pressure in men and women with mild hypertension: effects on cardiovascular, metabolic, and hemodynamic functioning. *Arch Intern Med*. 2000;160:1947-58. [PMID: 10888969]
12. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al.

- Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med.* 1987;317:1237-45. [PMID: 3313041]
13. **DeFronzo RA, Goodman AM.** Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med.* 1995;333:541-9. [PMID: 7623902]
  14. **Gold MR, Siegel JE, Russell LB, Weinstein MC.** Cost-Effectiveness in Health and Medicine. New York: Oxford Univ Pr; 1996.
  15. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care.* 2003;26:2518-23. [PMID: 12941712]
  16. **Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, et al.** Valuing health-related quality of life in diabetes. *Diabetes Care.* 2002;25:2238-43. [PMID: 12453967]
  17. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20:1183-97. [PMID: 9203460]
  18. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-53. [PMID: 9742976]
  19. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977-86. [PMID: 8366922]
  20. **Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, et al.** The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001;345:870-8. [PMID: 11565519]
  21. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:23-33. [PMID: 12114037]
  22. **Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G.** Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med.* 2000;342:145-53. [PMID: 10639539]
  23. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet.* 2000;355:253-9. [PMID: 10675071]
  24. **Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al.** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med.* 1996;335:1001-9. [PMID: 8801446]
  25. **Lewis EJ, Hunsicker LG, Bain RP, Rohde RD.** The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456-62. [PMID: 8413456]
  26. **Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al.** Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851-60. [PMID: 11565517]
  27. **Lewis SJ, Moye LA, Sacks FM, Johnstone DE, Timmis G, Mitchell J, et al.** Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med.* 1998;129:681-9. [PMID: 9841599]
  28. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998;339:1349-57. [PMID: 9841303]
  29. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA.* 1991;265:3255-64. [PMID: 2046107]
  30. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA.* 1984;251:351-64. [PMID: 6361299]
  31. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *Br Med J (Clin Res Ed).* 1985;291:97-104. [PMID: 2861880]
  32. **Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995;333:1301-7. [PMID: 7566020]
  33. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-9. [PMID: 7968073]
  34. **Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al.** Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364:685-96. [PMID: 15325833]
  35. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care.* 2002;25:2165-71. [PMID: 12453955]
  36. **Benjamin SM, Valdez R, Geiss LS, Rolka DB, Narayan KM.** Estimated number of adults with prediabetes in the US in 2000: opportunities for prevention. *Diabetes Care.* 2003;26:645-9. [PMID: 12610015]
  37. **Eddy DM, Hasselblad V.** FAST\*PRO, Software for Meta-analysis by the Confidence Profile Method. Boston: Academic Pr; 1992.

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38. **Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al.** A Markov model of disease progression and cost-effectiveness for type 2 diabetes. *June 2004*. Accessed at [www.annals.org/cgi/data/142/5/323/DC1/1](http://www.annals.org/cgi/data/142/5/323/DC1/1) on 15 June 2005.

39. The Diabetes Prevention Program: baseline characteristics of the randomized cohort. The Diabetes Prevention Program Research Group. *Diabetes Care*. 2000; 23:1619-29. [PMID: 11092283]

40. **Colhoun HM, Thomason MJ, Mackness MI, Maton SM, Betteridge DJ, Durrington PN, et al.** Design of the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. *Diabet Med*. 2002;19:201-11. [PMID: 11918622]

41. Mount Hood Challenge 4 Meeting Summary. 2-4 September 2004, Basel, Switzerland. Accessed at [www.thecenter.ch/mounthood4/mounthood.asp](http://www.thecenter.ch/mounthood4/mounthood.asp).

42. Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994). CD ROM Series 11, No 1. Hyattsville, MD: National Center for Health Statistics.

43. **Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al.** Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999; 341:410-8. [PMID: 10438259]

44. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-34. [PMID: 10189543]

45. **Colagiuri S, Cull CA, Holman RR.** Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes?: U.K. prospective diabetes study 61. *Diabetes Care*. 2002;25:1410-7. [PMID: 12145243]

46. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ*. 1995;310:83-8. [PMID: 7833731]

47. **Harris MI, Klein R, Welborn TA, Knudman MW.** Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care*. 1992;15:815-9. [PMID: 1516497]

48. **LaPorte RE, Matsushima M, Chang YF.** Prevalence and incidence of insulin dependent diabetes. In: Harris MI, Cowie CC, Stern MP, et al., eds. *Diabetes in America*. 2nd ed. Washington, DC: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:37-46. NIH publication no. 95-1468. Accessed at <http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter3.pdf> on 1 May 2005.

## APPENDIX: SUPPORTING INFORMATION

This appendix contains additional information about the Archimedes model pertinent to the analysis of the prevention and management of diabetes in high-risk people. It has 5 main parts: an introduction to object-oriented programming, which forms the structure of the model; an introduction to how we model human physiology; a comparison of the Archimedes model with Markov models, using a particular Markov model of diabetes prevention as an example; a description of some differences between the 2 models that could explain their different results; and additional information about the validation of the Archimedes model.

### Structure of the Archimedes Model: Object-Oriented Programming

The Archimedes model has an entirely different structure than other clinical models, such as Markov models. In this section and the next, we describe the structure and programming method and mathematical formulation of the Archimedes model. In the third section, we compare the Archimedes model with a Markov model applied to the same clinical problem—diabetes prevention.

The Archimedes model uses an object-oriented approach. This approach has several powerful features applicable to human physiology and health care. Almost any aspect of reality, either tangible or conceptual, can be represented as an “object.” Examples of objects in the Archimedes model are lungs, chest pain, a patient’s memory, a laboratory test, and an office visit. Objects are organized in a logical hierarchy, beginning with “classes” (for example, facilities), which can have “subclasses” (for example, hospitals), which can have “sub-sub-classes” (for example, emergency departments), down to any desired level of detail. All classes of objects at every level in the hierarchy can have specific examples (called “instances” in the object-oriented terminology). Thus, John Doe and Mary Smith are specific examples (instances) of the class “person.” John Doe’s heart is an instance of the class “heart.” For every class of objects at every level in the hierarchy, it is possible to give the instances “attributes” (for example, characteristics) and “functions” (things they can do). Attributes and functions (also called “instance variables” and “methods,” respectively) that are defined for a class of objects at a particular level in the hierarchy are inherited by every instance of that class and by all the instances of all of its subclasses. The specific values of the attributes and the executions of the functions can be unique for every instance of a class of objects. The functions of any instance of a class of objects can depend on its own specific attributes, as well as on the specific attributes and functions of other objects.

For a contrived example, a function of the object “person” might be “can pick up boxes.” An attribute of people might be “strength.” John’s particular value of the strength attribute might be “strength to pick up boxes weighing up to 50 pounds.” George’s strength attribute might be “strength to pick up boxes weighing up to 75 pounds.” An interaction between John and George might be, “John can pick up boxes heavier than 50 pounds but less than 125 pounds if George helps him.”

The hierarchical structure, the ability of classes to inherit characteristics and functions from the classes above them, and the ability to address interactions between the objects in any class enable the creation of very realistic and powerful models for health care. An example is human anatomy and physiology. A complete description of the Archimedes physiology model is not possible here, but the scope and depth can be illustrated by walking down one path in one hierarchy. In Archimedes, every particular patient has a physiology, which includes organs, one of which is the heart, each of which has 4 coronary arteries, 1 of which is the left anterior descending artery, a function of which is to carry blood to the heart muscle (myocardium). The left anterior descending artery has a channel (lumen), which can have an atherosclerotic plaque at any point, which can affect the blood flow downstream of that point, which can affect the myocardium’s contractility (a function of the myocardium), which, among other things, can cause pain (a type of symptom object) which has an intensity (one of the attributes of the symptom object “pain”) and a function (for example, to inform the patient’s mind—another part of the patient’s physiology—that something is wrong with the heart). Different types of objects at any level in the hierarchy can interact. For example, when a person (an instance of the class “patient”) with chest pain (a type of symptom object) telephones a call center (a type of facility object), the call will be answered by an operator (a type of health care–provider object), who will refer to a protocol (a type of policy/procedure object) to provide appropriate advice (a type of message object). The Archimedes model contains all of these objects.

