Cure, Care, and Commitment: What Can We Look Forward To?

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The prevalence of diabetes continues to increase at an alarming rate, with more than 9% of all adults and 20% of adults ≥60 years of age diagnosed with the disease (1). When those with impaired fasting glucose are added, about a third of the adult U.S. population has abnormal glucose metabolism. Equally alarming is that the cost of diabetes in 2007 was $175 billion, which includes $116 billion in excess medical expenditures and $58 billion in reduced national productivity (2). Thus, diabetes is a major, costly, and growing cause of morbidity and mortality in America. What should we be doing about this serious situation?

There are three obvious answers. First, we must redouble our efforts to find a cure for diabetes. This will take more research dollars invested into novel and imaginative ideas that explore the underlying cause of diabetes. Second, we must do whatever we can to reduce the likelihood that someone will develop diabetes. Although 100% effective prevention is not immediately in reach, there are many recent developments that hold great promise. Third, we must treat aggressively those who have or will develop diabetes to prevent the complications of diabetes from occurring. Despite the availability of a wide variety of glucose-lowering drugs and other relevant medications, supplies, devices, and well-established treatment guidelines (3,4), the majority of those affected by diabetes are not meeting the goals of therapy (5).

If diabetes can be cured or prevented or if the quality of care delivered to people with diabetes uniformly achieves recommended goals, undoubtedly there would be a major reduction in morbidity, mortality, and costs. If the impact of a cure for diabetes could be quantified, perhaps policy makers would be convinced that investing in diabetes research is not only the right thing to do, but the smart thing to do. Or if we could prevent diabetes from developing in virtually everyone, or if every person with diabetes received optimal care, how much would that affect the toll taken by diabetes in America? In the absence of clinical trials that might quantify such benefits, we turned to mathematical modeling and used the Archimedes Model to address these questions.

METHODS — The Archimedes model has been described in detail elsewhere (6–10). Briefly, it is a large scale simulation model of human physiology and health care systems. Unlike other regression equation, prediction models, or Markov models, Archimedes is built up from the underlying anatomy and physiology and uses scores of ordinary and differential equations to represent metabolic pathways, occurrence and progression of diseases, signs and symptoms, treatments, and outcomes. Objects and events in the model such as people, organs, tests, procedures, drugs, and outcomes correspond one to one with objects and events in the real world. Biological variables and their interactions are represented as continuous functions of time. Clinical events can occur at any time as happens in reality and are a function of the underlying biological variables and progression of disease. The effects of treatments are represented through their effects on the underlying variables. Test results are also functions of the underlying variables they are intended to measure. Currently the model includes diabetes and its complications, cardiovascular disease (CVD), congestive heart failure, and several other conditions, all in a single integrated model. This enables it to realistically represent comorbidities, syndromes, and biological variables that have multiple effects, such as insulin resistance risk.

The model includes methods for creating simulated people by making copies or "clones" of real people using person-specific data from surveys such as the National Health and Nutrition Examination Survey (NHANES) (11). This can be done at a high level of clinical detail, as in the case of NHANES, matching people on more than 40 variables relating to their demographic characteristics (e.g., age, sex), behaviors (e.g., smoking), physical examination (e.g., weight), past medical history, signs and symptoms, current treatments, and biomarkers. This ensures that the current values and correlations of biological variables and risk factors seen in real populations are accurately preserved in the simulated populations used in analyses.

In the model, costs are calculated by tracking all the cost-generating events that occur to each individual in the model, such as office visits, tests, treatments, and admissions, using micro-costing methods. The costs of specific cost-generating events were based on those experienced by Kaiser Permanente, Southern California, captured at the same level of detail required by Kaiser's cost accounting department. These costs represent real resource-based costs not distorted by charges, reimbursements, discounts, or diagnosis-related groups.

In this study, the costs of health care for conditions other than diabetes and its complications were also captured, and the analysis took into account that even with an immediate cure, there would still be some events (and costs) associated

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Abbreviations: CVD, cardiovascular disease; ESRD, end-stage renal disease; FPG, fasting plasma glucose; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey.

