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I hereby certify that Amarnath Bhat has passed the Final Examination for the degree of Doctor of Philosophy on December 17, 2002 and that this is the final and approved form of the dissertation.

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Measuring the Economic Impact of Diabetes Research

by

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Abstract

This study evaluates the economic outcomes of 25 years of diabetes research supported by the National Institutes of Health. The economic evaluation is conducted using three different methods: cost-effectiveness analysis; cost-utility analysis; and, cost-benefit analysis. The evaluations are based on outcomes of research activities, primarily clinical trials such as the Diabetes Control and Complications Trial, which were conducted by scientists and which encapsulated the increase in knowledge of diabetes during the period of 1975-2000. This study estimated the economic benefits of this research expected to accrue during the period 2001-2025.

The findings indicate that the economic impact of diabetes research is quite substantial. The cost-utility analysis demonstrated net present values (in 1975) of research costs ranging from $28,300 to $57,500 per discounted and QALY-weighted life year depending on the discount rate (3% and 7% respectively). The cost-benefit analysis used two different methods for valuing human life, with net benefits ranging from $158 billion to $12 billion using health capital methodology (willingness to pay), and from $83 billion to $2.8 billion using human capital methodology (discounted future earnings). Cost-benefit ratios ranged from 83 to 3.35 when comparing the gross benefits to the initial investment in diabetes research. Social rates of return were also calculated.

The results of these *ex post* analyses show the advantages and disadvantages of these types of methodologies for evaluating biomedical and behavioral research. Furthermore, they demonstrate that it is possible to conduct an economic evaluation of medical research in a manner that is methodologically sound, and not particularly burdensome. This research also shows that when taking a long-term view of the investment in diabetes research, the economic impacts are indeed substantial, and compares well to many private sector investments. This type of analysis does have value in that it allows to us examine what has transpired and draw some lessons from the experience. By examining the process and the results, we may be able to influence future decisions regarding the allocation of scarce resources. Nonetheless, care should be taken when using these types of indicators of performance when determining future outlays of medical research investment.

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Chapter 1: Introduction

Since the beginning of the 20th Century, and particularly in the last half, society began to accept that investment in research and development (R&D), particularly health-related R&D, is a public good and not a private good. Previously, scientists were reliant on private benefactors or their own resources in order to pursue their research. Corporate-funded research, particularly in health, was practically non-existent. With the advent of the first and second world wars, the U.S. Government gradually accepted the idea that an investment in science was a legitimate role for the Federal Government.[1] Thus, we saw the advent of both the National Science Foundation in 1950 and the National Institutes of Health as a grant-making body in 1946.

Public goods are goods jointly consumed by everyone in society. Classic examples of public goods are national defense, local police forces, national parks, and flood control projects. Scientific research is considered a public good because the results of such research are published in the scientific literature for all to read and to build from. Society

[1] Smith, Bruce L.R., *American Science Policy Since World War II*, (Brookings Press, Washington, D.C., 1990).

as a whole derives tangible benefits from such research, even when such benefits are difficult to measure.

The results of scientific research are often of a basic nature and not directly useful to any one individual or corporation. While some health research is a private good -- as in private pharmaceutical research -- its potential to enlighten and inform other research is diminished unless the knowledge gained is made publicly available, e.g. through scientific journals or conferences. Private corporations may also find the results of their own research so long-term and uncertain in its applicability as to not justify the investment. From society's perspective, this view leads to an underinvestment in research. However, in the years after World War II, policymakers came to the conclusion, articulated most cogently in the Vannevar Bush report, *Science—The Endless Frontier*, that

> *"Progress in the war against disease depends upon a flow of new products, new scientific knowledge. New products, new industries, and more jobs require continuous additions to knowledge of the laws of nature, and the application of that knowledge to practical purposes...Without scientific progress no amount of achievement in other directions can insure our health, prosperity, and security as a nation in the modern world."*[2]

The report concluded it would not serve our society well to underinvest in research and that it was the role of the Federal Government to place a portion of its resources into the research and development enterprise.

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[2] Vannevar Bush, Science, *The Endless Frontier*, (Washington: National Science Foundation, 1945, reprinted 1960), p. 12.

Throughout the years, this faith in research as a public good has been reaffirmed through the annual appropriations process of the Congress. Each year, subcommittee members of the Appropriations Committee sit and listen to reports made by the various directors of the National Institutes of Health on the state of research and hear projections on future directions and expected benefits. These benefits are almost exclusively expressed in terms of new therapies and drugs, new advances made, or numbers of scientists trained. Rarely, however, does NIH or other medical research advocates attempt to estimate the *economic* value of these publicly-funded medical advances; in those cases where economic values are provided, the evidence presented is typically anecdotal rather than systematic.

It is, however, an implicit assumption among many that there are substantial economic benefits to our investment in research and development. The evidence seems to be all around us. The nation has seen a tremendous growth in the economy, in part fueled by advances in science and technology. Thousands of new firms have been created, and hundreds of others have grown, making use of research advances and new technology. Over the years, the portion of the gross national product devoted to health care has grown from 5.1 % in 1960 to 13% in 1999, making it one of the largest sectors of the economy[3]. This growth is largely the result of publicly-supported health care for the elderly and indigent through Medicare and Medicaid, as well as the availability of private health insurance through employers.

The rapid and substantial growth in the share of the nation's resources devoted to healthcare suggests that there are correspondingly large economic returns to publicly supported medical research. But, measuring the economic benefits of scientific research generally is challenging, particularly so in the case of health-related research. Nonetheless, it is important to attempt to measure these benefits because of an increasing interest in societal returns to government investments, such as research and development. With the passage of the Government Performance and Results Act (GPRA) in 1993 and its requirements of performance goals and accountability to those goals, Federal science agencies have been required to develop systems for assessing their performance. The goal of this legislation was to force government agencies to set performance objectives and measure themselves against those objectives or benchmarks. If they fail to meet those objectives, they must then prescribe corrective measures. In this manner, Congress has determined that they can hold government agencies accountable.

Science agencies, including the NIH, are required to submit reports to Congress in response to GPRA. Thus far, NIH has focused on qualitative objectives and performance measures, shying away from quantitative and economic measures. This study proposes a methodology for developing an economic measure of biomedical research and development performance that may or may not be useful to NIH in fulfilling its GPRA obligations.

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[3] "Table 1 – 1999 National Health Expenditures," Center for Medicare and Medicaid Services, Office of the Actuary: National Health Statistics Group. Report found at http://www.cms.hhs.gov.

Since the mid-century, the Congress and the Federal Government have been making investments in NIH without knowing the economic returns on this investment. This is not to say that the Federal Government has been allocating resources on an arbitrary basis. Rather, because the results of scientific research are uncertain, there is an element of risk that has historically been accepted. This risk is acceptable because the public is reassured that in balance, this investment will be returned, perhaps many times over.

But there is a lingering question of the net social benefits of medical research. Is the investment in medical research justified and should we be investing more or less in research? How can we be assured of these benefits and what is the magnitude of this return? Given the overall scarcity in everyday life, we do not have unlimited resources to devote to scientific research. When can we say that the marginal costs of additional resources outweigh the marginal benefits? Secondarily, in the interests of improving the manner in which government policymakers allocate resources, how should we measure the "performance" of scientific research, specifically medical research, against other areas of research or even against other government services? Should NIH and other Federal research agencies be including measures of economic impact in their GPRA reporting? Should Congress have the benefit of knowing what, if any, economic returns there are to scientific research? Alternatively, is it fair and appropriate for NIH or other research agency to provide such economic data to Congress?

Economic benefits are not the sole or most important result of Federally funded research. Rather, it is but one desired outcome of research. In the Federal Government, the

primary purpose of funding research is related instead to the mission of the funding agency. In the case of NIH, it is the furtherance and application of scientific knowledge that leads to improvements in public health. However, Congress, through GPRA, has requested that agencies quantify their accomplishments or planned activities to the extent possible, in terms understandable to the general public. Despite the difficulty in quantifying these results, NIH and the other Federal science agencies are not exempt from this legislation.

Studies by Mansfield, Link, Terleckyj, Griliches showed positive correlation between general R&D investment and economic growth and productivity, focusing primarily on private sector investment, but they did not show direct causality. Biomedical R&D was not included in these assessments. The commonly accepted reason for their inconclusive results is that the complex nature of the scientific enterprise leads to multiple feedback loops and an inconsistent timeline between the input of resources and the output of results. Other studies have attempted to measure scientific output using well-established econometric methodologies, such as macroeconomic production functions, return on investment, rate of return, business opportunity analysis, consumer and producer surplus. Most of these studies have concluded that these measures are well-suited to private sector endeavors, particularly when timelines are short, but are less useful when evaluating public sector investments. Again, by and large, these assessments have not included measures of biomedical R&D performance.

When evaluating health care policies, a different set of methodologies has commonly been used to assess the impacts of various policies and programs. Generally, the needs are to determine which of two or more health interventions are more desirable, either from a clinical perspective, i.e. the perspective of the patient, or from a cost perspective, i.e. the perspective of the person or agency responsible for paying for the health care. Occasionally, cost studies from a societal perspective are also conducted, but as before they measure the performance of health intervention, not the underlying investment, i.e. the research and development investment.

Quantitative methods can be used to aid decision-making when one is evaluating a set of policies or programs. These methodologies include cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). These closely related methodologies allow one to examine the comparative benefits of one type of program or therapy versus another related program. CEA enables one to understand the relative value of alternative interventions for improving health in terms of cost per unit of health benefit—however that is defined in the health intervention—while CUA reduces or quantifies the benefits of a program or policy in terms of dollars per standardized units, such as quality-adjusted life years.

While these methodologies have been extremely useful in evaluating and comparing health interventions—and can be useful when comparing costs of research to lives saved or other well-recognized measures of health—they normally stop short of valuing these health interventions in terms of monetary benefits.