Time is handled through an object called an “event queue.” For every object in the model, we define the events of interest that relate to that object. At any instant, the equations in the model can be used to calculate for every object in the model the time of the next event affecting that object, as a function of all the other variables in the model. The event queue is an ordered list of all the upcoming events that will affect any of the objects, and the times those events will occur. When an event occurs to any object, the model calculates the effects of that event on every other object and then updates the queue. The model then goes to the time of the next event and repeats the process. In this way, the sequence of events occurring in the model will be as condensed (for example, minute-to-minute for the registration of chest pain by John’s brain, and calling the hospital) or as drawn out (for example, years between any health-related events for a healthy man in his thirties) as needed. The model does this for every object and variable in every simulated person in the model, usually thousands of people.

A final strength of the object-oriented approach is that the hierarchical structure makes it very easy to add, delete, or modify classes of objects and the attributes and functions of objects, at any level in the hierarchy. Whenever an attribute or function is added or changed for a class of objects, the addition or change is automatically inherited by all the instances of that class and its subclasses. Two practical implications of this are that the model is easy to update when new information becomes available and that the model can be expanded or pruned for particular applications.

## Modeling Human Physiology and Disease

We conceptualize the physiology of a person as a collection of continuously interacting objects that we call “features.” The concept of a feature is very general, but features correspond roughly to anatomic and biological variables. Examples in the current Archimedes model are systolic and diastolic blood pressures, stenosis of a coronary artery, cardiac output, visual acuity, and amount of protein in the urine. Features can represent real physical phenomena (for example, the number of milligrams of glucose in a deciliter of plasma), behavioral phenomena (for example, ability to read an eye chart), or conceptual phenomena (for example, the “progression” or “spread” of cancer). Features can be continuous, categorical, count, or dichotomous, corresponding to the type of variable they are representing in reality; as in reality, most are continuous. The full model contains hundreds of features, corresponding roughly to the variables discussed in medical textbooks and written in patients’ charts. When particular features for a disease are central to the occurrence, progression, and treatment of a disease, we call them “primary features.”

In Archimedes, features define diseases, cause symptoms, are the things measured by tests, respond to treatments, and cause health outcomes. At any moment, every feature in every patient has a value (for example, on 20 February at 8:45 a.m., John’s systolic blood pressure was 137 mm Hg). The values of most features change continuously over time, causing every feature in every individual to have a trajectory. As in reality, the trajectory of a feature in a particular person can be affected by the person’s characteristics, behaviors, other features, and random factors. When one or more features are considered to be abnormal, we say that a person has a disease. Because in reality concepts of abnormality can change, because many diseases are “man-made” (that is, based solely on the results of tests), because many diseases have multiple and changing definitions, and because diseases can overlap (comorbid conditions), Archimedes does not model a disease as though it were a physiologic object or state in its own right. Instead, it focuses on the underlying features (biological variables) that define a disease. For example, “diabetes” is said to be present when the fasting plasma glucose level is greater than 6.9375 mmol/L (>125 mg/dL) or the oral glucose tolerance test result is greater than 11.0445 mmol/L (>199 mg/dL). This approach enables the model not only to accommodate different definitions and changes in definitions but also to test the implications of different definitions. It also addresses comorbid conditions in a natural way.

The role of a test is to measure the value of one or more features. As features progress, they can cause certain clinical events such as signs, symptoms, and health outcomes to occur. This is accomplished mathematically by triggering the event when the values of a feature, or combination of features, meet certain rules (for example, reach a particular threshold or suddenly accelerate). The rules that define when events occur can vary from individual to individual, can depend on other features, and can include random factors.

The role of a treatment is to change the value, the rate of progression, or both of one or more features. The features af-

ected by a treatment are the ones identified through clinical research. For example, in the part of the Archimedes model that addresses diabetes, metformin acts on the hepatic production of glucose, triglycerides, and LDL cholesterol—all features in the model. Glyburide stimulates the secretion of insulin by pancreatic  $\beta$  cells and affects weight. Diet affects weight, blood pressure, and lipids. Treatments can affect features either indirectly (by changing risk factors) or directly (by changing the feature itself). Treatments that have direct effects can modify the value of a feature (for example, performing bypass surgery can open an occluded coronary artery) or can change the rate of change of a feature (for example, reducing a person’s LDL cholesterol level will slow the rate of occlusion of a coronary artery).

A final role of features is that the signs, symptoms, and outcomes they cause can set in motion a wide variety of logistic events. These, in turn, involve other types of objects in the care process and system resource parts of the model.

To do all this, Archimedes uses hundreds of equations. Many, such as the execution of a protocol or the tallying of the costs of a logistic event, are mathematically straightforward. To model features, their interactions with other features, their responses to tests and treatments, and their role in causing clinical events, we use differential equations to describe the rates of changes of the variables as functions of other variables. Every time an event occurs to an object, we integrate the differential equations to find the time of the next event.

Differential equations are essential to this model for 2 reasons. First, they preserve the continuous nature of both time and biological variables. Second, cardiac output (along with arterial compliance, peripheral resistance, and pulse pressure) affects blood pressure, which affects the development of plaque, which can cause a myocardial infarction, which can damage the myocardium, which affects cardiac output. The parameters of the equations are different for every person in the model in a way that reproduces the variability of diseases in a population.

Elsewhere we describe specific methods for deriving equations for features and their interactions, using different types of data sets (7). These include a “general solution” that can be used to derive equations from a set of person-specific data, as well as other methods that can be used when the available data have already been aggregated or otherwise processed (for example, publication of the mean and variance of a distribution rather than all the patient-specific values).

## Comparison of the Archimedes Model with a Markov Model

The Archimedes model is very different from other types of models used in clinical medicine, such as Markov models or regression equations. For the type of question being addressed in this paper, the most common approach is a Markov model. Indeed, the prevention or postponement of diabetes in high-risk people has already been analyzed with a Markov model (6). Thus, it is useful to compare the 2 approaches.

**Appendix Table 1** compares the 2 types of models. In this table, we use the recently published model of diabetes prevention by Herman and colleagues (6) as an example of the Markov type

Appendix Table 1. Comparison of the Archimedes Model with a Markov Model\*

Attribute	CDC-RTI Model		Archimedes	
	Method	Examples	Method	Examples
	<p><i>Overview:</i> Represents diseases as discrete clinical “states.” Allows annual transitions between states. Treatments modify chances of transitions between states. Outcomes are associated with entry into states and time spent in states.</p>		<p><i>Overview:</i> Is built up from the underlying anatomy, biological variables, and pathways. Biological variables continuously change and interact. Diseases are defined in terms of biological variables. Treatments affect biological variables and pathways. Signs and symptoms are physical and sensory manifestations of biological variables. Outcomes are the culmination of biological variables.</p>	
Basic building blocks	Defines clinical states.	Represents uncomplicated diabetes as 3 states: prediabetes, early diabetes (after onset, but before clinical diagnosis), and diabetes progression (after clinical diagnosis).	Models the underlying physiology and pathology.	Represents diabetes as insulin resistance, with its consequences for glucose metabolism pathways: e.g., basal hepatic glucose production, uptake of glucose by fat and muscle, insulin amount, FPG level, insulin production, $\beta$ -cell fatigue, HbA <sub>1c</sub> level, and 2-h OGTT result.
Scope	Includes 14 states.	The other 11 states are angina, history of cardiac arrest/MI, microalbuminuria, clinical nephropathy, ESRD, peripheral neuropathy, history of lower-extremity amputation, photocoagulation, blindness, history of stroke, and death. Because people can have multiple complications, particular people can be defined by 433 possible combinations of these states.	Includes scores of biological variables relating to diabetes, coronary artery disease, congestive heart failure, stroke, hypertension, obesity, and asthma.	Examples of other biological variables pertinent to diabetes and its complications are lipids (LDL cholesterol, HDL cholesterol, total cholesterol), triglycerides, blood pressure (systolic and diastolic), cardiac output, arterial compliance, peripheral resistance, weight, height, BMI, plaque, stenosis, myocardial viability, retinopathy (complete ETDR scale), urine protein, creatinine, peripheral neuropathy, foot ulcers of varying degrees of severity, and amputations.
	Includes 4 biological variables.	The 4 biological variables are systolic blood pressure, total cholesterol, HDL cholesterol, and HbA <sub>1c</sub> .		
Time	Discontinuous. People can move from state to state once every year.	Each year a person with prediabetes has a chance of moving to early diabetes.	Continuous. Any event can occur at any time.	Clinical events can unfold over minutes and hours (e.g., myocardial damage following a myocardial infarction) or years (e.g., a healthy 35-year-old).
Progression of biological variables	HbA <sub>1c</sub> levels are assumed to increase over time at a fixed rate. Biological variables are simplified. Systolic blood pressure, total cholesterol, and HDL cholesterol values are stipulated at the start to be either “normal” or “above normal.” Every year a person with normal blood pressure or total cholesterol level can become above normal.	HbA <sub>1c</sub> is assumed to be 6.4% at onset of diabetes and is assumed to increase 0.07% per year for the next 10 years. For people age 25–34 y, normal systolic blood pressure is defined to be 118 mm Hg, and above-normal systolic blood pressure is defined to be 160 mm Hg. Every year, a person with normal systolic blood pressure (118 mm Hg) has a 5% chance of developing above-normal systolic blood pressure (160 mm Hg).	Biological variables progress continuously and smoothly over time, as determined by other variables and the presence of diseases.	At every moment, a person has a glucose level, a diastolic blood pressure, a systolic blood pressure, an HDL cholesterol level, and so forth. Glucose levels are determined by hepatic glucose production, uptake of glucose by fat and muscle, insulin levels, and insulin resistance. In people with type 2 diabetes, insulin resistance affects the liver’s production of glucose, lipids, and triglycerides.
Definitions of outcomes	Outcomes limited to states in the model, or attached directly to them. Definitions of outcomes must correspond to the definitions used in the sources from which transition probabilities are drawn.	Because the CDC model uses the UKPDS risk engine, it can calculate fatal and nonfatal MIs (the outcomes calculated by the UKPDS CHD risk engine), but not silent MIs, coronary insufficiency, angioplasties, or bypasses because they are not included in the UKPDS CHD risk engine.	Outcomes can be constructed from any underlying variables using any rules.	The Archimedes model can calculate end points defined as any desired combination of, for example, fatal MI, nonfatal MI, silent MI, coronary insufficiency, angioplasty, and/or bypass.