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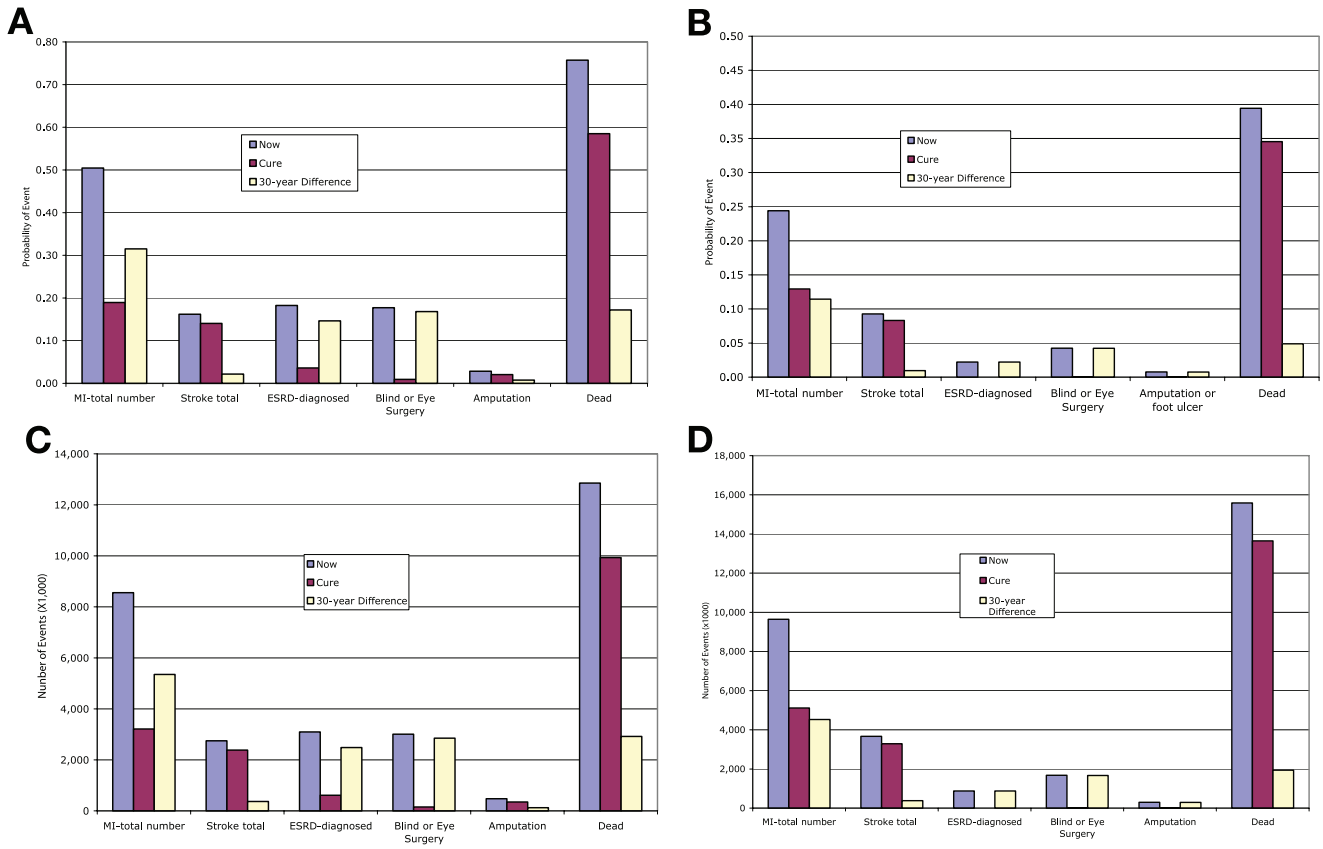

Figure 1—*The impact of a cure for diabetes.* A*: Subsequent 30-year per-person risk of complications for a typical person with diabetes alive today.* B*: Subsequent 30-year per-person risk of complications for a person with pre-diabetes (FPG >100 mg/dl) alive today.* C*: Subsequent total number of events that will occur over 30 years in people alive with diabetes.* D*: Subsequent total number of events over 30 years in people alive with pre-diabetes.*

with residual diabetes complications. Also, people cured of diabetes would be expected to live longer and have a higher probability of developing other conditions, and would thus experience costs that otherwise would not be seen. Such costs were also included. Indirect costs (e.g., lost time from work) or quality of life were not calculated in this analysis.

The accuracy of the methods for creating simulated individuals that match real individuals and the accuracy of the physiological equations have been validated by reproducing the results of ~50 major randomized clinical trials. The majority of these validations are "independent" in that no results from the trial were used to develop or modify the model. The methods and results for the initial validations have been published (8).

Specific methods for this analysis

For this analysis we asked three main questions: First, what would happen if "tomorrow" there is a cure for diabetes that could immediately be applied to everyone who is alive today with type 2 diabetes or pre-diabetes (defined as a fasting plasma glucose [FPG] >100 mg/dl)? Second, in the absence of a cure, what would happen if we could successfully treat people alive today with diabetes or pre-diabetes with 100% performance, compliance, and effectiveness in reaching treatment goals? Third, acknowledging that 100% performance and compliance are unrealistic, what would happen if we could succeed in achieving 80% performance and compliance or initiate a simple and straightforward treatment regimen, i.e., a polypill? For convenience we call these three scenarios "Cure," "Care," and "Commitment."

For each of these scenarios we determined the effects of the treatments on fatal and nonfatal myocardial infarctions (MIs), fatal and nonfatal stroke (hemorrhagic and ischemic), retinopathy (manifested by laser photocoagulation and blindness), neuropathy (end-stage renal disease [ESRD]), neuropathy (foot ulcers and amputations), life expectancy, and financial costs over the next 30 years. We compared the effects of each of the scenarios on what is expected to occur given current levels of care for people with diabetes or pre-diabetes.

Cure. For the first question we used person-specific data from NHANES IV (1998–2004) to create two simulated populations that matched the real populations. One simulated population represented people alive today in the U.S. with diabetes, defined here as FPG >125 mg/dl. The other represented people in the U.S. with pre-diabetes, defined here as FPG 100–125 mg/dl. To represent a cure for diabetes we created a hypothetical treatment that cured or "turned off" insulin resistance. This can be done in the Archimedes model because it contains a variable that represents the effect of insulin resistance on hepatic glucose production and uptake of glucose by fat and muscle. The value of that variable reflects the net effect of both the resistance of those organs to the effects of insulin and a change in insulin secretion. Thus, the variable takes into account the initial β-cell compensation to the development