Another methodology that has been used, though less frequently than CEA or CUA, is cost-benefit analysis (CBA). In CBA, one attempts to examine the monetized costs and benefits to society as a whole when considering if a policy or program is of benefit to society. CBA directly compares the costs against the benefits and determines whether the outcome is positive or negative. CBA is useful when exploring issues of allocative efficiency, that is, whether or not resources are being used to their highest value in terms of the goods or services they create. Furthermore, CBA allows us to compare one alternative against another in monetary terms, providing information about the relative efficiency of the competing alternatives.

This study attempts to achieve an understanding of medical research in terms of its economic impact. It is a fairly unique attempt to measure research benefits in a manner that is useful to policymakers without causing undue administrative burdens and without unduly biasing one type of research against another. Furthermore, it attempts to assist in the translation of research, from basic research through to clinical application, by adding another level of understanding or appreciation to what has been achieved.

To evaluate the economic impact, the relatively narrow field of diabetes research will be used as a case study. Using the commonly used methodologies of CEA, CUA, and particularly CBA, this *ex post* assessment measures the benefits of diabetes research, both for the patient with diabetes, and for society at large, by looking at the past advances of research and relating them to projected changes in the health status of people with

diabetes, then calculating the benefits to society both in terms of societal willingness to pay and in human capital (productivity).

Within a narrowly defined research area, such as the biomedical research devoted to one specific disease, one should be able to determine the entire universe of inputs to discovering new therapeutics, diagnostics, and preventive measures. By identifying all the Federally-funded research activities, i.e. the body of research grants funded by NIH, in the recent past that is related to diabetes research, one may be able to determine reliably the inputs or costs.

It is the intention of this study to demonstrate that an economic analysis of medical research is a valid method for valuing research benefits, one that is reliable, unbiased, and reasonably accurate. Furthermore, this paper strives to indicate the amount of work necessary to carry out such an analysis, and the nature of the results it may give.

A study of this nature not only adds to the body of knowledge regarding the evaluation of social returns to research, it especially gives one insights into the conduct of medical research and how the impacts of Federally-funded research are disseminated throughout society. While this study uses the case study of diabetes, and thus utilizes some of the special circumstances of diabetes and the complications that arise from this disease, one can also draw lessons about the social returns of medical research that are broadly applicable to other fields of disease-based research, such as cancer, cardiovascular disease, and other chronic diseases. Finally, when one considers GPRA and the mandate

to Federal agencies to report on the performance of their own programs, then we may consider economic analyses to be a useful and perhaps welcome addition to the other methods of measuring performance.

With validated and reliable methods for determining benefits, science agencies can more effectively make their case to Congress for greater investment in science and technology. Policymakers can better understand the connection between biomedical R&D investment and the society's overall health care. Additionally, science administrators can understand which aspects of their investment makes the greatest economic impact, based on criteria they deem important. If R&D is to be seen as both a public good and an investment for all Americans, then the public should know what return on their investment they are getting.

Chapter 2: Diabetes Care and Diabetes Research

Research versus Treatment

Before describing in detail the research design of this study, it is useful to gain a more complete understanding of the relationship between diabetes treatment and diabetes research. In the United States, health care and health research are a mixture of public and private goods. In the center is the person with a health problem, in this case diabetes. The person with diabetes is treated with both drugs and devices, and provided treatment, i.e. medical services, by health care personnel, including doctors, nurses, and auxiliary staff. Medical services also include long-term care, for example, nursing homes. These services and goods are private goods, meaning that they are supplied to one consumer only, with little or no possibility of any sort of free-ridership.

The person with diabetes does not, however, always reimburse directly the providers of the services and drugs, thus he or she does not apply normal supply and demand considerations to his or her care. Instead, the person will likely have health insurance, whether private and public, who in turn pays the health providers. The person with diabetes buys private insurance, while society at large supports public insurance, i.e.

Medicare and Medicaid, through taxes.[4] Thus, concerns of cost containment are at least partially transferred from the patient to either the hospital or the insurer, whether private or public. However, a significant amount of "out-of-pocket" expenses are directly borne by the person with diabetes.

Finally, another economic burden of the disease is lost work productivity, through days of work missed, time taken to visit their physician, and disability and premature retirement from the workforce. These costs are borne by both the patient and society at large. Any increases in productivity, as well as savings in health care costs, are generally benefits to society, and thus may be considered public goods, because of their nonexcludability.

On another dimension, society supports publicly supported research and development, primarily through taxes. A small amount of funding is also provided to researchers by charitable foundations and voluntary health agencies such as the American Diabetes Association who raise funds from private donations.[5] The pharmaceutical, biotechnology and medical device companies also supports private research and development (R&D). Of course, these companies invest in R&D that is directly related to products that they intend to market to people with diabetes through health care providers.[6] Accordingly,

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[4] It can also be said that society in general pays for private insurance, although not all individuals have health insurance.

[5] In 1999, total Federal R&D for health research was $16.9 billion and private sector R&D was $2.1 billion, not including pharmaceutical and medical device R&D. Privately-funded diabetes research, such as that supported by the American Diabetes Association, would be included in this $2.1 billion figure. Source: 1999 National Health Expenditures, Table 3, Health Care Financing Administration, Office of the Actuary, National Health Statistics Group, http://www.hcfa.gov.

[6] Thus, research expenditures are implicitly included in the expenditure class in which the product falls, in that they are covered by the payment received for that product. Nonetheless, the possibility of consumer

they are primarily interested in products that will increase their revenue. Thus, therapies that do not involve new drugs or devices are of little interest to them. Generally, their time frame for R&D is much shorter than the Government's.

Pharmaceutical R&D, while not included in this research, has many antecedents in publicly-supported research. For example, many of the leads that pharmaceutical company scientists pursue in developing new drugs come from basic research supported by NIH. The company many partner with the NIH or NIH-funded scientists in evaluating new drugs in clinical situations. Finally, scientists employed at pharmaceutical companies are often trained in graduate schools that receive significant support from NIH, either through training grants or through research projects. Thus, any discussion of the role of private investment in diabetes research must also include the role of NIH as a significant supporter of that research as well.

Benefits of diabetes research supported by private pharmaceutical or medical device companies are also a mixture of private and public goods. The private benefits of this research flow downstream through the medical drug and device companies to the person with diabetes, either directly through their products, or through health professionals. The public benefits flow back upstream to scientists funded by NIH or other public-sector funding organizations when the privately-funded researchers publish in the open literature, report their findings at scientific conferences, or partner with publicly-funded scientists.

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surplus does exist. The economic consequences of this consumer surplus *may* be mitigated by the pharmaceutical companies' use of research results generated by NIH-funded research.

Benefits from government-supported R&D are mostly public in nature. Not constrained by short-term profit motives--as private companies are--benefits from NIH-funded research may be tangible products, e.g. leads on new drugs which may be further developed by private firms, or more intangible improvements to therapies or a better understanding of the disease prevalence in the population. Eventually, we will see new methods to prevent diabetes, thus benefiting people with diabetes (or rather people with a propensity to develop diabetes) in an entirely different manner. Advanced training of scientific and health personnel may also be considered an intangible public benefit.

The results of publicly supported research are almost always published in the open literature and thus are public goods. However, in order for the public to benefit from these public goods, these results must be transformed into private goods that are controlled by private sector organizations, such as drug and device companies, hospitals and physicians. Private pharmaceutical companies accomplish this transformation by using the leads generated by publicly funded researchers to develop new medications that are in turn utilized by hospitals and physicians in the treatment of patients.

Diabetes Research Investment in the United States

When attempting to evaluate the economic impact of public investment, one should be careful to delineate how the analysis should be conducted. From whose perspective should the analysis be conducted; who has standing? A global perspective would include all the benefits and costs to everyone, including those outside the United States. More

narrower perspectives might include the costs and benefits to U.S. society, Congress, the NIH, the health care industry, or the patient. This economic evaluation of diabetes research is limited to the perspective to the U.S. Congress and by extension U.S. society. Since Congress must weigh the annual appropriations to NIH based on its anticipated benefit to the American taxpayer, this analysis also only counts as benefits the increases in productivity to U.S. society at large, and as costs, the contributions of Congress to the NIH budget. It should be noted that Congress might not view their annual appropriations to NIH as costs but as investments in the health of Americans, i.e. a benefit. Certainly, the advocates lobbying for increased medical research characterize the annual appropriation process as an opportunity to distribute benefits. For the purpose of this analysis, investments in research are viewed as costs.

On one hand, U.S. society pays the taxes that support both government R&D and public insurance. On the other hand, society receives benefits from the increased productivity of people with diabetes. Therefore, taxes which support the existence of publicly-funded R&D and public insurance, flow back to society in the form of increased productivity. Despite the large distance from the laboratory bench to society, one can begin to see how it is possible to monetize the benefits to society from government-supported R&D.

Costs of Research: NIH Research and Research Training Activities

NIH, primarily through the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), supports research, research training and health education dissemination throughout the United States and abroad. While the greatest share of research related to

diabetes is supported by NIDDK, other institutes of NIH also support diabetes-related research, especially as it impacts other areas of research, such as vision research, neurological or cardiovascular conditions, and even mental health. All of these costs are considered as relevant for this study, since all of these activities can potentially add to the body of knowledge needed to improve the health of people with diabetes. For example, in the training of future researchers, these trainees do participate in actual research and publish their results in scientific journals. In the course of developing programs to disseminate information about how to treat or prevent diabetes, researchers may gain insight into the social or environmental factors that affect the ability of people with diabetes to adopt new practices or modify old practices. These findings may be fed back into the scientific discussions leading to new and improved practices later on.

In many ways, clinical trials are the final (or in some cases, near-final) stop in a long, winding road toward improving health. Much research had been conducted prior to the initiation of clinical trials that provided the foundation--research commonly referred to as basic research. A clinical trial is an opportunity to test one or more hypotheses about possible interventions in the management of human disease. In order to generate the hypotheses, years of basic research are needed to develop and refine experimental models of how disease manifests itself and progresses in the human body. Without this body of knowledge, clinical trials would essentially be shots in the dark. With this earlier research, clinical researchers benefit from a road map and compass. Taken from a different perspective, clinical trials are the logical conclusion (or next step) in the process of generating and applying new knowledge.