Appendix Table 1—Continued

Attribute	CDC-RTI Model		Archimedes	
	Method	Examples	Method	Examples
	<p><i>Overview:</i> Represents diseases as discrete clinical “states.” Allows annual transitions between states. Treatments modify chances of transitions between states. Outcomes are associated with entry into states and time spent in states.</p>		<p><i>Overview:</i> Is built up from the underlying anatomy, biological variables, and pathways. Biological variables continuously change and interact. Diseases are defined in terms of biological variables. Treatments affect biological variables and pathways. Signs and symptoms are physical and sensory manifestations of biological variables. Outcomes are the culmination of biological variables.</p>	
Progression of diseases	Each year, a person can move from one state to the next. The chance of doing so is determined by annual rates called transition probabilities.	On the basis of DPP results, each year a person with prediabetes has a 10.8% chance of moving to early diabetes. This probability is assumed to persist for 70 y.	Underlying causes of diseases are continuously progressing and affecting other variables.	In a person with prediabetes, insulin resistance gradually progresses, $\beta$ cells respond, $\beta$ cells fatigue, hepatic glucose production increases, glucose uptake by fat and muscle decreases, and plasma glucose levels increase. Diabetes is diagnosed when the FPG level is $>6.9375$ mmol/L ( $>125$ mg/dL) or OGTT result is $>11.0445$ mmol/L ( $>199$ mg/dL).
Effects of treatments	Treatments change transition probabilities.	Lifestyle modification decreases the transition probability of prediabetes to early diabetes from 10.8% to 4.82% (that is, by 55.3%).	Treatments act on the underlying biological variables.	Lifestyle modification reduces weight; decreases blood pressure; improves LDL, HDL, and total cholesterol levels; and lowers FPG levels. Metformin lowers FPG level and 2-h OGTT result (by decreasing hepatic glucose production), lowers LDL cholesterol and triglyceride levels, and retards weight gain.
Costs	Based on regression model.	Treatments enter cost function in a multiplicative fashion, based on regression equation of costs, with demographic characteristics, complications, and treatments (including oral antidiabetic agents and insulin) affecting costs.	Standard accounting model.	When a person begins receiving insulin, the cost of the insulin (with any associated visits or tests) is added to the other costs.
Logistics (procedures, visits, admissions, drugs, other interventions)	Not explicitly in model; implicitly affect overall costs in the regression equation.	Not in model.	Detailed logistics included in model.	39 different types of primary care office visits, 67 types of procedures, 57 types of admissions, 55 types of interventions, 50 different symptoms, and 68 different types of decisions physicians can make. For base case, treatment protocols based on Kaiser Permanente.
Validation	In theory, Markov models capable of sufficient clinical detail could be validated by comparing model results with real results of well-designed trials.	Formal validation not published.	Validated by simulating epidemiologic studies and clinical trials and comparing predicted with real results.	For example, the Archimedes model prospectively and independently predicted the results of the DPP trial. The rates of diabetes in the placebo, metformin, and lifestyle groups predicted by the model at 3 y were 27.4%, 21.9%, and 13.2%, respectively; the reported results were 28.9%, 21.7%, and 14.4%, respectively. See other sections of the Appendix for additional examples.

\* As described elsewhere in this Appendix, the Archimedes model is based on a set of differential equations, which are too complex to be described here. For more information about the model, a Technical Report can be obtained through [www.archimedesmodel.com](http://www.archimedesmodel.com). BMI = body mass index; CDC = Centers for Disease Control and Prevention; CHD = coronary heart disease; DPP = Diabetes Prevention Program; ESRD = end-stage renal disease; ETDR = Early Treatment of Diabetic Retinopathy; FPG = fasting plasma glucose; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; OGTT = oral glucose tolerance test; UKPDS = United Kingdom Prospective Diabetes Study.

of model. That model was built by the Centers for Disease Control and Prevention and RTI International and will be referred to as the “CDC-RTI model.” The most fundamental difference between the 2 models is how diseases are represented. As described in the previous section, Archimedes begins with the underlying anatomy and physiology. Biological variables such as insulin, insulin resistance, plasma glucose, HbA<sub>1c</sub>, and symptoms are calculated continuously. Diseases are then defined in terms of those underlying variables, as occurs in reality. For example, a person can be said to have diabetes if their FPG is tested and found to be greater than 6.9375 mmol/L (>125 mg/dL), or if their oral glucose tolerance is greater than 11.0445 mmol/L (>199 mg/dL). The progression of the disease is represented by the continuous progression of these and other biological variables that define diabetes and its complications, such as signs of retinopathy, development of stenosis in coronary and cerebral arteries, urine albumin and serum creatinine, and tests of neuropathy and ulcers. In contrast, the type of Markov model used in clinical medicine typically represents diseases as discrete clinical states such as “prediabetes” and “diabetes.” In those models, the progression of a disease is represented by people moving from one state to another (for example, from prediabetes to early diabetes) at fixed time intervals, usually annual.

The 2 approaches have strengths and weaknesses. A potential strength of Markov models is the ease with which their structures can be understood; the states are typically chosen to correspond to the way people talk about diseases. For example, it is common to say that a person “has prediabetes” or “has diabetes,” even though the underlying biological events are far more complex. The Markov structure is also convenient for tallying events that correspond to the states and the annual time interval, such as the annual incidence of diabetes or heart attacks in a population. However, with this simplicity come some limitations. One is that the discrete states and annual time intervals may be too superficial to capture all of the events of interest. For example, suppose the clinical question is the risk for a heart attack in people who have the “metabolic syndrome” as defined by the Adult Treatment Panel III (ATP III) versus the World Health Organization (WHO). The ATP III defines the metabolic syndrome as any 3 of the following: 1) waist >102 cm, 2) triglyceride level at least 1.695 mmol/L ( $\geq$ 150 mg/dL), 3) HDL cholesterol level less than 1.036 mmol/L (<40 mg/dL), 4) blood pressure at least 130/85 mm Hg, or 5) glucose level at least 116.105 mmol/L ( $\geq$ 110 mg/dL). The WHO defines the metabolic syndrome as impaired fasting glucose, impaired glucose tolerance, or insulin resistance and at least 2 of the following: 1) waist-hip ratio greater than 90, 2) triglyceride level at least 1.695 mmol/L ( $\geq$ 150 mg/dL) or HDL cholesterol level less than 0.9065 mmol/L (<35 mg/dL), 3) urinary albumin level greater than 20  $\mu$ g/min or albumin-creatinine ratio at least 30, or 4) blood pressure greater than 140/90 mm Hg. To analyze this question, a model needs to include all of these variables along with any additional variables pertinent to the metabolic syndrome (for example, insulin resistance and inflammation) and the development of heart attacks (for example, plaque and stenosis). Thus, this type of problem would not be suitable for a Markov model. The

Archimedes model is better suited to this type of problem because it includes these variables and their relationships. The drawback is that the model itself requires more advanced mathematics, and therefore is not as easy to understand.