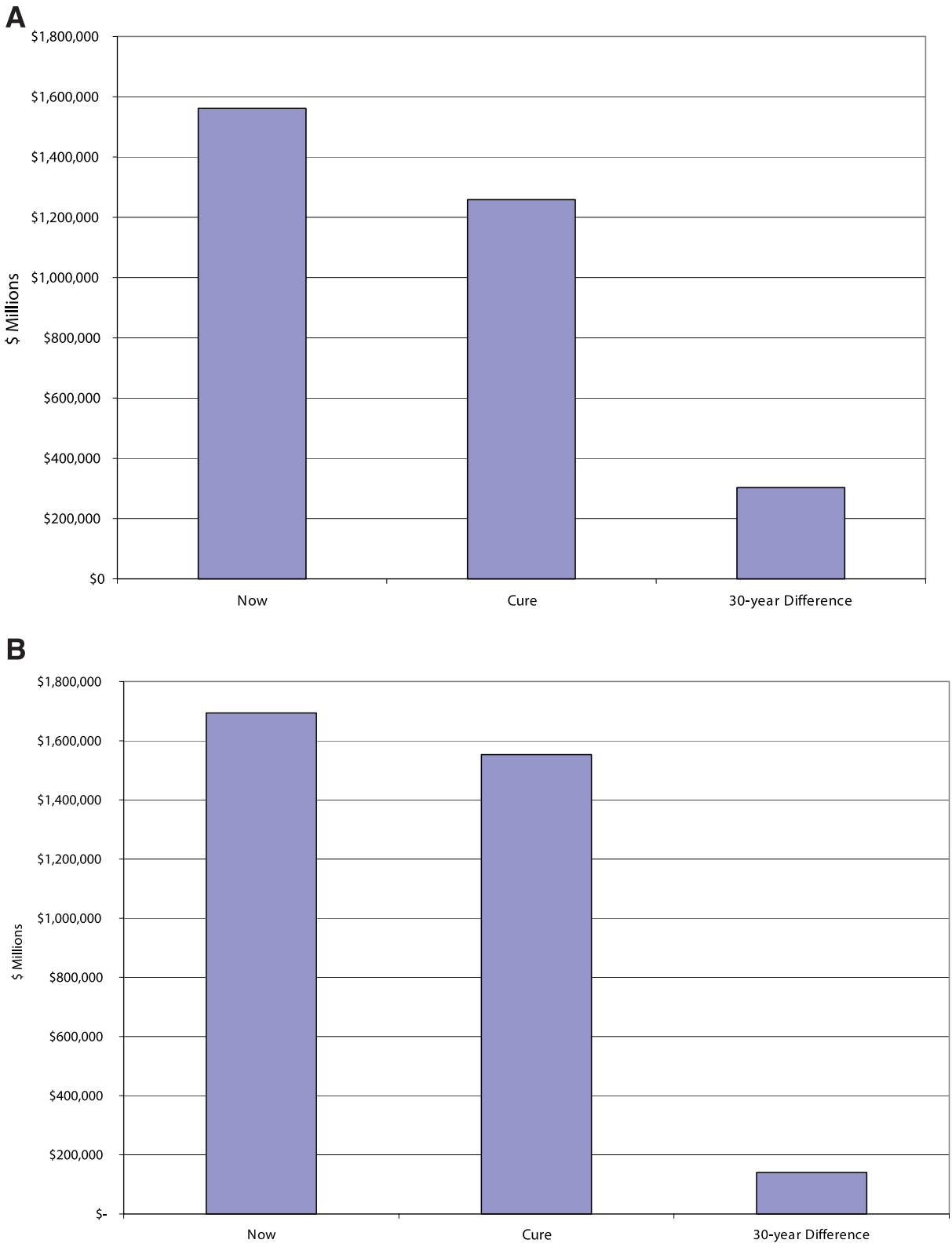

Figure 2—*The impact of a cure on the direct costs of diabetes.* A*: Subsequent 30-year total medical costs for people with diabetes.* B*: Subsequent 30-year total medical costs for people with pre-diabetes.*

of insulin resistance, and eventual β-cell fatigue, in addition to the effects of insulin resistance on liver, muscle, and fat. For each individual the hypothetical cure changed the person's level of insulin resistance from its current level to the average level inferred in people without insulin resistance (such as in those aged 20–25 years). Because the model represents the effects of insulin resistance on many variables, curing insulin resistance affects not only glucose levels, but also