Thus, while it is certainly appropriate to include the costs of the clinical trials in question, it is just as appropriate to include the background basic research that led to the questions answered in the clinical trial. Rather than be selective in the choice of which basic research studies led to these clinical trials, an expansive view of the diabetes research portfolio has been taken. The rationale is that basic research does not flow in simple lines, with one research activity leading to another and so on until the clinical trial. Rather, over time we see multiple feedbacks with researchers absorbing and borrowing ideas from many others in their search for clues enabling them to understand how the body works. To determine the lineage of one clinical trial would be a long and ultimately unsatisfying exercise and beyond the scope of this study.

Instead, it is better to consider the entire portfolio of what is considered to be diabetes research at NIH. Indeed, with this somewhat arbitrary criterion, some research that benefited the thinking of diabetes research was undoubtedly omitted. Furthermore, research that did not lead to the clinical trials in question has been included. But when viewed as a portfolio as it is by NIH scientific administrators, the body of research supported by NIH is designed to advance the overall field of diabetes research. Some studies will naturally move forward the field more than others. It is difficult, if not impossible, to predict in advance, or even after the research is completed, which studies will move the field significantly forward. Thus, the entire portfolio of diabetes research should be taken as a whole, rather than parsing out particular studies.

A second question is how to calculate what should be included in the portfolio of diabetes research. NIH program directors oversee a collection of grants much like an investment manager oversees a collection of stocks. These portfolios are arranged thematically and are designed to move the field in a particular direction, usually to exploit and extend one or more particularly promising scientific opportunities. The program director has some discretion as to which activities to fund, but is largely directed by the ratings provided by the study sections. The expertise of the program director is most necessary in determining which studies on the cusp of the payline should be funded and which cannot be funded.

For this research, data for the cost-of-research component from Fiscal Years 1975 to 2000 came from the budget records of National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which regularly reports to Congress on the total NIH investment and impact of diabetes research. As mentioned previously, the U.S. Congress has, since 1975, placed increased scrutiny on NIH-funded diabetes research. Since that time, NIH has sought to delineate which part of their budget appropriations has been devoted to diabetes research. Because of this regular reporting requirement, the NIDDK has developed a fairly consistent manner for identifying research activities with primary focus on diabetes. This consistency, based on the professional judgement of subject area experts within NIDDK, is important since much of the basic research that leads to new understanding of cellular mechanisms governing diabetes or glucose intolerance may also be relevant to other diseases, and thus may be assessed accordingly in other accounting exercises. Given that diabetes often leads to other complications, including

cardiovascular diseases, only those research activities directly related to diabetes or with some connection to diabetes are included. A general rule is that if the research is contained within certain diabetes-related portfolios, then it should be considered a diabetes research activity. Implicit in this rule is that scientist-administrators have a limited budget and a mandate to advance the field of diabetes research. If they feel that a research proposal is important enough to be funded, it must rightfully be considered a diabetes research activity. Thus, while there may be a few type 1 and type 2 errors in accounting for diabetes-related research, by and large, the figures given are reasonable approximations of the amount of diabetes research supported by NIH. However flawed, these are the best estimates available and are thus used in this analysis.

NIH provided separate figures for NIDDK's diabetes research and the trans-NIH diabetes research investment; the latter figure includes all diabetes-related research supported by other NIH institutes and is the figure used in this analysis. All budget figures were given by NIDDK in current dollars. For example, the NIH investment in diabetes research in 1975 was $39.1 million (in 1975 dollars). By 2000, the investment in diabetes had risen to $525.1 million in current 2000 dollars. For comparison purposes, these figures were converted to 1975 dollars using price indices provided by the Bureau of Economic Analysis, U.S. Department of Commerce. Thus, the entire investment in diabetes research from 1975-2000 (undiscounted) is valued at $2.87 billion in 1975 dollars. See Table A below. Again, it should be emphasized that the results of research investments during a time period are normally not realized until years or even decades later. Thus, some of the research begun in the late 1980's or early 1990's, while valuable to other

researchers, will not make a substantive impact on the health status of people with diabetes for some years to come.

Table 2-A: NIH Diabetes Research Investment

Fiscal Year	Trans-NIH (current dollars)	Trans-NIH (1975 dollars)
1975	$39,100,000	$ 39,100,000
1976	$42,700,000	$ 40,408,534
1977	$81,500,000	$ 72,466,570
1978	$108,400,000	$ 89,969,977
1979	$125,900,000	$ 96,455,062
1980	$134,200,000	$ 94,179,979
1981	$147,800,000	$ 94,860,253
1982	$148,400,000	$ 89,667,200
1983	$165,200,000	$ 96,006,911
1984	$177,900,000	$ 99,682,769
1985	$188,900,000	$ 102,614,561
1986	$189,100,000	$ 100,513,517
1987	$234,100,000	$ 120,791,738
1988	$240,800,000	$ 120,174,841
1989	$258,800,000	$ 124,411,721
1990	$249,200,000	$ 115,310,091
1991	$261,500,000	$ 116,750,446
1992	$278,400,000	$ 121,345,296
1993	$285,800,000	$ 121,643,530
1994	$293,600,000	$ 122,412,332
1995	$295,100,000	$ 120,416,442
1996	$298,900,000	$ 119,649,670
1997	$319,500,000	$ 125,449,583
1998	$387,200,000	$ 150,160,977
1999	$457,600,000	$ 174,837,530
2000	$525,100,000	$ 200,627,594
TOTAL	**$5,934,700,000**	**$ 2,869,907,125**

Source: NIH National Institute of Diabetes and Digestive and Kidney Diseases Budget Office and Bureau of Economic Analysis, GDP tables: 1940 to 1999

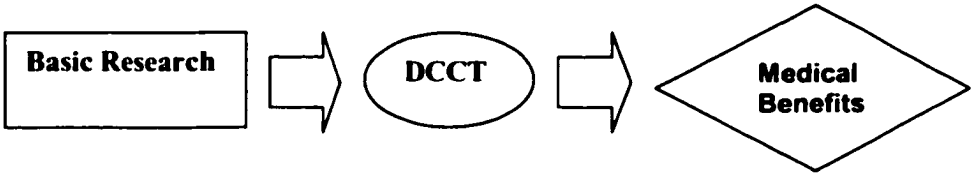
Medical Benefits of Research: The Diabetes Control and Complications Trial (DCCT)

Diabetes is one of the most complicated diseases that scientists have ever studied. Not only are there more than one type of diabetes, type 1 and type 2 being the most common, there are multiple complications that arise from diabetes, such as neuropathy and retinopathy. Finally, prevention of diabetes is likely to be a mixture of both drug interventions and behavioral modifications to keep those susceptible to diabetes in the best health possible. Thus, researchers around the world are pursuing a complex and rich diabetes research agenda, including basic research on topics such as cell signaling and regulation, genetics, autoimmunity, clinical research on obesity and vascular complications, and behavioral studies of diet and nutrition.

Since 1975, when Congress first took a strong interest in diabetes research conducted by the NIH, there has been an intensive research agenda developed to respond to the problem of diabetes in the United States. From 1983 to 1993, a landmark clinical study was undertaken by NIH, known as the Diabetes Control and Complications Trial, which encapsulated much of the previous research on diabetes. In general, clinical studies such as the DCCT are important for translating developments in basic and clinical research into directly applicable medical benefits. The clinical trial tests a specific hypothesis (or set of closely related hypotheses) in a controlled environment, involving a large number of patients randomized into a control and treatment group. In essence, the clinical trials take the result of the years of previously conducted research and turns them into treatment protocols to be evaluated by clinicians. In the case of diabetes, clinical

investigators were able to evaluate theories regarding the control of diabetes and its complications in a trial large enough to measure and evaluate the benefits of the new, intensive treatment. The DCCT showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of eye, kidney, and nerve diseases caused by diabetes.[7]

Figure 2-A: Continuum of Diabetes Research



This study utilizes the medical benefits that were determined as a result of the DCCT and other related clinical trials and derives the economic impact of those studies. Because of the landmark nature of these trials and the comprehensive nature of the results, the presumption is that a measurement of these economic impacts represents the overall benefits of diabetes research since 1975.

The DCCT compared conventional treatment to intensive treatment in patients with type 1 diabetes. The trial demonstrated that a regimen of intensive therapy aimed at maintaining near-normal blood glucose values markedly reduced the risk of development of type 1 diabetes when compared to a conventional treatment regimen.

The central biological premise for the DCCT was the glucose hypothesis, which postulated that the risk of complications was directly related to the degree of glycemia, and that a prolonged history of hyperglycemia was responsible for the development of

[7] http://www.niddk.nih.gov/health/diabetes/pubs/dcct1/dcct.htm.

complications, such as neuropathy, nephropathy, retinopathy and cardiovascular conditions. However, it was not possible to test this hypothesis directly, because of the inability to control exactly the level of glucose in the blood. Thus, patients could not be assigned specific blood glucose levels and expected to maintain that level.

Instead, the DCCT randomly assigned type 1 diabetes patients to the two treatment standards, intensive and conventional, and watched for the development of complications. Those using intensive therapy monitored their blood glucose levels more closely than those using conventional therapy. This enabled the person using the intensive therapy, with the aid of his or her physician, to more closely achieve normal levels of glycemia. The intensive therapy group was able to maintain an average 7.2% glycated hemoglobin A_{1C} (HbA_{1C}), compared to 10% HbA_{1C} for the conventional group. A person without diabetes has an average 6% HbA_{1C}. The lower average HbA_{1C} resulted in an at least 50% decrease in the proportional hazard rate for complications. In other words, they dramatically reduced, but did not eliminate, the likelihood of developing complications, delaying the onset by a number of years. This in turn led to increased lifespan and higher quality of life for those people with type 1 diabetes. The DCCT failed to find a significant correlation between control of HbA_{1C} and the rate of heart disease, although some evidence of a relationship did exist. Researchers associated with the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and the United Kingdom Prospective Diabetes Study later applied this same hypothesis to patients with type 2 diabetes and reached similarly promising results.[8]

[8] Klein R. et al. "Wisconsin Epidemiologic Study of Diabetic Retinopathy." *Arch Ophthalmol* 107: 244-249, 1989.