Every model involves some simplifications. For example, while the Archimedes model includes the effects of insulin resistance on plasma glucose levels, it does not try to model the actual cellular mechanisms. The critical question is whether a model has the level of clinical detail or realism needed to accurately answer the question being asked.

### Comparison of Archimedes' Results with the Results of Herman and Colleagues

The results of our analysis of strategies for managing people at high risk for diabetes differ significantly from those of the recent analysis by Herman and colleagues (6), which showed a larger effect on benefits and savings and a lower cost/QALY. There are several possible explanations.

First, the way we formulated our analyses differed. Herman and colleagues primarily focused on the long-term (70-year) cost/QALY of the DPP lifestyle program and metformin compared with placebo from a societal perspective. Our analysis included those interventions but added another intervention—beginning a lifestyle modification program after a person is determined to have diabetes. Because this is a viable management option, with a cost/QALY that is lower than that of the DPP lifestyle program, it affects the marginal cost-effectiveness. Our analysis also included information pertinent to individuals and health plans as well as the societal perspective. We also used a shorter time horizons—5 to 30 years instead of 70 years. We chose a 30-year horizon because it stays within the existing evidence from clinical trials, because it has greater practical meaning for individuals and health plans, and because the longer the time horizon the lower the probability that assumptions made today will still hold in the future.

A second set of explanations involves the structures of the models. As shown in **Appendix Table 1**, the 2 models have entirely different structures. The structure of the Archimedes model enables it to operate at a considerably higher level of biological detail and clinical realism. This affects the abilities of the models to accurately represent the populations, interventions, and outcomes of interest in an analysis. These, in turn, have obvious effects on the estimated benefits and costs of an intervention.

A third set of reasons arises from the fact that the CDC-RTI model includes several assumptions that differ significantly from the way we modeled the disease and its costs. They relate to both the natural history of the disease, which determines the clinical outcomes and QALYs, and the calculation of costs, which is the other half of the cost-quality ratio. **Appendix Table 2** summarizes the differences. Information about the Markov model was obtained from the publication (6) and from the technical report that accompanied that paper (38).

It is not possible to determine the net effects of the structure and assumptions used in the CDC-RTI model about the costs, QALYs, or cost/QALY they calculated. Sensitivity analysis does

**Appendix Table 2. Additional Differences in Assumptions Made in the Model Used by Herman and Colleagues (6) (the CDC-RTI Model) and the Archimedes Model**

Model Assumptions	CDC-RTI Model	Archimedes Model
Progression of the disease	The 3 states used to represent diabetes have very different mechanisms of progression. Prediabetes: assumes a fixed 10.8% annual probability of moving from prediabetes to early diabetes (6, p. 324). Early diabetes: assumes that everyone will progress to clinical diabetes in exactly 10 y (6, p. 325). Diabetes progression (clinical diabetes): assumes that everyone's HbA <sub>1c</sub> level will increase 0.2% per year (technical report [38], p. 37).	Does not define discrete states or stages; rather, represents the progression of a disease in terms of the underlying biological variables. For type 2 diabetes, the underlying cause is assumed to be insulin resistance, and the values of other biological variables are calculated continuously as functions of insulin resistance and each other. Rates of progression of each variable differ for each person depending on a variety of biological and behavioral factors, including random or unknown factors. The ranges of progression of the variables and the correlations between variables match the ranges in real populations, as illustrated in Appendix Table 3 and Appendix Figures 3 and 4.
Interdependencies between complications of diabetes	With 1 exception, assumes that the progressions of each complication (retinopathy, neuropathy, nephropathy, and cardiovascular disease) are independent of each other. For example, the presence of severe nephropathy is assumed to be unrelated to the risk for any other complication. The exception is that everyone with microalbuminuria is assumed to have hypertension, which is a risk factor for cardiovascular disease and strokes (38, section 1 and p. 76).	All complications stem from the underlying insulin resistance and its effects. The occurrence and progression of any one complication are correlated to the occurrence and progression of other variables through insulin resistance. Other variables, such as hypertension, are affected by insulin resistance and affect several complications.
Occurrence of retinopathy	Assumes that retinopathy cannot occur until a person has developed clinical (symptomatic) diabetes (prevalence at time of clinical diabetes is assumed to be 0) (38, p. 9). Note: In 9 studies, the prevalence of retinopathy at time of clinical diagnosis has ranged from 7% to 29% (48).	Retinopathy can occur and progress continuously in people with preclinical diabetes. Prevalence and progression of retinopathy at clinical diagnosis match the rates seen in real populations and trials, such as the UKPDS.
Progression of HbA <sub>1c</sub>	In their published paper (6), the authors say they assumed that HbA <sub>1c</sub> levels increased at the rate of 0.07% per year in every person (p. 325). Note: This rate does not match what occurred in the UKPDS (18), where the annual increase in HbA <sub>1c</sub> level with conventional treatment was about 0.14% per year over 10 y and 0.11% over 15 y.	HbA <sub>1c</sub> (and FPG) levels change continuously, with different rates of increase in different people; changes depend on a variety of other factors and treatments. The average rates of increase match the rates seen in the DPP study and UKPDS.
Progression of FPG	The assumption that people progress from onset to clinical diabetes in 10 y implies a rate of increase in FPG level at least 3 times higher than seen in real populations. The average FPG level at onset of diabetes in the DPP study was <6.9375 mmol/L (<125 mg/dL). The average FPG level of "newly diagnosed" patients in the UKPDS was >11.1 mmol/L (>200 mg/dL) (32). Thus, during "early diabetes," FPG level increases more than 4.1625 mmol/L (75 mg/dL) (11.1 – 6.9375 = 4.1625 mmol/L [200 – 125 = 75 mg/dL]), on average. The assumption of a fixed 10-y transit time from onset to clinical diabetes implies that FPG level must increase at a rate of at least 0.41625 mmol/L (7.5 mg/dL) per year. In fact, in the DPP, FPG level increased at a rate of <0.111 mmol/L (<2 mg/dL) per year (4), and in the UKPDS, it increased <0.1665 mmol/L (<3 mg/dL) per year (10, 32).	The rate of progression is determined by the progression of insulin resistance. FPG progresses at the rates seen in the DPP study and UKPDS (Appendix Figures 3 and 4).
HbA <sub>1c</sub> level at the time of clinical diagnosis	Assumes that HbA <sub>1c</sub> level is 7.1% at time of clinical diabetes (6, p. 325). Note: In the UKPDS, HbA <sub>1c</sub> level in "newly diagnosed" patients was 9.1% (46). The HbA <sub>1c</sub> level of 7.1% was reached only after an initial dietary treatment initiated after diagnosis.	Average HbA <sub>1c</sub> level of "newly diagnosed" people is 9.1%, and a dietary treatment given after diagnosis decreases the HbA <sub>1c</sub> level to about 7.1%.