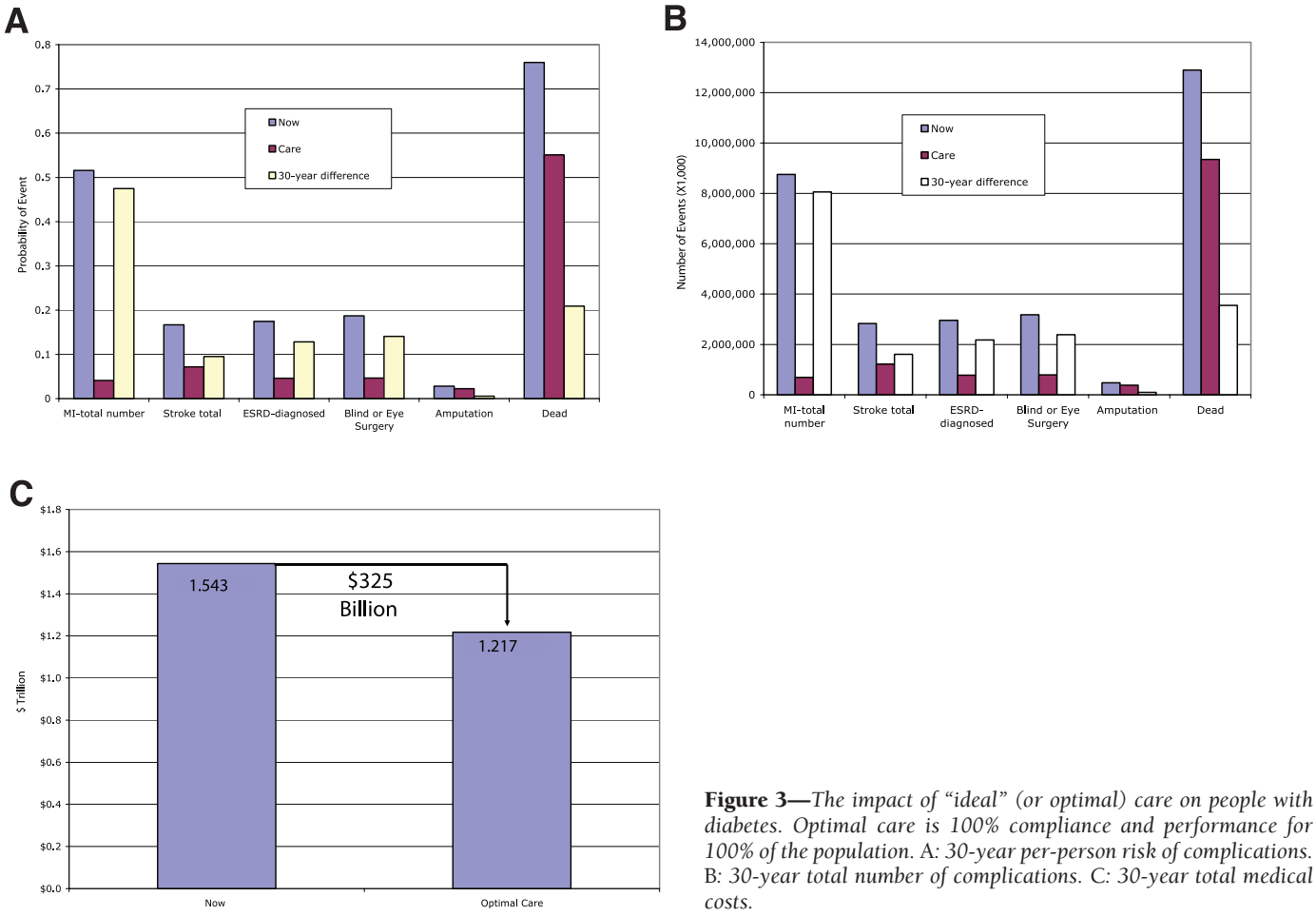

Figure 3—*The impact of "ideal" (or optimal) care on people with diabetes. Optimal care is 100% compliance and performance for 100% of the population. A: 30-year per-person risk of complications. B: 30-year total number of complications. C: 30-year total medical costs.*

blood pressure, triglyceride, and HDL cholesterol levels. In this analysis the cost of developing or administering the cure itself is not considered.

For the comparison or "control," we had each individual continue to receive the care they were currently receiving, as reported in NHANES. Depending on the person, in some cases they were at recommended treatment goals (e.g., A1C <7%, blood pressure <130/80 mmHg), and therefore that level of care was assumed to continue subject only to the natural progression of their conditions with age. In other cases the person was not being managed according to guidelines (e.g., A1C >7%), and for them we assume that their (inadequate) level(s) of care would continue and that their conditions would progress naturally with age. In all cases the current levels of care were obtained from NHANES (11).

Thus, to address the first question we took a simulated population of 5,000 people with diabetes or pre-diabetes, who matched the real people in NHANES, and "managed" them in two different ways, analogous to two arms of a clinical trial. One management program was usual care, as described above. The other management program was to cure their insulin resistance immediately. To minimize sampling error we used the same group of simulated people for both management programs. We followed everyone for 30 years, recorded all the pertinent outcomes as they occurred, and reported results at normal intervals.

Care. For this question we used the same simulated population created for the previous question; however, instead of curing insulin resistance we specified that everyone in the treated arm would receive therapy that resulted in attainment of all the following treatment goals: A1C <7%, blood pressure <130/80mmHg, LDL cholesterol <100 mg/dl, HDL cholesterol >40 mg/dl in men and >50 mg/dl in women, triglycerides <150 mg/dl, daily aspirin for those over 40 years of age, cessation of smoking, and BMI <25 kg/m^2 (4). The actual level to which a variable was treated was set to match the average level of that variable seen in real people who are treated to the target in the U.S. population (e.g., the average blood pressure in people with diabetes whose blood pressure levels are <130/80 mmHg). We labeled this regimen "optimal care." We compared optimal care to usual care as defined in the Cure scenario above and used the same sample sizes and 30-year timeline.

Commitment. For this question, we used methods similar to the second question, but with a few important differences. First, for the "treatment arm" of the simulation we specified that treatment would include only glucose, blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, and aspirin; we omitted control of BMI and smoking. Second, for the treatments that remained, instead of postulating that 100% of the population would achieve complete performance, we allowed for a random sample of only 80% of the population achieving complete performance.

We also examined the effects of having a random sample of 80% of the individuals receive a "diabetes polypill,"