A second question the DCCT focused on was the effect of intensive therapy on those who utilized intensive therapy soon after diagnosis of diabetes (greater than one year, but less than five years and before the appearance of complications, referred to as primary prevention) versus after a period of years (one to 15 years after diagnosis, but *after* minor complications had begun to appear—secondary prevention). The DCCT demonstrated that the maximum benefits were found in those people who had recently been diagnosed with diabetes, not only for the increased exposure to the intensive therapy and thus less time spent in a harmful hyperglycemic condition, but also for adherence reasons. Patients who shifted from conventional therapy had poorer compliance than patients who were initially trained in intensive therapy.

The DCCT and WESDR represented the culmination of twenty-five or more years of diabetes research. As a result of these trials, people with diabetes and their physicians know with certainty that by more aggressively managing their disease, they can improve their quality of life and delay the onset of complications. Yet, because no new technologies, i.e. drugs or devices, were introduced during the trials, there was no significant involvement of the for-profit sector. Indeed, the products of these trials were pure public goods, in that the results are nonrivalrous and nonexclusive. The trials represent an advance based primarily on the efforts of the NIH and other public sector biomedical research support organizations.

This is not to deny the importance of new drugs and devices to the management of diabetes. However, these new drugs and devices can be incorporated into either form of

therapy and does not make possible either intensive or conventional therapy. Indeed, it is anticipated that new drugs and devices, particularly those devices which measure blood glucose, will enable people with diabetes to monitor and treat their condition more often and more comfortably in the future, thus enhancing compliance to the intensive regimen.

Because the DCCT and WESDR have only recently been completed, and because of the comparatively burdensome nature of intensive therapy from the patient perspective, intensive therapy has not been universally adopted by the diabetes community and indeed must be studied further before full adoption can be expected. Thus, the benefits of this treatment standard must be projected into the future and universal adoption is not assumed.

Understanding the Medical Impact of the DCCT: While the DCCT and WESDR were able to provide a tremendous amount of information on the health and well being of individuals enrolled in the trial, it is not immediately obvious how the results will translate when applied to the general population of those with diabetes in the United States. One reason is that the trial was limited to only a few years—long enough to determine the positive benefits to individuals with diabetes, but not over the course of a person's lifetime. In other words, if the new method of treatment is applied throughout the lifetime of an individual with diabetes, what can we expect to be the outcome? How much better is the new treatment than the old one?

In order to understand better the medical impacts of the DCCT, researchers associated with the trial developed a Monte Carlo/Markov simulation model to estimate the direct costs of intensive therapy on people with type 1 diabetes over the course of their lifetime and the expected benefits in terms of additional years of life lived.[9] The researchers used data collected during the course of the DCCT. The researchers began by creating a hypothetical cohort of 10,000 individuals with type 1 diabetes who met the criteria of the DCCT. Note that the actual DCCT admitted 1,441 people with diabetes; admission criteria were such that potentially only about 17% of 700,000 people with type 1 diabetes (120,000 people) in 1993 in the United States would have been eligible for the trial.

The hypothetical cohort was created with the characteristics of the approximately 120,000 people with type 1 diabetes eligible for the trial, based on survey data. This included information regarding race and ethnicity, age at onset of disease, and other pertinent characteristics. By using data gathered from the DCCT, the researchers were able to calculate with some degree of reliability the risk or proportional hazard rate of developing complications as a result of diabetes. See Box 1 for additional details. Different hazard rates for acquiring the same complications were applied depending on which treatment regimen was in use. By applying first one treatment standard, then the other, the cohort was then used to model the course of the person's disease over his or her expected lifetime. Furthermore, by modeling the course of the disease, the simulation model was also able to calculate the expected cost of treatment of the disease, based on the type of treatment and the complications suffered by the person. These costs (and

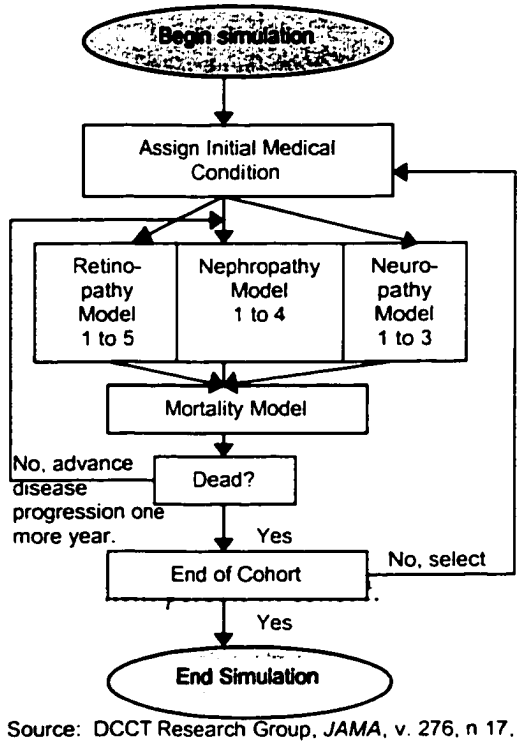
[9] DCCT Research Group, "Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trial," JAMA, v. 276, n. 17, Nov. 6, 1996, p. 1409-1415.

medical benefits) of the hypothetical cohort of 10,000 were then aggregated and validated with data from the DCCT to develop average lifetime costs and benefits for the two treatment standards. Note that cost calculations do not include the additional costs of administering and conducting the DCCT research activity.[10] Details on the calculation of lifetime costs and benefits are given below.

A second hypothetical cohort based on the first cohort was developed by researchers targeting the population of people with type 2 diabetes (Eastman, et al., 1997). The second cohort used the same treatment standards, intensive vs. conventional, and utilized data collected through the WESDR.

To validate the simulation models, treatment outcomes were matched with data collected during the DCCT and the

Figure 2-B: Proportional Hazard Rates
The DCCT provided a wealth of empirical data on the progress of diabetes in individuals over the course of the nine-year study. Over the course of the study, participants experienced a number of different complications due to diabetes, the progress of which was dependent to some degree on which type of treatment they were undertaking. The data on the progress of disease were captured and placed into Weibull models to estimate the development of these complications. Retrospectively, these data were used to develop the models estimating the occurrence of complications such as neuropathy, retinopathy, kidney disease, etc., with the presumption that the incidence of complications in out-years was similar to the years during the course of the nine-year study. The estimates of disease incidence were used in turn to estimate a constant hazard rate for the complications associated with diabetes. Thus, researchers were able to assess the risk of progression from the initial emergence of the complication to end-stage disease and ultimately death. Mortality hazard rates, similar to those found in life tables, were used in the simulation models conditional on age and disease status, particularly those predictive of mortality status. The flow chart below illustrates the simulation model used by the researchers.



Source: DCCT Research Group, *JAMA*, v. 276, n 17, pp. 1410-1411.

[10] Herman, WH, and Eastman, RC, "The Effects of Treatment on the Direct Costs of Diabetes," Diabetes Care, v. 21, Supp. 3, Dec 1998, p. C20.

WESDR. For example, with intensive therapy, the treated population (regardless of the type of diabetes) had on average 7.2% HbA_{1C} in their blood, while with conventional therapy, the average percentage of HbA_{1C} was 10%. As mentioned above, the level of HbA_{1C} in the blood is directly correlated with the rate at which complications and other signs of morbidity and mortality occur in the person with diabetes.

For the major complications, health stages were created and assigned to clinical definitions. For example, retinopathy had five stages, ranging from a normal state to blindness. The probability that a person will advance to a more severe stage of disease in a given year is dependent on the person's current state of health, level of HbA_{1C}, treatment standard (conventional vs. intensive), and treatment duration. For each "year" or cycle, the model randomly assigns each "person" in the cohort a disease state based on the proportional hazard rates, either continuing the person's current disease or advancing the person to the next stage of disease, e.g. from stage one of nephropathy to stage two. Next, the model determines whether the person is alive or dead. To continue the nephropathy example, if a person has advanced to the final stage, i.e. end-stage renal disease, this person does not have long to live. If alive, then the model returns to the last step that advances the disease. The model assumes that each person received the appropriate treatment for her complication, in other words, ignoring the possibility that someone did not receive appropriate health care. If the person is dead, then the model selected the next person in the cohort, until 10,000 person-lives were simulated.

Overall statistics collected for the cohort included number of years spent disease-free, and average number of years alive after diagnosis. Table B1 below details the average number of years free from selected complications by patients managed under the two different therapies. Note that this table applies to only people with diabetes type 1. Table B2 provides similar data generated for people with diabetes type 2. This data show the cumulative incidence expressed as a percentage of cohort. It should be emphasized that once symptoms of complications appear, patients were treated similarly for those complications regardless of the treatment group to which they were assigned. The only difference was in the manifestation of those symptoms.

Table 2-B: Average Number of Years Free From Selected Complications—Type 1 Diabetes

Health State	Conventional	Intensive	Difference*
Background retinopathy	23.7	27.5	3.8
Proliferative retinopathy	39.1	53.9	14.7
Macular edema	44.7	52.9	8.2
Blindness	49.1	56.8	7.7
Microalbuminuria	34.5	43.7	9.2
Albuminuria	49.7	59.5	9.7
End-stage renal disease	55.6	61.3	5.8
Neuropathy	42.3	53.2	10.9
Lower extremity amputation	55.2	60.9	5.6
First significant complication	37.0	52.2	15.3

*Differences may not be exact due to rounding.
Source: DCCT Research Group, "Lifetime Benefits and Costs of Intensive Diabetes Therapy," JAMA, v. 276, n. 17, Nov. 6, 1996, p. 1413.

Table 2-C: Comparison of Outcomes as Percentage of Cohort —Type 2 Diabetes

Health State	Conventional	Intensive	Percent Change
Background retinopathy	79	27	-66
Proliferative retinopathy	19	1	-94
Macular edema	52	15	-71
Blindness	19	5	-72
Microalbuminuria	53	32	-39
Macroproteinuria (Albuminuria)	40	5	-87
End-stage renal disease	17	2	-87
Symptomatic distal polyneuropathy	31	10	-68
Lower extremity amputation	15	5	-67
Cardiovascular disease	39	40	+3

Source: Eastman RC, et al., "Model of Complications of NIDDM," *Diabetes Care*, v. 20, n. 5, May 1997, p. 738.