*Continued on following page*

Appendix Table 2—Continued

Model Assumptions	CDC-RTI Model	Archimedes Model
Cumulative damage of diabetes	<p>Assumes that the annual risk for progressing to greater severity of a complication does not depend on how long one has had the complication. For example:</p> <p>The annual risk for developing clinical nephropathy does not depend on how long a person has had microalbuminuria or its severity (38, pp. 10–14).</p> <p>The annual risk for developing ESRD does not depend on how long a person has had clinical nephropathy or its severity (38, pp. 10–14).</p> <p>The annual risk for developing a foot ulcer does not depend on how long a person has had neuropathy or its severity, or whether a person is prone to develop ulcers as demonstrated by a previous ulcer (38, p. 13).</p> <p>The annual risk for needing photocoagulation does not depend on how long a person has had retinopathy or on its severity (38, pp. 10–14).</p> <p>The annual risk for going blind does not depend on how long ago a person needed photocoagulation (38, pp. 10–14).</p>	<p>The chance of developing a particular complication depends on the severity of the disease and the cumulative damage. For example, the chance of developing proliferative retinopathy with soft exudates depends on the degree of retinopathy as measured by the ETDR scale.</p>
	<p>Uses the UKPDS risk engine to calculate the effects of treatments (38, p. 15). Note: This assumes that the risk for an MI, for example, in a person whose glucose, blood pressure, total cholesterol, or HDL cholesterol value was changed (e.g., from HbA<sub>1c</sub> level of 9% to HbA<sub>1c</sub> level of 7%) will be the same as the risk in a person whose untreated value was at that level (e.g., HbA<sub>1c</sub> level always 7%). This assumes no cumulative organ damage, such as the build-up of plaque or microvascular damage.</p>	<p>Calculates instantaneous rates of development of variables such as plaque. Reducing systolic blood pressure will slow the rate of development of new plaque but will not eradicate existing plaque. Stenosis can be reduced only by procedures such as bypass, percutaneous transluminal coronary angioplasty, and stenting.</p>
Treatment of diabetes	<p>No treatment was given during early diabetes. During clinical diagnosis, people received intensive dietary and drug treatment, which lowered their HbA<sub>1c</sub> level to 6%. This value was used to calculate the risk for MI thereafter.</p>	<p>People were given intensive dietary and drug treatment when their HbA<sub>1c</sub> levels exceeded 7%. Thereafter, their HbA<sub>1c</sub> levels increased gradually at rates seen in the UKPDS.</p>
Effect of cholesterol on stroke	<p>Assumes that cholesterol levels do not affect the risk for stroke (38, p. 44).</p>	<p>Cholesterol levels (and cholesterol-lowering drugs) affect the development of plaque in carotid and cerebral arteries and therefore the risk for strokes.</p>
Angina and MI	<p>Someone who has recovered from an MI cannot later develop angina (38, p. 9).</p>	<p>People can develop angina before the occurrence of an MI or afterward, depending on the progression and location of stenosis and the occurrence of sudden heart attacks.</p>
Effect of lifestyle modification	<p>Assumes lifestyle modification reduces the chance of moving from the state “prediabetes/DPP” to the state “early diabetes” by 55.3% every year, forever (p. 324). Note: In the DPP trial, the percentage reduction slowly declined over the duration of the trial (incidence decreased 55.3% after the average follow-up of 3 y). It was 68% after 1 y, 63% after 2 y, 50% after 3 y, and 44% after 4 y (2). The relative effect would probably have continued to decline after longer follow-up.</p>	<p>Calculates the progression of FPG level and OGTT result, which, in turn, define when diabetes develops. It calculates this from the effects of lifestyle (e.g., diet and exercise) on glucose metabolism and other variables. The calculation independently predicted the gradual decline in the effect of lifestyle on incidence of diabetes seen in the DPP study, as shown in Appendix Figure 2.</p>
Costs	<p>Costs are assumed to be multiplicative (6, p. 325). This has several counterintuitive implications. For example:</p> <p>In the CDC-RTI model, all drug treatment protocols are assumed to increase a person’s cost by 10% from whatever the costs were without drug treatment.</p> <p>If a person is switched from drugs to insulin, their costs are increased by 41% of whatever their total costs were before the switch was made.</p>	<p>Costs are additive.</p> <p>Includes detailed step-wise treatment protocols. The costs depend on which drugs are needed, at what doses and in which combinations, and their prices, along with any necessary tests and visits.</p> <p>If a person is switched from drugs to insulin, the cost of the drug protocol is subtracted and the cost of the insulin protocol is added. All downstream effects of the changes in treatments are tracked and tabulated as they occur.</p>
Source of assumptions about costs	<p>Baseline costs (before treatment or complications) were calculated from a population with a mean age of 66 y and a mean duration of diabetes of 8 y and were assumed to apply to people with “early diabetes” (reference 25 in Herman et al. [6])</p>	<p>Calculates costs for each person on the basis of the cost-generating events that occur to them (e.g., tests, visits, treatments). These, in turn, vary with the severity of their disease and with the progression of the disease.</p>
Cost of retinopathy and neuropathy	<p>Assumes retinopathy and neuropathy do not affect costs (Table 2 in Herman et al. [6]).</p>	<p>These complications and their management do affect costs.</p>

\* DPP = Diabetes Prevention Program; ESRD = end-stage renal disease; ETDR = Early Treatment of Diabetic Retinopathy; FPG = fasting plasma glucose; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HDL = high-density lipoprotein; MI = myocardial infarction; OGTT = oral glucose tolerance test; UKPDS = United Kingdom Prospective Diabetes Study.

not address these issues well because this technique for exploring uncertainty uses the very model about which we have the uncertainty. More specifically, there are 2 main types of uncertainty about any model. One is its structure—the equations it uses. The other is the accuracy of the values that are assigned to the variables in the equations. Sensitivity analysis explores uncertainty about the latter, but only within the context of the former. Far from exploring uncertainty about the structure, traditional sensitivity analysis assumes that the structure is correct.

The limitations of traditional sensitivity analysis are best appreciated with an example. Suppose the problem is to estimate the time required to get across town in New York City by car, and we set up the model “distance = rate  $\times$  time”, or “time = distance/rate.” For the base-case analysis, we might look up the distance, about 2 miles, and assume a speed of, say, 20 miles per hour (mph). We could use sensitivity analysis to explore uncertainty about the speed, by varying the 20 mph up and down 5 mph (from 15 to 25 mph). Indeed, we could vary both the speed and the distance and do a multiway sensitivity analysis. However, these will never tell us about the equation itself. While it is correct in general that distance does equal rate multiplied by time (that is, that the equation has “face validity”), a real cross-town trip will involve dozens of stop lights, 1-way streets, congestion, double-parked delivery trucks, schools letting out, open manholes, possible detours, and pedestrian traffic, not to mention time of day, day of week, weather, and so forth. A sensitivity analysis that just varies the speed of the car within the  $T = D/R$  equation will never discover the effects of these; they require a much more detailed and accurate representation of the problem itself. The only way to discover this is to vary the structure of the model itself. Since by far the largest assumptions in a Markov model involve simplifying the disease into a small number of discrete states and simplifying time into annual intervals, a complete sensitivity analysis would require rewriting these. It is pertinent that the sensitivity analysis described in Table 5 of Herman and colleagues’ paper addresses only 1 of the dozens of simplifications listed in our **Appendix Table 2** (the assumption that lifestyle reduces the transition from “prediabetes/DPP” to “early diabetes” by 55.3%).

Ideally, questions about the structure of a model and its assumptions would be tested by simulating real clinical experiences such as clinical trials. Ideally, these comparisons would be independent of any sources used to estimate the model’s parameters and would span the natural history of the disease and its complications. This has not been done for the CDC-RTI model. The only available information on this issue comes from a 2004 conference in Basel, Switzerland. Researchers who were from the same group as Herman and colleagues and who cited the same technical report (39) used a model to retrospectively simulate the Collaborative Atorvastatin Diabetes Study (CARDS) (40). The model overestimated the rate of fatal and nonfatal myocardial infarctions by a factor of about 50% (41). A bias in this direction would overestimate the clinical benefits and the cost-savings of preventing diabetes by lifestyle and would underestimate the cost/QALY. Another result of that exercise is that the CDC-RTI model predicted a greater 20-year rate of fatal MIs than total MIs; that is,

more people die of MIs than get them in the first place. The results of a blinded prospective prediction by the Archimedes model were considerably more accurate, as discussed later.

### **Validation of the Archimedes Diabetes Model for the Analysis of Diabetes Prevention**

A previously published paper (9) describes the validation of the Archimedes diabetes model. This section summarizes aspects of the validations that are particularly pertinent to the analysis of diabetes prevention. First, we present the values of parameters calculated in the model and compare them with values observed in epidemiologic studies and clinical trials. Then we describe methods for validating the model by simulating clinical trials. We illustrate the methods with a particular example—a simulation of CARDS. Finally, we present the results of simulations of other clinical trials that address the prevention of diabetes and the progression of the disease after it occurs.