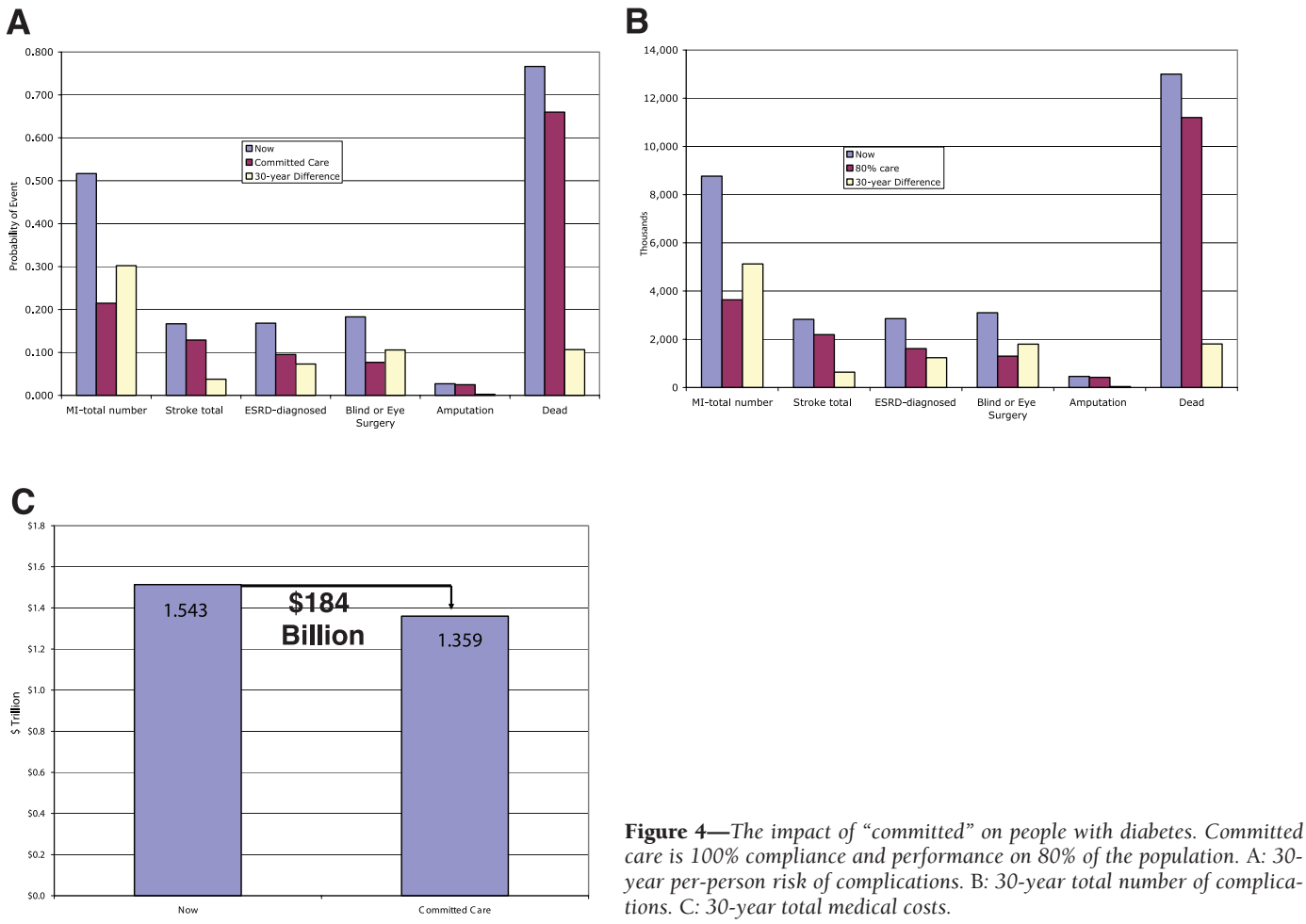

Figure 4—*The impact of "committed" on people with diabetes. Committed care is 100% compliance and performance on 80% of the population.* A*: 30-year per-person risk of complications.* B*: 30-year total number of complications. C: 30-year total medical costs.*

consisting of metformin (1,000 mg/day), aspirin (81 mg/day), simvastatin (40 mg/day), and lisinopril (10 mg/day). Consistent with the intended use of a polypill, this therapy was given to each person with diabetes, regardless of the person's current A1C, blood pressure, or LDL cholesterol levels, and was administered in addition to whatever "usual care" the person was otherwise receiving. We focused on the potential positive effects of a polypill on diabetes and CVD events and did not try to calculate the occurrence of untoward side effects of the polypill.

Finally, as part of this scenario, we examined the benefits of each of the particular treatments (e.g., glucose control, blood pressure control) one-by-one and in various combinations, letting the other variables and risk factors remain at their current levels. For each of the parts of this scenario, the comparison was usual care as defined in the Cure scenario, and the sample sizes and 30-year timeline was used.

It is important to note that in the Care and Commitment scenarios the degree of benefit a particular person would receive varies from person to person depending on the number and type of abnormal variable(s) present. Those who have or will develop all the risk factors will gain the most, and those who have or will never have any values above the goals of therapy will benefit the least.

RESULTS

Cure

The effect of a cure on the 30-year probabilities of complications for an average person with diabetes or those with prediabetes who will develop diabetes are shown in Fig. 1*A* and *B*, respectively. The risk of complications is dramatically reduced by a cure for all the important complications of diabetes. The risk of a heart attack declines the most, nearly 40%. For the U.S. population as a whole, Fig. 1*C* and *D* show that a cure for diabetes would prevent nearly 9.5 million heart attacks, 2.5 million cases of ESRD, 4 million cases of blindness or eye surgery, and nearly 4.5 million deaths in the U.S. over a 30-year period. In economic terms, a cure for diabetes would reduce total health care costs by about $303 billion dollars in those who currently have diabetes (Fig. 2*A*) and $141 billion in people who have pre-diabetes (Fig. 2*B*) over the next 30 years. These results apply to people alive in the U.S. today; they do not include the effects of a cure on future generations.

Care

Fig. 3*A* shows the effects of optimal care on the 30-year risk of complications for individuals currently diagnosed with diabetes; it indicates the benefits that would occur to a typical person with diabetes if existing recommendations for management of risk factors could be followed with 100% success. Figure 3*B* shows the number of events that would be prevented over the next 30 years in people in the U.S. population today who currently have diabetes. Figure 3*C* shows the effect of optimal care on 30-year medical costs related to CVD, diabetes, and its complications. Optimal care has its greatest ef-