Other examinations of the data show that the population groups most able to benefit from the newer therapies were the younger people with diabetes, that is, those people whose diabetes were diagnosed earlier in life and were able to implement the newer therapy early on. Those who developed diabetes later in life had fewer years of extended life. Thus, the total benefits associated with these people were lower than in the younger population groups. While some doctors and people with diabetes may question the value of implementing the more rigorous intensive therapy when diabetes is diagnosed late in life, the benefits are most convincing when diabetes is diagnosed much earlier in life. Note however, 80% of the people with diabetes are 45 years of age and above.

Factoring in Quality of Life Measures

A later study by Testa and Simonson demonstrated a secondary short-term set of benefits on quality of life associated with the effect of intensive therapy over conventional therapy.[11] The salient benefit for the purpose of this research was that patients with type 2 diabetes with good glycemic control on a day-to-day basis had demonstrably higher quality of life over patients with glycemic control found in conventional therapy (average HbA_{1C} = 9.3%), as measured in work days lost due to sickness. Patients with good glycemic control (average HbA_{1C} = 7.5%) experienced less absenteeism (9 vs. 20 days per 500 working days) and fewer days in bed or other forms of restricted activity (16.2 vs. 19.3 days per 1000 days). Furthermore, the active therapy arm of the study, i.e. those with good glycemic control, experienced higher retention of employment (97% vs. 85%) and a greater retained productive capacity (99% vs. 87%) compared with the placebo

group. Therefore, patients who chose to use intensive therapy not only delayed the onset of complications—resulting in additional years of life—but also experienced a higher quality of life on a daily basis resulting in less absenteeism.

In a separate article, Testa and Simonson asked study participants to value the improvements in their quality of life. Patients' own rating of their health correlated "modestly but significantly" with all quality of life scales used in the previous study. The authors suggest that health care outcomes such as quality of life be closely monitored and evaluated when considering different treatment modalities. Furthermore reimbursement should be tied to both objective standards, such as maintaining glycemic control, and subjective standards such as quality of life. In other words, patient priorities should also be kept in mind.

Cost of Intensive Treatment vs. Conventional Treatment

The DCCT and WESDR demonstrated the unmonetized medical benefits of intensive treatment over conventional treatment, translating the research advances of the previous quarter century into defined and understandable improvements in people's health. The simulations described above give an estimation of those medical benefits over a person's lifetime. But, implementing the protocols is not free, i.e. there are costs associated with using the newer therapy instead of the older therapy. In order to appreciate the economic impact of diabetes research, one must examine more closely the cost of implementing the new therapy and combine these costs with the underlying investment.

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[11] Testa MA, Simonson DC, "Health Economic Benefits and Quality of Life During Improved Glycemic

Importantly for this research, costs associated with the treatment of each person over the course of his or her "lifetime" were collected and averaged for each treatment group. Summary statistics are given in the table below. Note that only direct medical costs were collected, such as inpatient care costs, outpatient visits, medications, supplies, and laboratory tests. Non-medical costs such as transportation, lodging and family care while debilitated were not included. Nor were gains or losses in work productivity calculated; estimations of changes in work productivity were calculated in the course of this study.

Table 2-D: Lifetime Costs (1994 dollars)

Therapy	Type 1 Diabetes	Type 2 Diabetes
Conventional treatment (10% HbA1C)	$66,076	$62,769
Intensive Treatment (7.2% HbA1C)	$99,822	$76,691
Incremental Lifetime Cost	$33,746	$13,922

Source: DCCT Research Group, "Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trials," JAMA, v. 276, n. 17, 6 November 1996, pp. 1409-15, and Eastman, RC, et al., "Model of Complications of NIDDM," Diabetes Care, v. 20, n. 5, May 1997, pp. 735-744.

While efforts were made to model accurately the U.S. population of people with diabetes type 1 and 2 and to include only those who would optimally benefit from intensive therapy, in the end, it can not be assumed that all doctors will choose to prescribe such a therapy (or to prescribe a therapy exactly as designed by the DCCT researchers and endorsed by the American Diabetes Association), and that all patients will agree to such a therapy. Intensive therapy, despite its demonstrated short- and long-term benefits, does not appeal to all people with diabetes. It is not merely the administration of a different set of drugs, but a lifestyle choice requiring multiple daily injections or an insulin pump

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Control in Patients with Type 2 Diabetes Mellitus," JAMA, v. 280, n. 17, pp. 1490-1496.

plus strict adherence to dietary restrictions. Nonetheless, through testing over a long period of time and by conducting behavioral studies, DCCT researchers were able to gauge patient compliance and the variation in patient's adherence to the clinical trial protocol was integrated into the overall results. As a result, only a fraction of all people with diabetes were included in the simulation models and ultimately in the cost-benefit models described in the following chapters.[12]

Describing the Economic Impact of Diabetes Research

The authors of the studies described above provide useful information regarding the long-term medical benefits of the previous quarter century of research by NIH-funded researchers. In terms of the research and development continuum, the researchers involved in the DCCT and WESDR completed the last or penultimate steps needed to translate basic research advances into protocols that physicians and patients can use.

If one were wishing to compare the two interventions, intensive versus conventional treatment of people with diabetes, cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) would be adequate methodologies. Using a limited form of CEA and CUA, researchers demonstrated how the newer intervention, while not free in terms of direct costs, the newer treatment actually provides considerable savings over the long-term through the delayed onset of complications. The delay in the onset of complications translates into additional years of life gained, which, while not monetized, is generally

[12] Seventeen percent of people diagnosed with diabetes type 1 in any one year and 85% of people diagnosed with diabetes type 2 in any one year were included in Models 1 and 2 respectively.

valued much more highly than the marginal treatment costs. In short, from a patient's perspective, the newer treatment was shown to be economically feasible.

However, these analyses stops short of determining whether or not the investment in diabetes research was worthwhile from a societal perspective. The objectives of this study are to evaluate the investment by Congress in diabetes research from a societal perspective. To do so, one must consider not only the simple cost of the research investment but also the costs associated with using the new treatments. The costs of the two types of treatments, as well as the benefits of intensive treatment in terms of number of additional years of life lived and additional days of work per year, were estimated by the researchers in the studies described above. However, by not factoring in research costs into the equation, the researchers stopped short of demonstrating the value of the economic investment by society in diabetes research.

Through the simulations detailed above, we learned that intensive therapy on average costs more than conventional therapy, but that people who used this therapy lived longer and had a higher quality of life. This comparison is extremely useful in that it allows one to examine independently the benefits of diabetes research without the potentially confounding effects of changes in the overall health care structure in the United States. As well, the impacts of new technological developments supported purely by the pharmaceutical and drug device companies will be mitigated, as these new technologies

are integrated into both treatment regimes, and what is being evaluated are the modes of their application.

Chapters 3 and 4 lay the conceptual foundations for measuring the economic and social returns of scientific research. Then, in Chapters 5 and 6, using the simulation models to "model" how research translates into benefits, is a comparison of the incremental benefits of these two types of treatments to the cost of the research that led to the development of intensive therapy. In doing so, one can begin to appreciate the benefits of the previous 25 years of Federally-funded diabetes research.

Chapter 3: Measuring Economic Returns to Research

This is an introduction to some of the literature of relevance to the topic of measuring costs and benefits of diabetes research. It is divided into three primary sections: research as a public good and evaluating the returns of scientific research; the conceptual underpinnings of cost-benefit analysis; and finally, the economics of diabetes. A table providing a complete literature review is contained in Appendix B.

Research as a Public Good

Among the major tenets of the modern Federal research system is the idea that basic research is the prime driver of U.S. science and technology policy and by extension U.S. economic growth. Basic research is what provides the advances that sustain the pace of invention and innovation in the United States. However, benefits that accrue from basic research are far removed from the initial investments. Thus, if it were left to the private capital markets and private philanthropy, the country would routinely underinvest in research.

In the years since World War II, the United States has invested great amounts in our research enterprise, funding through national institutions such as the National Science Foundation and the National Institutes of Health, as well as the Energy and Defense Departments. A significant amount of these funds have found its way to universities and medical schools in the U.S. which are now the major sources of new ideas and new scientific knowledge.

The desired output of these investments is not principally economic returns; generation of economic returns is considered to be the role of private industry. Rather, the goal of public investment in scientific research is to generate new knowledge, which would later be applied to the development of new devices, drugs or inventions that would eventually add to the country's economic development.

In our market-oriented system, the United States has seen enormous economic progress. We are now the largest economic force in the world, far outpacing our nearest rivals. That said, a purely market-based system has its strengths and weaknesses. Among those weaknesses are acknowledged market failures where the government has stepped in to correct deficiencies in the market. Markets cannot be expected to function well under all conditions, particularly in the absence of perfect information, and the existence of externalities, natural monopolies and public subsidies. One important example is public goods.

Public goods are goods enjoyed by everyone, such as homeland security, public health, parks and streetlights. The goods are nonrival in consumption, meaning that more than one person can enjoy the good without impinging on another's ability to enjoy the good. Also, public goods are nonexclusive—it is difficult, if not impossible as in the case of homeland security and national defense, to prevent others from enjoying the good, a phenomenon often referred to as free-ridership. Note that some public goods, such as parks, zoos, and roads, it may be possible to restrict the goods to fee-paying customers, however, in those cases, the marginal costs of adding another customer are zero up to the capacity of the park or other public good.

In the case of public goods, if it were up to the marketplace, public goods would be underallocated or in the case of scientific research, underinvested. The reason for this underallocation is that there would be incentives to individuals to understate his or her preferences and thus avoid paying for the goods, or alternatively, may genuinely have a lower demand for the good than the market can bear. For example, Company A would decline to invest in the basic research necessary to develop new products if the company has reason to believe that a rival company, Company B, would do the same. Since much of scientific knowledge is nonexclusive and nonrivalrous, a certain portion of the benefits of that investment would accrue to Company A. Furthermore, Company B, having invested in the research, has incentives to keep private the results of this research, which could have been shared widely with Company A with little to no marginal cost. Alternatively, both Company A and B may each feel that their willingness to pay for the new knowledge is less than the marginal costs of the investment, and thus would choose

not to invest in the research. However, if summed together, their marginal benefits may outweigh the marginal costs of investments. In the absence of a market mechanism to reveal individual preferences, a third party, such as government, must step in to ensure that there is an optimal allocation of resources to the scientific research enterprise. This third party must also ensure that the scientific knowledge generated through this process is made as widely available as possible, in order to ensure that marginal benefits are maximized.