#### **Comparison of Parameter Values**

Because the model includes scores of biological variables that interact continuously, it is not possible to describe the Archimedes model in terms of simplified “states,” transitions, or events at discrete time intervals, as is often done for Markov-type models. However, the behavior of the model can be checked by examining the annualized rates of change of the main biological variables and the annualized rates of occurrence of the main clinical events, as calculated by the model. These in turn can be compared with rates for comparable events observed in epidemiologic studies and clinical trials (**Appendix Table 3**). Because the rates in the model were calculated by the model and not simply inputted from the referenced trials, the values observed in the trials confirm or validate the model. For example, the annualized progression from “prediabetes” to diabetes with no intervention (0.101) was calculated in the model by using 11 equations. The annualized rate observed in the DPP for this group (0.107) was not used to derive or fit any of those equations, and thus independently validates that part of the model. Other variables in **Appendix Table 3** validate other parts of the model. Both observed and calculated rates are affected by sampling variability. We say that there is a “statistical match” if there is no statistically significant difference between the calculated and observed values.

#### **Methods for Validating the Archimedes Model by Simulating Clinical Trials**

This section walks through an example of a validation. The steps are as follows: For each validation exercise we create a “virtual trial” by repeating the steps taken in the real trial, and then compare the outcomes seen in the virtual trial with those that occurred in the real trial. To set up the validation exercises, we first have the model create a large virtual population that contains a broad spectrum of ages, sexes, races/ethnicities, characteristics, behaviors, and diseases. This is done by having the model give birth to a large number of people of different sexes and races/ethnicities and letting them grow up (that is, letting their physiologies function according to the equations in the model). We used information from the National Health and Nutrition Ex-

**Appendix Table 3. Values of Representative Variables Calculated by the Model, and Comparisons with Published Sources: Annual Rates and Costs\***

Variable and Treatment	Calculated by Model	Confirmation/Validation		
		Trial (Reference)	Value in Reference Trial	Statistical Match
<b>Incidence of diabetes (example of Hispanic men)</b>	0.00795	Diabetes in America (48)	0.00787	Yes
<b>Progression of prediabetes to diabetes</b>				
None	0.101	DPP (2)	0.107	Yes
Metformin	0.079	DPP (2)	0.078	Yes
Lifestyle	0.046	DPP (2)	0.05	Yes
<b>Progression of diabetes (rate of increase in FPG level): conventional treatment</b>	See Appendix Figure 2	UKPDS (18)	See Appendix Figure 2	Yes
<b>Rate of MI in people with newly diagnosed diabetes</b>				
Conventional	0.018	UKPDS (18)	0.017	Yes
Intensive	0.0138	UKPDS (18)	0.014	Yes
<b>Rate of MI in people with diabetes and high risk for coronary artery disease</b>				
Placebo	0.034	Micro-HOPE (23)	0.0340	Yes
Ramipril	0.0235	Micro-HOPE (23)	0.0265	Yes
<b>Rate of development of albuminuria in people with newly diagnosed diabetes</b>				
Conventional	0.0338	UKPDS (18)	0.0341	Yes
Intensive	0.0198	UKPDS (18)	0.0215	Yes
<b>Rate of development of proteinuria in people with newly diagnosed diabetes</b>				
Conventional	0.0086	UKPDS (18)	0.0090	Yes
Intensive	0.0065	UKPDS (18)	0.0068	Yes
<b>Rate of development of ESRD in people with diabetes and microalbuminuria</b>				
Placebo	0.101	IRMA (20)	0.0860	Yes
Irbesartan, 150 mg	0.054	IRMA (20)	0.0510	Yes
Irbesartan, 300 mg	0.0297	IRMA (20)	0.0250	Yes
<b>Rate of development of ESRD in people with newly diagnosed diabetes</b>				
Conventional	0.00081	UKPDS (18)	0.0008	Yes
Intensive	0.0001	UKPDS (18)	0.0006	Yes
<b>Rate of development of 2-step retinopathy in people with newly diagnosed diabetes</b>				
Conventional	0.056	UKPDS (18)	0.0545	Yes
Intensive	0.04	UKPDS (18)	0.0400	Yes
<b>Rate of development of legal blindness in people with newly diagnosed diabetes</b>				
Conventional	0.00486	UKPDS (18)	0.0035	Yes
Intensive	0.00336	UKPDS (18)	0.0029	Yes
<b>Rate of amputations in people with newly diagnosed diabetes</b>				
Conventional	0.0004	UKPDS (18)	0.0016	Yes
Intensive	0.000134	UKPDS (18)	0.001	Yes
<b>Costs</b>				
Excess direct medical cost for people with diabetes (annual), \$	4241	Kaiser Permanente	\$4683	Yes
Direct medical cost for people with prediabetes (annual), \$	1552	DPP (5)	\$1670	Yes

\* DPP = Diabetes Prevention Program; ESRD = end-stage renal disease; FPG = fasting plasma glucose; HOPE = Heart Outcomes Prevention Evaluation Study; IRMA = Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria; MI = myocardial infarction; UKPDS = United Kingdom Prospective Diabetes Study.

amination Survey on the marginal and joint distributions of patient characteristics and other risk factors to ensure that the model accurately represents the correlations between variables, and that the resulting population is representative of the U.S. population (42). Other populations could be constructed if desired (for example, a Native American reservation).

To simulate a particular clinical trial, we begin with the initial description of the trial, focusing in particular on the inclusion and exclusion criteria, the treatment protocols, and the follow-up protocols. We then have the model do the following: 1) Search the large population to identify people who meet the entry criteria for the trial. Confirm that their characteristics (for example, age, sex, other conditions, treatments, laboratory results) match the distribution of characteristics published in the description of the trial. If not, oversample or undersample as required, as would occur for a real trial. From that group, randomly select people to match the number of people in the trial. At the end of this selection process, the distribution of characteristics, biological variables, current and past medical histories, medications, and behaviors (the information often reported in "Table 1" in reports of clinical trials) of the people in the virtual trial should look like "Table 1" of the real trial, within sampling error. 2) If the description of the trial calls for any interventions, such as a diet, to be given before the people are randomly assigned, then have simulated providers give that intervention. 3) Randomly assign the people into the number of groups used in the trial. 4) Have simulated providers give the people in each group the designated treatments, using the protocols described for the trial. Include any important breaches in either provider or patient adherence that are described for the trial. 5) Let the people's physiologies continue to function, including the effects of whatever treatments they are receiving. 6) Follow each patient with simulated appointments and tests at the intervals used in the real trial. 7) In the model, as in the real trial, let patients do the following between scheduled visits: Develop symptoms, seek care, make appointments, have visits, be tested, be diagnosed, and be treated. 8) Record the results at the time intervals used in the real trials. 9) Process the results and compare them with the results described for the real trial.

### **An Example: CARDS**

The methods just described can be illustrated with a blinded, prospective prediction of CARDS, which compared atorvastatin, 10 mg, with placebo in people with diabetes and other risk factors for coronary artery disease (40). The primary end points were major cardiovascular events.

To conduct this simulation, we used preliminary descriptions of the trial's design published by Colhoun and colleagues (40) and the description of the baseline characteristics in an unpublished manuscript by Thomason and colleagues (Thomason MJ, Colhoun HM, Livingston SJ, Mackness MI, Betteridge DJ, Durrington PN, et al. Baseline characteristics in the Collaborative Atorvastatin Diabetes Study [CARDS] in patients with type 2 diabetes. Unpublished manuscript. March 2004).