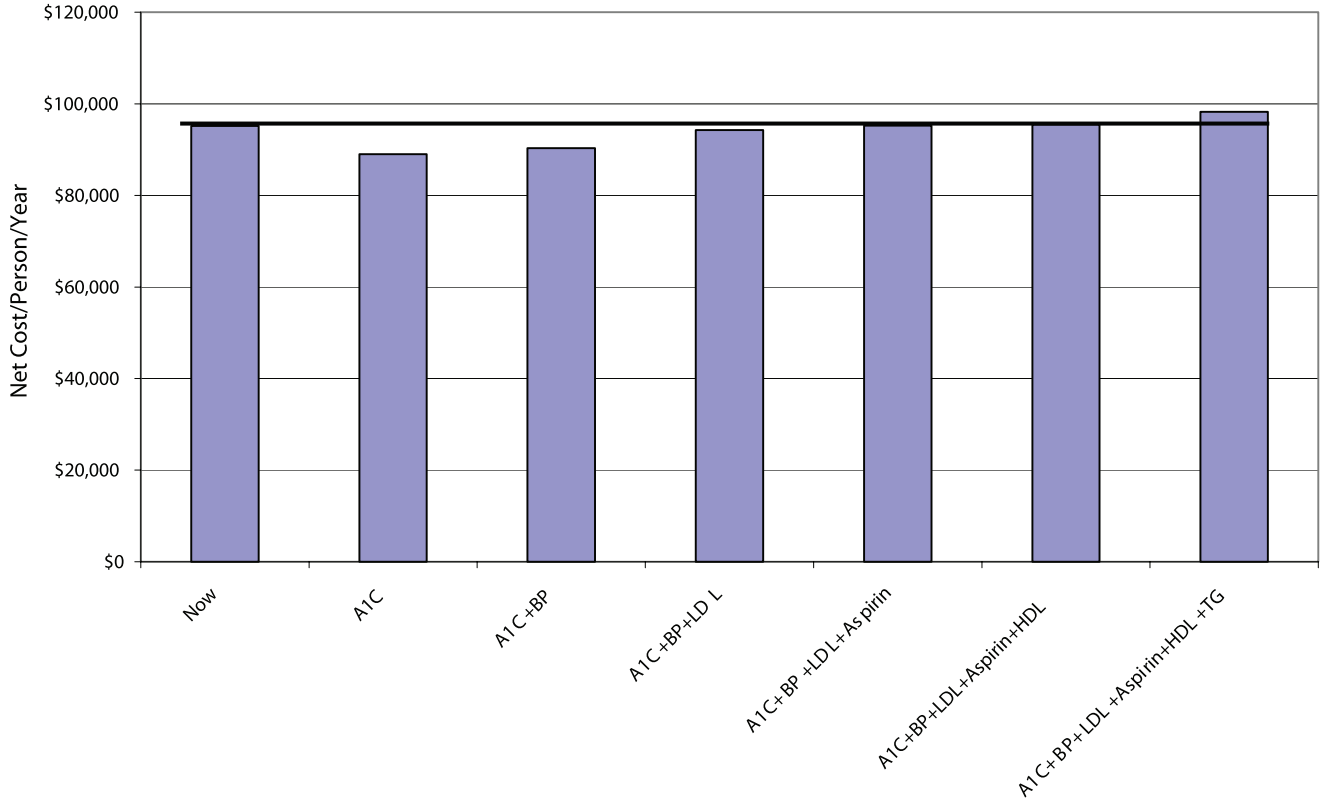

Figure 5—*Net cost per person of a cascade of treatments on the medical cost of diabetes and its complications over a 30-year period in individuals receiving "committed care." All costs assume an additional $100/year in office visits and $300/year in drug costs for each variable controlled, to a maximum of $1,500/person. Aspirin was assumed to be free. BP, blood pressure; TG, triglycerides.*

fect on MIs, reducing an individuals risk by 92% and preventing 8.06 million MI events over 30 years. In addition, the effects of optimal care are also important for nearly all the other complications, such as amputations (20% reduction) and ESRD and eye complications (75% reduction). The number of lives saved with optimal care would add ~3.55 million life-years to people alive today with diabetes and would reduce the medical costs of diabetes and its complications by $325 billion.

Commitment

Figure 4*A* and *B* shows the effect of committed care on the 30-year risk of a complication faced by a person today with diabetes and on the number of outcomes that would occur over 30 years, respectively. For a typical person today with diabetes, the risk of a heart attack would decline by 57%, and for the population of people with diabetes, 5.13 million fewer events would occur. Also, the death rate would decline by 16%, and 2.8 million person-years of life would be added. On average, each person with diabetes would live an additional 2.2 years (data not shown). Figure 4*C* shows that over 30 years this more realistic scenario would also save approximately $184 billion in costs associated with diabetes and CVD.

Since the performance described in committed care would require more resources than currently used, we asked what would be the net cost (increase or decrease) of committed care if an additional $100/year were spent on office visits and an additional $300 were spent for each drug used to better control A1C, blood pressure, and lipids up to a maximum of $1,500 to control all three parameters. Figure 5 shows the net medical cost of diabetes and its complications per person per year allowing for these additional treatment costs. As the figure shows, lowering A1C to <7% by itself, or lowering A1C to <7% and lowering blood pressure to <130/80 mmHg, actually saves money. Achieving both of those goals and all the others in 80% of people with diabetes is cost neutral.

The effect of providing a polypill in addition to usual care is shown in Fig. 6. Over 30 years the polypill would reduce the number of MIs by 51%, ESRD by 21%, eye complications by 34%, and deaths by 10%. The polypill did cause in a modest increase in the number of amputations (from 510,820 to 516,592) and strokes (from 2,580,074 to 2,857,129) because it kept people alive for a longer time. Overall, if 80% of the diabetic population took a polypill without otherwise changing their current levels of care (including no change in the frequency of office visits, drugs taken, and tests performed) there would be ~7.3 million fewer serious complications over the next 30 years.

We also calculated the financial impact of the polypill. Figure 7 shows that if the cost of the polypill were $500/year, our health care system would begin to save money by year 10. At $400/year the polypill becomes cost-saving by the fifth year. Of note, Kaiser Permanente in Southern California adopted the polypill concept at an annual cost of about $100 (personal communication), which suggests that this therapy could be very cost-saving very soon after implementation.