Of course, by allowing a third party to control the investment in scientific research begins to put some distance between the generation of new knowledge and its application, and thus increases the difficulty in measuring the benefits that are derived from the initial input of resources, i.e. the costs. This phenomenon will be examined further in the next section.

Measuring the Return on Investment from Research

The assumption that economic benefits accrue from scientific and technological research has been essential to government science policy since the end of World War Two. Vannevar Bush, in his landmark 1945 report, "Science--The Endless Frontier" postulated a linear model, now mostly set aside, that showed a simple progression from basic research through applied research and product development, leading eventually to economic growth and technological progress. This assumption, coupled with the realization that private sources of research funding were not generous enough to meet the needs of the nation, led the policymakers to establish Federally-funded institutions whose

primary purpose was to fund research and development activities in a variety of scientific arenas.

Economic benefits are not the sole or most important result of Federally funded research. Rather, it is but one desired outcome of research. In the Federal Government, the primary purpose of funding research is related instead to the mission of the funding agency. In the case of NIH, it is the furtherance and application of scientific knowledge that leads to improvements in public health. However, policymakers have requested that agencies quantify their accomplishments or planned activities to the extent possible, in terms understandable to the general public.

Studies by Mansfield, Link, Terleckyj, Griliches and others showed positive correlation between R&D investment and economic growth and productivity, focusing primarily on private sector investment, but they did not show direct causality. For example, in 1992, Griliches summarized the findings of this literature:

> *In spite of [many] difficulties, there has been a significant number of well done studies all pointing in the same direction: R&D spillovers are present, their magnitude may be quite large, and social rates of return remain significantly above private rates.*[13]

[13] Griliches, Zvi, "The Search for R&D Spillovers," *Scandinavian Journal of Economics*, 1992, v. 94, p. 43.

Economic studies of Federal R&D have been less conclusive, and thus less useful (Terleckyj, 1974 and 1977), showing little or no positive economic effects due to government R&D. The authors reasoned that this was due to the more complex nature of the relationship between government R&D and commercial products. The distance is greater, the benefits more dispersed, and even the inputs are murky.

Private sector studies have shown conclusively that productivity increases are directly due to the amount of R&D invested by the company. In a study of 33 industries between 1948 and 1966, Terleckyj (1977) estimated a 28 percent productivity return on private R&D investment. Zvi Griliches in a 1975 study of 883 companies in all types of industries found a 17 percent rate of return. In general, the economic studies to date show that if anything, there is an underinvestment in research, as opposed to an overinvestment. However, these studies do not show how much more we can profitably invest research.

In a 1997 paper for the Federal Reserve Board, Charles Jones and John C. Williams notes that the social rate of return to R&D range from 30% to 100%, again supporting the notion that not enough is invested in privately funded research and development. In their paper linking growth theory to empirical results, the authors demonstrate that the estimates in the literature represent lower bounds on the social rate of return to R&D, confirming earlier findings. Using an estimate of 30% for social returns and 7% found in

the private rate of return, optimal R&D spending as a share of GDP, they claim, is more than four times larger than actual spending.[14]

Other measures of scientific research: Different econometric approaches to measure research output have been used with varying results. Most of the analytic approaches used to measure Federal R&D programs have been drawn from the private sector. These include return-on-investment, which focus principally on monetary outputs and ignore other intangible benefits to society. Also, most of the landmark studies have looked at large sectors, such as aviation, agriculture and health research, or all Federal R&D as a whole, rather than case studies. Note that there are a number of other methods used to quantify returns from R&D investment, including bibliometric studies, and citation and patent analyses. These are not discussed since they are not directly related to the subject of this study.

In 1986, the now-defunct Congressional Office of Technology Assessment published a report on a number of well-known methods for quantifying economic returns to research: macroeconomic production functions; return on investment; cost-benefit analysis; rate of return; business opportunity analysis; consumer and producer surplus. This report provided a concise summary of the relevant studies to date, and gave an analysis of their usefulness in the Federal context. The report also emphasized that the primary purpose behind Federal R&D is not to produce an economic return. Rather, it is to encourage

[14] Jones, Charles I. and John C. Williams, "Measuring the Social Return to R&D," Finance and Economics Discussion Series, Federal Reserve Board, 1997-12.

research in areas of national interest, but which the private sector is not likely to support.[15]

The report found that most measurement methods are better suited to private business circumstances, particularly at the development stages of products when the expected risks and benefits are well characterized, i.e. there is a short, foreseeable distance between investment and commercialized product. In contrast, most Federal R&D can be characterized as public goods, and thus, by their very nature, are difficult to capture in economic terms. Also, these analyses tend to look at average output over a whole range of investments, e.g., econometric studies at the national level, rather than the advantages given by incremental increases of R&D funding. Finally, no reliable formula exists to estimate a return because each investment gives a unique return that is impossible to predict.

Previous Attempts to Evaluate NIH Research

Congressional interest in quantifying accomplishments has been especially true of NIH, which has been asked at various times to justify its decision-making process. With health care taking up such a large portion of the overall gross domestic product ($1.2 trillion or 13.0 percent of the gross national product in 1999[16]) and health R&D being 42.4 percent of all non-defense Federal R&D[17], the question of whether and how much economic

[15] *Research Funding as an Investment: Can We Measure the Returns? A Technical Memorandum*, (Washington, D.C.: U.S. Congress, Office of Technology Assessment, OTA-TM-SET-35, April 1986).
[16] Source: Health Care Financing Administration, Office of the Actuary, "Highlights—1999 National Health Expenditures"
[17] Source: National Science Foundation, *Science & Engineering Indicators–2000*, Appendix Table 2-23.

benefit is derived from biomedical research has occurred to policymakers before. Of course, measuring health R&D in economic terms is problematic given that one must put a value on human life and productivity. Nonetheless, despite the misgivings of economists and others, agencies have been directed by Congress to provide some estimates of the cost of illness.

The first attempts to estimate the cost of disease came from Selma Mushkin (1979). Her model included both direct costs, such as hospital stays, nursing home care, physicians' services, and indirect costs, such as lost work productivity and premature death, from 1900 to 1975. During those years, the national mortality rate fell dramatically, and people generally lived longer. Mushkin attempted to model the contribution of various public health measures to this phenomenon. In order to estimate the contribution of better sanitation, improved nutrition and safer working conditions on mortality rates, Mushkin used regression analyses, with other variables to measure access to health care, economic, environmental, and social factors. Due to the difficulty of determining adequate indicators of R&D advances, she was forced to assign the residual values in her model to technological advances, i.e. any reduction to mortality not accounted for by the other variables was attributed to R&D contributions. This methodology is similar to those employed in macroeconomic studies mentioned above. Mushkin concluded that biomedical research accounted for 20-30 percent of the reduction in mortality from 1930 to 1975. She also estimated that an incremental one-percent increase in biomedical research funding led to a lowered mortality rate of 0.05 percent. Similarly, 39 percent of the reduction in lost workdays was attributable to biomedical R&D. Finally, Mushkin

found a return of $145-167 billion on an investment of only $30 billion or an internal rate of return of 46 percent.[18]

This analysis brings out some of the difficulties in estimating the economic benefits for biomedical research. Since there are often no direct lines of causality from research activity to measurable improvements in health, and because there are many other contributors to health overall, the contributions of research must often be deductively reasoned by elimination of other possible factors. This is a problem common to other types of scientific and technological activity, in that research is treated as a black box, with little or no attempt to parse out the specific factors responsible for advances. Thus, it is impossible to assign improvements to investment in Federal vs. private sector research, domestic vs. foreign research, or even basic vs. applied research.

More central to this particular research, Burton Weisbrod in 1971 published a cost-benefit case study of medical research using poliomyelitis.[19] Because of the nature of the disease—polio, an infectious disease—and because there was a vaccine developed that successfully prevented contraction of the disease, the analysis had some significant differences from this study. Nonetheless, some important parallels can be seen. As in this research, a time stream of research expenditures related to polio was determined; a stream of benefits resulting from the application of the vaccine; and finally associated

[18] Mushkin used estimates of $76,000 per premature death averted and $12,250 for each work-year gained when illness averted. Mushkin, Selma, *Biomedical Research: Costs and Benefits*, (Ballinger Publishing, Cambridge: 1979).

[19] Also found in *Economics and Medical Research*, Weisbrod, BA, AEI Studies, American Enterprise Institute, Washington, D.C., 1983.

costs of applying the vaccine. These figures were used to develop an internal rate of return on the research expenditures.

In calculating the stream of research expenditures, an independent organization, Science Information Exchange, was used to determine which research was relevant to polio. Significant assumptions were made and stated. Benefits per case of polio prevented were also calculated using estimates of productivity loss due to mortality, morbidity, treatment and rehabilitation of polio victims. Treatment costs included cost of application of the vaccine not only to those with a high likelihood of being infected, but also other non-high-risk groups. The internal rate of return is estimated to be between 11 and 12 percent, depending on the time horizon selected. Note that this rate of return only applies to the United States, and is not applied to benefits external to the United States, which would perhaps raise the rate of return.

Important comparisons to this research on the economic benefits of diabetes research can be seen. Polio research differs significantly from the current state of diabetes research. One cannot yet calculate the value of preventing or curing the disease since neither a cure nor a vaccine exists. However, other benefits do exist in that life has been extended and improved for those with diabetes. One can calculate the value of lengthening the life of a person with diabetes and improvements to his or her quality of life. Weisbrod also notes other issues confronted in this research, including the problem of either overstating research expenditures in order to capture research activities not initially directed toward polio research, or underestimating expenditures at the cost of ignoring external benefits.