Because this was a prospective prediction, at the time we

conducted the simulation there was no information in these papers or any other sources about any biological outcomes (for example, cholesterol levels) or clinical outcomes in the 2 treatment groups. We then used Archimedes to simulate the trial, as follows:

1. We had the Archimedes model "give birth" to many simulated people. The model does not create a person by simply specifying an age, sex, race/ethnicity, glucose level, and so forth, and insert him or her into the simulation, as might be done in the Framingham equation, UKPDS Risk Engine, or a Markov model. Rather, Archimedes grows each individual up from age = 0. The simulated babies span a wide distribution not only by sex and race/ethnicity but by all the other variables that determine people's fates as they grow up, for example, behaviors such as smoking and genetic propensities to be obese or develop plaque in coronary arteries. As each of these simulated individuals is growing up, their hearts are producing cardiac output, their livers are producing glucose, their  $\beta$  cells are producing insulin, and so forth. This goes on starting at age 0 and continuing over their entire lifetimes. Furthermore, these individuals are living their lives out in a simulated health care setting, where simulated physicians respond to their symptoms, do simulated tests, give simulated treatments, comply or fail to comply with guidelines, and so forth. For example, one of the simulated people might develop type 1 diabetes at 10 years of age, have complications, and end up dying, at age 54 years, of renal failure. Another one might smoke, not take aspirin, develop angina at age 45 years, have a bypass to the left anterior descending artery, have a hemorrhagic stroke at age 56 years, have a second myocardial infarction (in the circumflex artery this time) at age 58 years, develop congestive heart failure at age 65 years, live for another 7 years, and then die. Eventually, some of the simulated people get to the age range at which they might be considered for inclusion in a trial such as CARDS.

2. We then had Archimedes search that group to identify approximately 4000 people who met the general inclusion criteria for the trial. Those criteria are as follows: 1) type 2 diabetes by the World Health Organization definition; 2) age 40 to 75 years; 3) at least one of the following: systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg, microalbuminuria, macroalbuminuria, and current smoker; 4) LDL cholesterol level less than 8.88 mmol/L (<160 mg/dL) and triglyceride level less than 6.78 mmol/L (<600 mg/dL); 5) no history of myocardial infarction, angina, cardiovascular surgery, cerebrovascular accident, or severe peripheral vascular disease; and 6) none of the listed exclusions.

3. We then compared the characteristics of the simulated people selected in the previous step (the "simulated participants") with the participants of the real CARDS. **Appendix Table 4** shows the results. The correspondence is good, with the possible exception of nephropathy.

4. We had simulated providers give a placebo to a "control group" and give atorvastatin, 10 mg, to a "treatment group."

5. The equations of the model then calculated the progression of biological variables that determine the fates of the simulated participants, including the possibility of having a myocar-

**Appendix Table 4. Comparison of Baseline Characteristics in Actual and Simulated Collaborative Atorvastatin Diabetes Study (CARDS)\***

Characteristic	Actual Trial	Simulated Trial
Age, y	62.8	62.1
Men, %	68	58
Duration of diabetes, y	6	7.3
Body mass index, kg/m <sup>2</sup>	28.7	28.6
Hemoglobin A <sub>1c</sub> level, %	7.7	7.7†
Fasting plasma glucose level, mmol/L (mg/dL)	9.2685 (167)	9.0465 (163)
Retinopathy, %	30‡	15§
Microalbuminuria or macroalbuminuria, %	11	10¶
Current smoker, %	23**	23
Systolic blood pressure, mm Hg	143	139
Diastolic blood pressure, mm Hg	83	80
ACE inhibitors, %	44	53
β-Blockers, %	16	19
Diuretics, %	19	15
Aspirin, %	15	15
Total cholesterol level, mmol/L (mg/dL)	5.3613 (207)	5.4131 (209)
LDL cholesterol level, mmol/L (mg/dL)	3.0562 (118)	3.2116 (124)
HDL cholesterol level, mmol/L (mg/dL)	1.352 (52.2)	1.3727 (53)
Triglyceride level, mmol/L (mg/dL)	1.695 (150)	1.7289 (153)

\* ACE = angiotensin-converting enzyme; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† During treatment.

‡ Nonproliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye.

§ Retinopathy score > 21 on Early Treatment of Diabetic Retinopathy scale.

|| Albumin-creatinine ratio ≥ 2.5 mg/mmol or albumin excretion ≥ 25 μg/min.

¶ Albumin excretion ≥ 34 μg/min.

\*\* 43% of study participants are former smokers.

dial infarction. Appendix Table 5 shows the particular equations used to calculate the occurrences of a myocardial infarction.

6. We had the simulated participants followed for 5 years in simulated time, with follow-up examinations every 6 months.

7. At the checkpoints, conducted every 6 months, each simulated participant was evaluated for the primary outcomes of the trial, the main one of which was major coronary events: sudden cardiac deaths (defined as a death that occurs within 1 day of the onset of myocardial infarction), nonsudden cardiac deaths (a death occurring more than 1 day after a myocardial infarction), and nonfatal myocardial infarctions, including silent myocardial infarctions.

8. We put our predictions in a signed, sealed, dated envelope and mailed it to the principal investigators and sponsors of the trial on 26 March 2004.

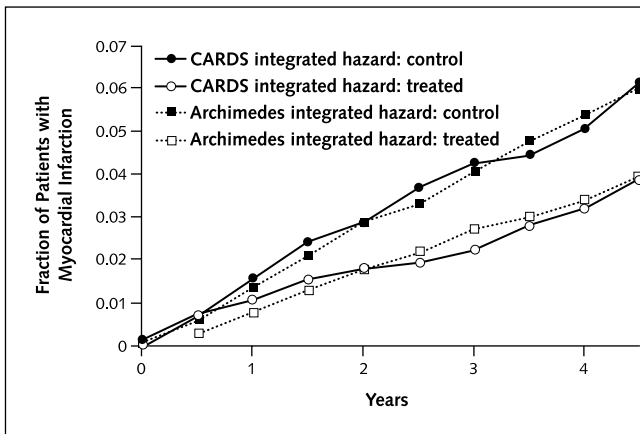
9. The real results were announced on 8 June 2004.

Appendix Figure 1 shows the results we predicted and the real results. The accuracy of the prediction for the control group confirms such things as the model's representation of the anatomy and physiology of coronary artery disease (for example, anatomy of coronary arteries and progression of plaque), and the effects of such factors as patient characteristics (for example, age, sex, race/ethnicity), medical history, current conditions, duration and severity of disease, comorbid conditions, and current medications (that is, the variables in Appendix Table 4). The model's accuracy for the treated group confirms the model's representation of the biological effects of atorvastatin, 10 mg, on cholesterol and the extra-cholesterol (pleiotropic) effects of atorvastatin on development of plaque in coronary arteries. Because the simulation began with the birth of the simulated participants, the re-

**Appendix Table 5. Description of Equations Used To Calculate Myocardial Infarctions in Collaborative Atorvastatin Diabetes Study**

This Variable . . .	. . . Is a Function of These Variables
Myocardial infarction	Stenosis/plaque
Stenosis	Sex, insulin resistance, glucose, blood pressure, lipids, tobacco, inflammation, genetics, fate, medications, interventions, and time (age)
Insulin resistance (type 2 diabetes)	Genetics (e.g., family history), race/ethnicity, sex, obesity, diet, exercise, fate, and time
Glucose	Basal hepatic glucose production, insulin, efficiency of insulin use by liver fat and muscle
Basal hepatic glucose production	Age, sex, diet and exercise, medications
Efficiency of insulin use by liver fat and muscle	Insulin resistance, diet and exercise, medications
Lipids	Hepatic production of lipids, efficiency of lipid removal
Hepatic production of lipids	Age, sex, race/ethnicity, diet, exercise, medications
Efficiency of lipid removal	Insulin resistance
Blood pressure	Cardiac output, arterial compliance, peripheral resistance, pulse pressure, diet and exercise, medications, time
Cardiac output	Age, myocardial infarction/heart damage, congestive heart failure, medications
Myocardial infarction/heart damage	Location of stenosis (which artery, how far distal the location), time following occlusion, medications, procedures
Arterial compliance	Age, sex, race/ethnicity, diet, exercise, medications
Peripheral resistance	Age, sex, race/ethnicity, diet, exercise, medications
Insulin	Type 1 diabetes, β-cell function, insulin resistance, medications
Type 1 diabetes	Genetics (e.g., family history), race/ethnicity, sex, fate, time
Weight	Age, race/ethnicity, sex, diet and exercise
Diet and exercise	Willpower
Age	Plastic surgery

Appendix Figure 1. Model's predictions of myocardial infarctions in Collaborative Atorvastatin Diabetes Study (CARDS).



sults also test the long-term stability and realism of the physiology equations.