DISCUSSION— In this analysis we show that over $300 million could be saved annually by curing diabetes in those affected by the disease today. Such sav-

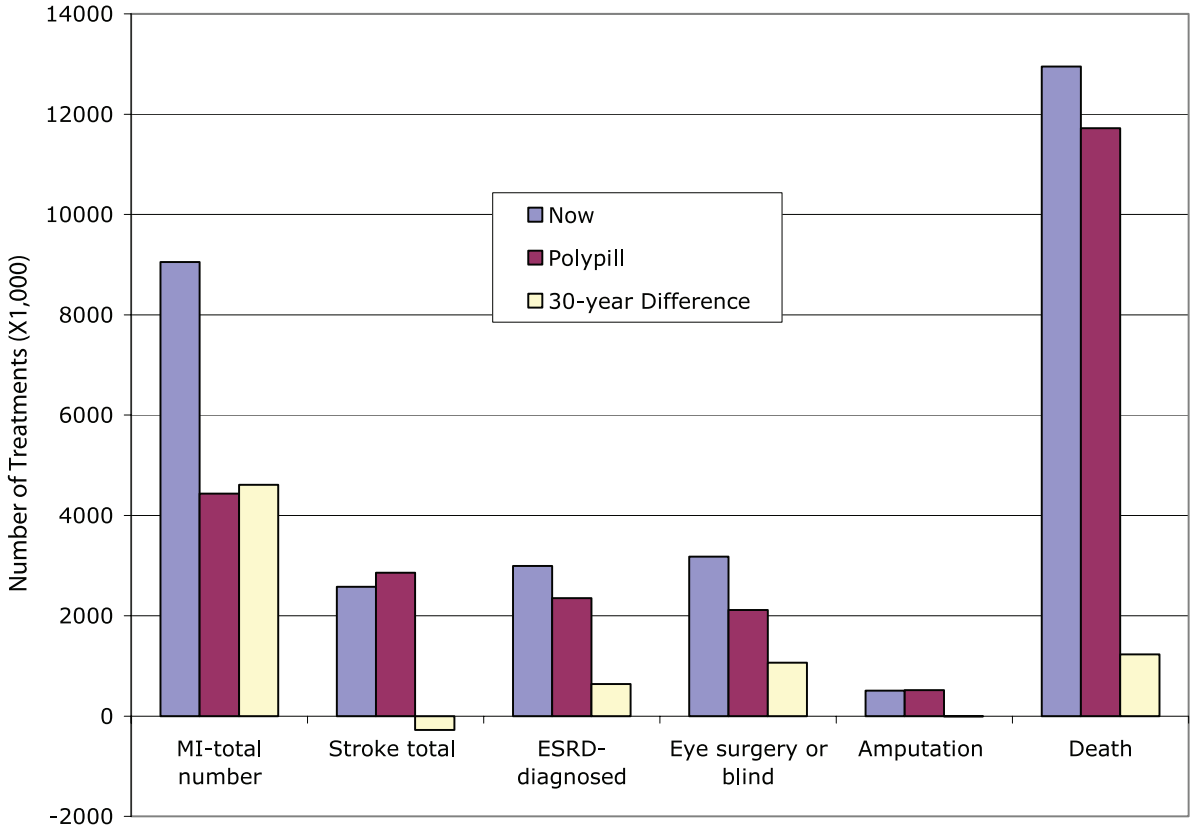

Figure 6—*Impact of a polypill taken by 80% of the population with diabetes who are receiving usual care. Data shown are the 30-year total number of events.*

ings suggest that investing far more in diabetes research to develop a cure should be a high priority for the Federal Government and private organizations. Surely the size of the investment should be commensurate with the risk that diabetes represents to our citizens. If not stopped, the diabetes epidemic has the likely potential to overwhelm our health care system and to undermine our economy.

In the absence of a cure, we show that improvements in diabetes care can also have a dramatic effect on reducing the rate of complications. Other studies have also documented the enormous burden of diabetes complications (2,12), and there is ample evidence that adherence to nationally recommended guidelines can be greatly beneficial (13–17). Our analysis indicates that in an ideal scenario where all the goals of therapy are achieved in every person who has diabetes, we could expect a marked reduction in medical expenditures and a reduction in the complications related to diabetes. Achieving similar performance levels but in fewer people also offers a great return in lives saved and complications avoided as well as reduced medical expenditures (Fig. 4). In other words, the increased cost to bring 80% of those with diabetes to all treatment goals could be offset by the savings that result from the prevention of complications. Moreover, even if the cost of care increases modestly in order to have performance improve, millions of lives can be saved and serious complications prevented with no increase in current net medical costs (Fig. 5). If, as almost certainly will occur, prevention of life-threatening complications increases productivity and length of participation in the workforce, then the return on investment from optimal care of diabetes becomes even greater.

In other words, a reasonable increase in cost to bring 80% of those with diabetes to all the goals of therapy would be more than offset by the savings that result from the prevention of diabetes complications.

Finally, we explored the impact of a more simplified care delivery scheme. That is, by administering a "polypill" comprised of generic glucose, LDL cholesterol– and blood pressure–lowering drugs along with low-dose aspirin, given in addition to current usual care, we observed a dramatic reduction in costs and complications. A similar cocktail has been proposed by others (19) and was found to be cost-effective in reducing the burden of CVD (20). In the present study, administering a polypill not only holds promise of substantially reducing the medical burden of diabetes, but is also very likely to save money within a few short years.

There are many important caveats to our study. First, there is no way to confirm the accuracy of the results we obtained, or the results of any modeling study, when the predictions have not been confirmed empirically in clinical trials. Although we used a highly detailed, extensively validated mathematical model that simulates human physiology, a variety of diseases, and their treatments and health care systems, all to a very high degree, clinical research is needed to confirm our findings.