This is especially true for diabetes research given the complexity of the disease and the complications caused by the disease, which may be viewed as the primary or secondary cause of premature death. Finally, Weisbrod brings up questions regarding the appropriate time horizon. Should benefits be counted for 30, 40, 50 or more years? It would be difficult to estimate when or whether a newer, safer, more effective vaccine would be developed, obviating the present technology, or as is the case in reality, the success of the vaccination program has been so complete as to eliminate polio practically from the world.[20]

Given what is known about the epidemiology of poliomyelitis, and that polio is nearly eliminated from the world, it would be interesting to revisit Weisbrod's analysis and update from a global perspective. Even though a vaccine was developed in the 1950s and introduced in 1957, polio has not yet been completely eradicated from the world and research into polio continues to this day, particularly in studying and developing new vaccines against mutant strains.

Elsewhere in his book, *Economics and Medical Research*, Weisbrod (1983) notes the dearth of economic research on the benefits from biomedical research, despite the increasing amount of expenditures devoted to biomedical research, approximately $3.6 billion in 1982. He also notes the rise or surge in private and governmental programs to provide health insurance and access to medical care, and the effects of those programs.

[20] World Health Organization estimates that polio will be eliminated by 2005 or so. It now only exists in pockets in Africa and South Asia.

The connection between health care and biomedical research, he laments, has not adequately been investigated.

More recently, Congress asked the NIH to do a cost-of-illness (COI) analysis, and to juxtapose their findings against the amount of funding made available for each disease in that year. The Congressional request was found in the Fiscal Year 1995 report of the Senate Appropriations Committee. The specific focus of the committee was on the top 15 causes of death in the country, including diabetes, as defined by the Centers of Disease Control and Prevention. NIH was specifically instructed not to generate new cost estimates, but to rely on previously researched COI studies. See Table 1 in Appendix E for summary of results.

Aware of the potential uses by Congress of the results of this study, the NIH focused much of the report not on the implications of the results, but on the manner in which the individual results were prepared. For example, the NIH indicated that COI estimates provide "order of magnitude indicators of the economic burdens" of various diseases, emphasizing that the estimates themselves were not very accurate, but merely indicated the scope of the cost of disease. They emphasized also the variability of methods used to generate data, both in capturing indirect and direct costs, and how in some instances, one may see double counting, particularly when one disease was merely a contributing factor in death, as diabetes often is. The reliance on previously published data also limited the NIH; those diseases that did not have cost estimates were not represented.

Finally, as was noted by Dr. Harold Varmus, Director of NIH, in testimony before the Senate, while COI studies may be useful in assessing the magnitude of disease and its impact on society, their usefulness in planning prospectively for NIH is limited. Unlike food stamps or Medicare, scientific opportunity does not often follow the lines of economic burden or even epidemiology. Research findings in one area of science, e.g. cancer, may inform scientists working on other diseases, such as diabetes or arthritis. To base funding decisions solely on demographic data, rather than on what opportunities lay ahead, would be detrimental to scientific progress.

Economics of Diabetes

Burden of Illness: Several studies of the burden of diabetes, both domestically and globally, have been done. The most comprehensive of these studies has been done by the American Diabetes Association (ADA). The ADA studies have made estimates of the "economic consequences" of diabetes in a yearlong period; the most recent of which was 1997. In these studies, they have looked at both direct medical care expenditures, ranging from hospital stays, drugs and nursing home costs, to indirect costs, such as lost productivity due to work days missed or premature death. Typically, they have used data from a variety of sources, such as the National Center for Health Statistics and the Census Bureau, which themselves are compilations from a variety of years. To standardize the data, they extrapolated the data when necessary to 1997. Estimates of diabetes research was not included in the overall cost of diabetes ($98 billion in 1997), but if they were, they would be less than 0.5% of the overall burden.

Other burden of disease studies focusing on diabetes have come up with varying results. The 1995 NIH COI study gave a total estimated economic cost of diabetes to be $137.7 billion in 1992. This figure included $91.1 billion in direct costs and an additional $46.6 billion in indirect costs. These estimates were significantly higher than those found in the ADA study. The NIH study criticizes the ADA study for relying on data sources that listed diabetes as a diagnosis. According to the authors, these survey instruments routinely and severely underestimate health care utilization by patients with diabetes and mortality of person with diabetes. Instead, the NIH study relies on a second study commissioned by the Diabetes Treatment Centers of America, Inc. (a.k.a. the "Rubin Study") which took the approach of identifying the actual charges to Medicare, Medicare and private sources of insurance in assessing the total direct costs for treating diabetes, using the National Medical Expenditure Survey. The indirect cost estimate in the NIH COI study is the same given in the ADA study.

A study by Bengt Jonsson uses data from the Global Burden of Disease (GBD) compendium authored by Christopher Murray, et al. for the World Health Organization and the World Bank. The GBD survey is a cross-regional study that looked broadly at regions around the world, and using disability-adjusted life years (DALY) estimated the cost-of-illness (both direct and indirect) around the world. Jonsson isolated the data relating to diabetes. The data are very dependent on assumptions made by Murray about the disabilities associated with different diseases, and thus open to reinterpretation. Another significant concern in the study was the use of non-standardized figures to estimate the health care costs in each country, i.e. costs were collected using different

systems and formats. One interesting implication was that while developing countries do not invest at the same level in health care to treat diabetes, they have much greater indirect costs due to lost work productivity of their citizens. This burden of illness is likely to grow over the next few decades as the prevalence of diabetes grows, as the trend indicates.

Frank Vinicor analyzed the burden of diabetes from a public health perspective in an article. In the article, he commented on the growing burden of diabetes around the world due to increased incidence and better and earlier detection. Vinicor makes the case that society should take proactive measures to prevent the disease, rather than treating preventable diseases. Furthermore, these measures should be taken at the societal level, rather than the retail level, where the patient meets the physician expecting treatment of their condition. Through measures should as primary prevention, early detection, and good access to health care, we can reduce the overall burden of the disease. In a related article, Robert McDonald postulated that managed care organizations also have a role to play in that they can and should invest more in preventive care and integrate the newest findings into their health care guidelines given to physicians.

Chapter 4: Evaluating Social Returns to Research

The objective of any type of economic evaluation, particularly of government programs or policies where society at large is the beneficiary, is to sum all the relevant benefits and subtract all the associated costs of the program or policy. In order to do this, one must place a value on the inputs and outputs. In valuing various policy outcomes, benefits are the sums of the amounts that people are willing to pay to gain services that they see as desirable; costs are the sums of amounts that people are willing to pay to avoid undesirable outcomes. Willingness-to-pay is a basic concept behind cost-benefit analysis that enables us to value in economic terms the outcomes of various policy alternatives. Estimating costs and benefits enables us to estimate changes in social surplus, and thus determine whether a specific program or policy is worthwhile or not.

In the welfare economic framework, the goal is to maximize social surplus, that is the sum of both consumer and producer surplus. At the point where social surplus is maximized, net benefits are also maximized, hence Pareto efficiency. However, in order to know whether or not we have maximized social surplus, both demand and supply curves must be known. In the case of evaluating medical research, the demand curve is

characterized by the demand or willingness to pay for better health through research, and the supply curve is the cost of providing the research necessary to improve health. This situation differs from most other programs to supply public goods in that the distance between the supply and the demand is so great. Furthermore, the demand of good health can be partially met through a number of different mechanisms, which are the focus of other government and private sector programs. These include private and public insurance schemes, the provision of public health functions at the federal, state and local level, and even private charity. The result of all these different streams of activity to improve health serves to confound and make difficult the valuation of benefits due to medical research. Thus, measuring changes to consumer surplus is not a straightforward matter.

In examining most programs, particularly government programs, it is useful to use observed prices in order to value benefits and costs. While we have a variety of data, derived from surveys and economic analyses, that give us an indication of the economic value or "price" of health, we have no single, comprehensive measure of health in economic terms. Where observed prices do not exist, we use some sort of *shadow pricing*. This surrogate measure of what the market or society would be willing to pay is used in valuing health in society.

In matters of health policy, one must place a value on good health in order to evaluate these policy alternatives. Valuing the health of a population and the benefits of different health interventions has been a difficult and contentious topic. While at some level we

understand and appreciate the benefits to society of improved public health—e.g., better sanitation and hygiene, vaccines and immunizations, broader access to health care especially to seniors—we have difficulty in assessing an economic value to those benefits.

By way of example, Bunker, Frazier and Mosteller (1994) estimate the changes in life expectancy due to improved medical care, including prevention and curative services. However, they characterize the changes in terms of additional years or months of life lived, stopping short of placing an economic value on those additional years. While indicative of the positive benefits of medical research, calculations of large-scale nature do not demonstrate definitively the economic returns of medical research.

As described by Cutler and Richardson (1997) "health" is a multiattribute concept and not all of its attributes are well defined. For example, someone who is afflicted by a disease may see not only her physical well being suffer over time, but also her mental well-being and her economic productivity may also decline. Health interventions, such as medications or therapies, may change or improve over time, impacting one set of attributes but not all. A person's access to adequate health care may also change over time, as one's economic or health situation changes. Finally, as in the case of diabetes, one may see a primary affliction lead to many secondary complications, which collectively reduce quality of life.

Cost-Effectiveness Analysis and Cost-Utility Analysis

Two related methods have evolved over the past few decades to evaluate and compare health interventions: cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). Both are methods for summarizing information on the inputs and outcomes of health programs but in a manner that stops short of placing an economic value on the health outcomes of programs or policies. Instead, policy and program analysts who use these methods have limited themselves in their analyses to describing positive or negative outcomes in the form of years of life gained or number of people treated. An example of CEA would be an analysis of a program that treated people for a specific health condition. The CEA would yield a ratio such as cost per person treated or cost per number of lives saved. The CEA normally considers direct costs, e.g. costs of the program, and not indirect costs, such as the time and out-of-pocket costs of enrollees in the program. Furthermore, CEA normally would not include a value or approximation for the quality of the service provided program enrollees. For example, the CEA ratio would not give an indication of how well an enrollee had been served in the course of his or her involvement in the treatment program.