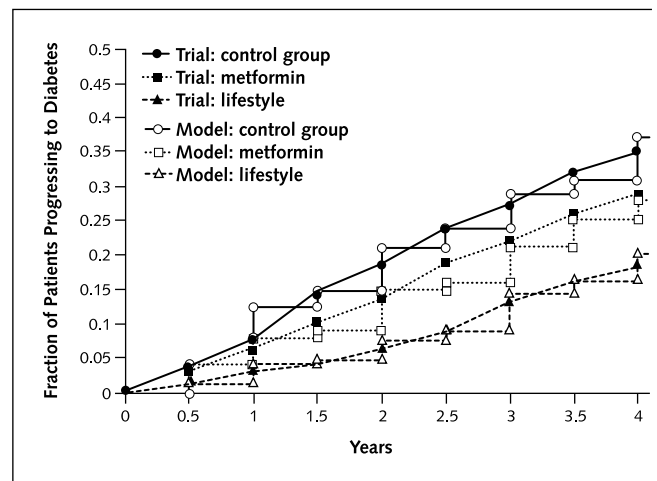
### Results of Other Simulations of Epidemiologic Studies and Clinical Trials

As described elsewhere (9), the Archimedes diabetes model has been subjected to many other validation exercises that involve simulating real clinical trials at a high level of detail and comparing the model's results with the results actually observed in the trials. Thus far, the model has been validated against 20 clinical trials (2, 12, 18–33, 43). The trials were chosen by an independent committee convened by the American Diabetes Association to span the natural history of the disease, its complications, and its treatments.

Of these, 2 trials are particularly important for analyzing the value of interventions to prevent diabetes. One is the DPP study, in which people who were at high risk for diabetes but did not yet have the disease as it is currently defined were given lifestyle modification, metformin, or placebo. For obvious reasons, it is important that the model be able to predict the results of that trial. In our case, we used the Archimedes model to perform a prospective, independent, blinded prediction of the DPP study's results. On the basis of initial descriptions of the DPP study (39, 44), but before publication of the trial's results, we used the Archimedes model to simulate the trial and predict its results. The rates of diabetes in the placebo, metformin, and lifestyle groups predicted by the model at 3 years were 27.4%, 21.9%, and 13.2%; the reported results were 28.9%, 21.7%, and 14.4%, respectively (2). Appendix Figure 2 illustrates these findings.

Another critical aspect of this analysis is the rate of progression of the disease in people with prediabetes or diabetes. Disease progression in the model was validated by comparing the rates of increase of fasting plasma glucose level calculated by the model with those observed in the control groups of the DPP study (2) and the UKPDS (18, 45). In the DPP study, the average fasting plasma glucose level was approximately 5.9385 mmol/L (107 mg/dL) at the start of the trial and increased to approximately 6.327 mmol/L (114 mg/dL) after 4 years (2). The fasting plasma

Appendix Figure 2. Model's predictions of outcomes in Diabetes Prevention Program (DPP) trial.

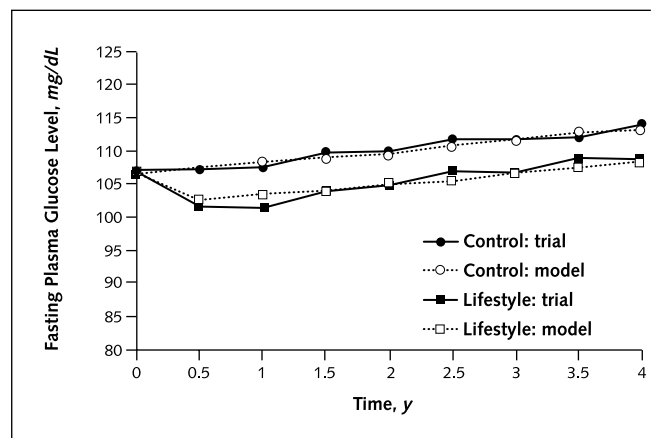


Comparison of proportions of people progressing to diabetes in the control group (circles), metformin group (squares), and lifestyle group (triangles) observed in the real DPP (black symbols) and in the simulation of the DPP by the Archimedes model (white symbols).

glucose levels calculated by the model were 5.91075 mmol/L (106.5 mg/dL) and 6.2882 mmol/L (113.3 mg/dL), respectively.

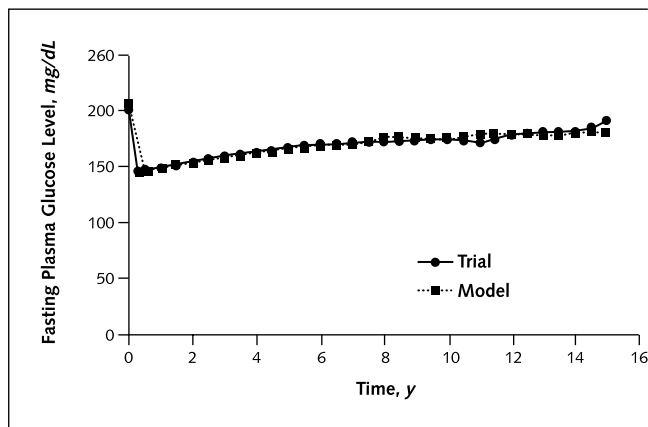
Appendix Figure 3 illustrates these findings. For the UKPDS, the average fasting plasma glucose levels were 11.1555 mmol/L (201 mg/dL) at presentation, 8.103 mmol/L (146 mg/dL) after an initial diet, and 10.101 mmol/L (182 mg/dL) at 14 years (18, 46). The numbers calculated by the model were 11.433 mmol/L (206 mg/dL), 8.1585 mmol/L (147 mg/dL), and 10.0455 mmol/L (181 mg/dL), respectively. Appendix Figure 4 illustrates these findings. The model also indicates that the rates of increase in fasting plasma glucose level are constant across the entire range of fasting plasma glucose levels (that is, no sharp accelerations or decelerations occur). An analysis of UKPDS data for 3 strata of fasting plasma glucose levels at presentation ranging from less

Appendix Figure 3. Model's predictions of progression of fasting plasma glucose levels in the Diabetes Prevention Program trial.



To convert fasting plasma glucose values to mmol/L, multiply by 0.05551.

*Appendix Figure 4.* Comparison of model's calculations and results of the United Kingdom Prospective Diabetes Study: progression of fasting plasma glucose levels in control group.

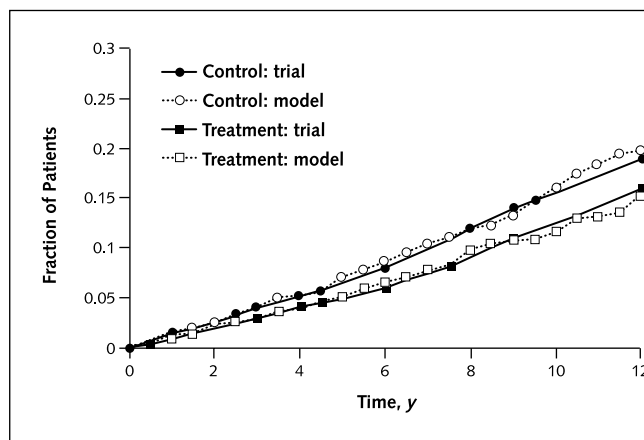


To convert fasting plasma glucose values to mmol/L, multiply by 0.05551.

than 6.993 mmol/L (<126 mg/dL) to greater than 13.32 mmol/L (>240 mg/dL) confirms this finding (47).

**Appendix Figure 5** shows an example of the model's accuracy in calculating long-term outcomes. This figure compares the rate of myocardial infarctions calculated by the model for people with newly diagnosed diabetes versus the rates seen in the UK-PDS. In that trial, all patients were put on a diet that decreased their fasting plasma glucose levels before they were randomly assigned to the 2 treatment groups. Many more examples of validations involving the complications of diabetes and long-term outcomes have been published (9).

*Appendix Figure 5.* Comparison of model's calculations and results of the United Kingdom Prospective Diabetes Study: rates of myocardial infarction in control and treated groups.



We consider these validations to be a distinguishing feature of the Archimedes model. Taken together, they span from people who do not yet have any disease through to the occurrence of late complications, a span of several decades. The validations also span a variety of populations, organ systems, interventions, and outcomes. Most of the validations are independent in the sense that the outcomes being predicted by the model were not used to help build the model. This not only tests the model's accuracy but also protects against overfitting of the model; there can be no overfitting if no fitting occurred in the first place. Taken together, we believe that these validations build confidence, but do not guarantee, that the results of this analysis of the management of people at high risk for diabetes are accurate.