Second, we intentionally designed our analysis to derive estimates of benefit knowing that there are many variables that cannot be quantified or might be considered. We attempted to provide a framework for what the future holds and excluded a detailed sensitivity analysis that could encompass a wide-range of possibilities. For example, in our analysis of "cure" we do not know the mechanism,

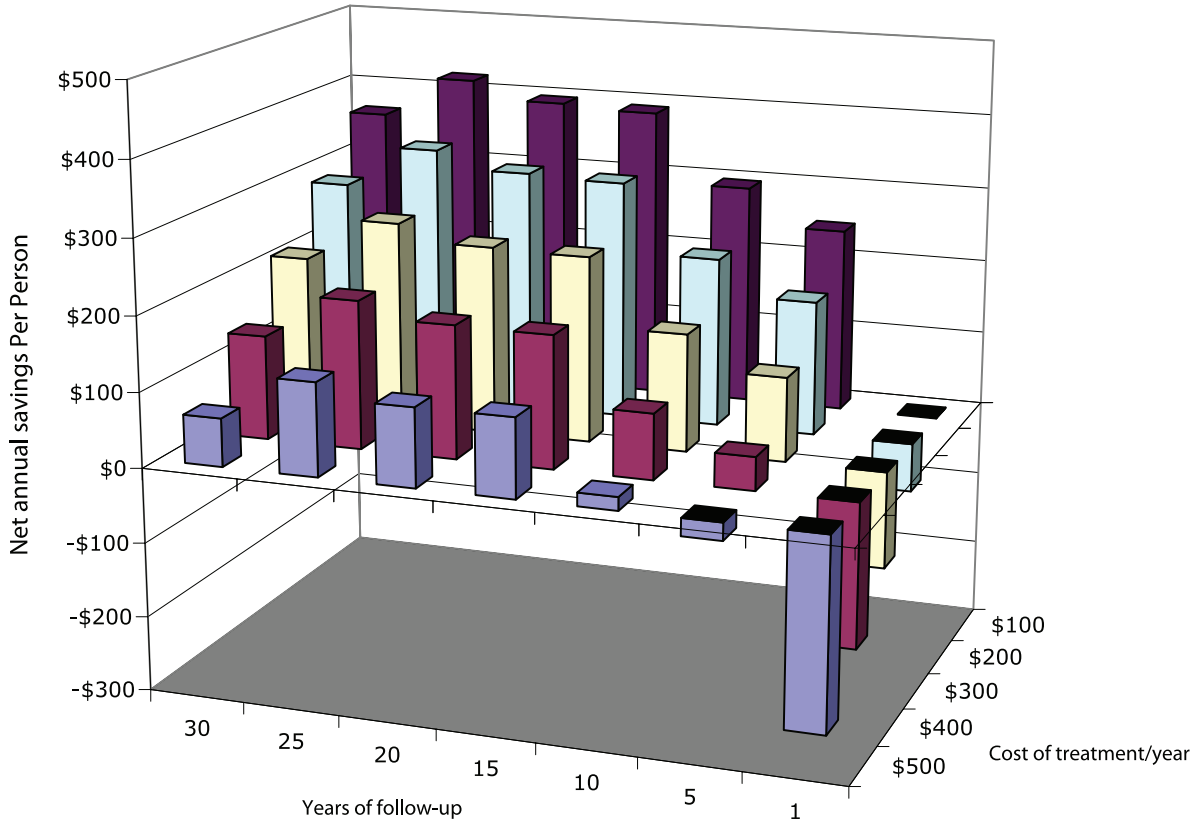

Figure 7—*Net average annual savings per person from treating 80% of people with diabetes with a polypill.*

delivery, or cost of such a cure, nor do we know if a cure for diabetes is associated with any ill-toward side effect that may impose its own financial costs.

Third, in our analysis of the impact of "committed" care, achieving all the goals of therapy in a very high proportion of a population with diabetes is currently not routinely feasible, and even if it were now possible, the performance levels we assumed would be difficult to sustain over 30 years. There are, however, health care plans and practices that have achieved these performance levels in a smaller proportion of patients, which provides encouragement that high quality diabetes care can be provided. To actually achieve nationwide, the performance levels we studied may require a systematic structural change in care delivery that addresses the key features of chronic disease versus our current system, which is orientated far more toward the delivery of acute episodic care.

Fourth, we used the actual costs and protocols of a single, relatively efficient system (Kaiser Permanente, Southern California); these costs may be different in other settings. Visit frequency, tests performed, and medications used may also vary to achieve the desired results, and other settings may have a more expensive cost structure. Conversely, while we showed only the benefits of improved performance as they relate to diabetes and CVD, additional benefits would likely be seen. For example, smoking cessation impacts the incidence of lung cancer, weight loss affects the incidence of a wide variety of diseases, and aspirin may decrease the incidence of certain cancers. Also, we did not factor the myriad of indirect benefits that would accrue with improved diabetes care such as improved workplace productivity. The Archimedes model is primarily based on and validated against clinical trial data. The extent to which predictions of the model reflect those in diverse populations is not known.

Can any of the treatments we studied become reality? We believe that first and foremost America must invest heavily in diabetes research. Second, we must provide an environment to create and sustain heath care systems whose structure insures that every person with diabetes receives the best possible care. We must renew our commitment to people with diabetes, acknowledging that current performance is not acceptable and that we will improve. Finally, we must be willing to explore novel approaches to therapy, such as the polypill, which offers great promise of being an inexpensive yet very effective approach to achieving the results we want.

The treatment of diabetes is neither complex nor particularly difficult. A wide array of drugs and devices are available, and the goals of therapy are supported by a rich evidence base. But like all chronic diseases, diabetes requires the active involvement of the patient, a support system, and an engaged clinical team. It also requires regular follow-up visits, careful monitoring, and attention to a wide variety of risk factors and possible complications.

A world without diabetes and its complications is certainly possible, and the appropriate care for people with diabetes is within our grasp. Both, however, require unrelenting commitment and resolve (21). We can succeed.

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