CUA differs from CEA in that the outcome of the analysis is expressed in terms of a ratio measured in standard units such as dollars per QALY or disability-adjusted life-years (DALY). This measure thus combines traditional CEA with the Von Neumann-Morgenstern (VNM) utility theory of 1947, which stated simply that when comparing various alternatives, one should choose the alternative that maximizes utility. VNM-utility is completely general and not tied to any illness, thus VNM-utility allows one to

measure health states regardless of the nature of the illness. However, it does not allow one to express this utility in monetary terms. Nonetheless, the CUA is useful in expressing the outcome of the analysis in standardized terms, such as cost per QALY gained, or cost per standard unit of service. Thus, it has some benefits over normal CEA.

As will be recalled, QALYs are concerned not only with the lengthening of life, but also the quality of the life lengthened. The DALY measure is in a sense a refinement of QALY introduced by Chris Murray in 1993 in a World Bank study. Both measures are useful when comparing health outcomes across diseases, such as cancer, diabetes, or mental illness.

One drawback of this type of measure is that the value of a year of life is independent of the stage of life of a person, e.g. young vs. old. A corollary is that there is no difference in value between a person who is brought from 90% of full health to 100% of full health and a person who is brought up from 20% of full health to 30%, although general opinion may be otherwise. A second drawback is the assumption that a person is risk neutral between the choices of a year of health versus a 50% percent chance of two years of health or zero years. However, CEA and CUA, which uses such non-economic values, are useful for comparing different medical treatment methodologies, where the common standards of effectiveness are the lengthening of life and the improvement of quality of life.

CEA and CUA seem to be the most useful when comparing two or more health programs or interventions against each other. Normally, these two interventions or programs should be mutually exclusive, i.e. one cannot be enrolled in both programs simultaneously. An example would be a comparison of the two types of diabetes therapies, intensive versus conventional. A direct comparison of this sort would appropriately ignore the research investment as sunk costs, and strictly include direct and possibly some indirect costs of the therapies. Thus, one would be able to capture most of the benefits by simply comparing standardized health outcomes, e.g. life-years gained, without delving into controversial issues of willingness-to-pay or valuing human health. At least with this type of analysis, one could determine which of the two interventions, intensive or conventional, is more cost-effective without regard to how those interventions were developed and whether the development process itself was a good investment. More specific to the objectives of this study, one might consider comparing different types of health research, if the outcomes, e.g. additional years of life, were the same. Chapter 5 examines the potential of using CEA and CUA in evaluating diabetes research more closely.

Cost-Effectiveness Analyses of DCCT and WESDR

As part of the analysis of DCCT and WESDR, researchers associated with these clinical trials also performed cost-effectiveness analyses. To aid in the analysis, the researchers constructed simulation models to estimate the lifetime direct costs and medical benefits associated with the new treatment. These simulation models were discussed in Chapter 2. In general, through the simulation models, the researchers found that the

direct costs associated with intensive therapy were significantly higher than conventional therapy, but with a statistically significant increase in the lifespan of individuals. This was true of both type 1 and 2 diabetes. Thus, the primary and long-term health benefits of transitioning from conventional to intensive therapy exist in delaying the onset of complications. The primary costs were related to more comprehensive, and thus expensive, treatment associated with the use of increasingly more sophisticated drugs and labor-intensive therapies. Not accounted for in the analyses were the indirect costs saved due to increased work productivity. Health benefits in the two simulation studies were not monetized, i.e. impacts were characterized as cost per additional years of life lived. In the case of the two studies, researchers came up with a value of $28,661 per year of life gained for people with type 1 diabetes, and $16,002 per QALY gained for people with type 2 diabetes.[21]

Cost-Benefit Analysis

A third approach to evaluating health interventions is cost-benefit analysis (CBA). In CBA, one examines the costs and benefits to society as a whole when considering if a policy or program is of benefit to society. CBA directly compares the costs against the benefits and determines whether the outcome is positive or negative. CBA is useful when exploring issues of allocative efficiency, that is, whether or not resources are being used to their highest value in terms of the goods or services they create. Furthermore,

[21] DCCT Research Group, "Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trial," JAMA, v. 276, n. 17, Nov. 6, 1996, p. 1409-1415 and Eastman, RC, et al., "Model of Complications of NIDDM," Diabetes Care, v. 20, n. 5, May 1997, pp. 735-744. Note, it is unclear from the text how the researchers determined the figure of $28,661 per year of life gained for people with type 2 diabetes.

CBA allows us to compare alternatives against one another, providing information about the relative efficiency of the competing alternatives.

For the purposes of this research, and in many other situations where one is considering competing public policies, we are concerned about the costs and benefits to society as a whole. Thus, we are looking at the issue of social returns to medical research from the perspective of U.S. society, not from particular individuals or from the perspective of the health care industry or the performers of research, i.e. scientists.

Other considerations of perspective include when one should examine these costs and benefits. Should we estimate costs and benefits prospectively (*ex ante*), during the course of the project or policy (*in media res*), or retrospectively, after the project has ended (*ex post*). Each has its own advantages and usefulness to policy makers. *Ex ante* analyses are most useful when one is trying to decide where to put future resources, however, they may suffer in accuracy since these are in essence predictions about future returns. *Ex post* analyses are likely to be the most accurate because the analyst can rely on verified data to make the cost-benefit calculations. However, they may only be able to provide policy makers with lessons learned, rather than specific guidance on future projects. Finally, *in media res* analyses can be used for mid-course corrections, however it is uncommon in practice that one cancels projects due to CBA taken place in the middle of an activity. Combinations of the above type of analyses are also possible and would naturally combine some of the advantages and disadvantages outlined above.

Option-Pricing Approach

An innovative method for analyzing investments in publicly-funded scientific research was earlier outlined by Vonortas and Hertzfeld (1998) and others when examining techniques for justifying various investments, particularly technology investments. They drew comparisons between the role of government R&D managers and individuals investors using stock options. In the case of stock options, investors make a small investment in a stock option, which permits (but does not oblige) the owner of the option to purchase stock at a set prices upon the expiration date agreed to in advance. If the stock has risen in price above the set price, the investor can make a profit, assuming he has exercised the option to purchase. If the price is equal or below the set price, he in essence loses his earlier investment.

Similarly, government R&D managers can choose to make a small investment in an uncertain research project and upon receipt of early results, choose to make additional investments in that line of research. The authors use *ex ante* estimations of net present value and the probability of success to evaluate potential research investments. At NIH, the review panel, which weighs the quality of the ideas and the likelihood of accomplishing the stated goals, plays the role of R&D manager jointly with the program director, who must weigh the cost of the investment against the risks as judged by the panel. Additional mechanisms, such as planning or training grants, encourage the development of and investment in riskier ideas, but imposing lower limits on available funding, in the hopes that a certain percentage of these ideas will pay off and will merit additional funding in future years. Regardless, after the initial research period, additional

information is gathered which allows the investigator, the review panel and the program director to determine whether further research along those lines is warranted. If successful, additional capital is invested; if not successful, then the initial investment is lost, although perhaps not entirely, and further investments are not made. The latter is analogous to a call option that is not exercised.

While stock options are a relatively minor weapon in the investors arsenal, the analogous mechanism for a government R&D manager is arguably a much more potent a weapon. Without investments in relatively risky research as a way of gathering additional information about potentially significant lines of inquiry, NIH and other research agencies would have no way of knowing whether or not they were making worthwhile investments. This technique combined with the constant deferment of research proposals ensures that new ideas are both encouraged and allowed to be refined and explored.

Other Considerations in CBA

While one may argue about the different methods to be used in measuring the costs and benefits, one universal understanding is that we are trying to achieve Pareto efficiency. In the welfare economic framework, Pareto efficiency is defined as the allocation of goods that is most efficient; we can devise no other allocation of goods that can make at least one person better off without making anyone else worse off. The link between Pareto efficiency and CBA is that when comparing competing policy alternatives, a policy has net positive benefits if it is possible to compensate through side payments those who are worsened by a policy alternative without making anyone else worse off.

While one may not actually make those side payments to the individuals made worse off, those payments or transfer are at least theoretically possible. How large those payments should be gets to the issue of willingness-to-pay which is taken up in the next chapter.

Another important consideration when considering CBA is opportunity costs. How much are we sacrificing by placing resources in the currently debated policy or program? How else could those resources be used and will they provide a better social return? In the medical research supported by the Federal government, medical research can be considered a subcomponent of either the overall research budget, or the overall health budget. Thus, Congress must decide how much of the Federal *science* budget to allocate to medical research, or perhaps how much of the Federal *health* budget should be devoted to medical research. CBA of medical research can perhaps assist Congress in making those determinations. However, it should be noted, as it is elsewhere in this research, that economic returns are but one aspect of medical research in which Congress is interested. Other budget allocation criteria are more qualitative in nature, stemming from the widespread interest in addressing society's major health problems and the expressed need for new drugs and therapies. Indeed, economic returns are not even a minor consideration currently when evaluating the social benefits of NIH research. Current focus of evaluation is on scientific progress, training of the next generation of scientists, and progress towards dissemination of results to the public.[22]

[22] *National Institutes of Health Revised Final FY 2002 GPRA Annual Performance Plan and FY 2001 Annual GPRA Annual Performance Report*, U.S. Department of Health and Human Services, February 2002.

To achieve Pareto efficiency as mentioned above, it is necessary to maximize social surplus, the sum of the producer and consumer surpluses. To determine what the producer and consumer surpluses look like, it is necessary to know the supply and demand curves. In CBA, the demand curve helps us determine the extent of society's willingness-to-pay for policy changes, using consumer surplus as the measure. The supply curve and producer surplus help us determine opportunity costs, i.e. the next best use of the resources needed to make a particular product or perform a particular service. When market forces are working adequately, the marginal costs of producing the good matches the price to society, market equilibrium maximizes social surplus, and thus Pareto efficiency is achieved.

CBA is an appropriate method for measuring economic benefits of medical research because it aids us in decision-making as it relates to the allocation of resources. In comparison to CEA and CUA outlined previously, CBA allows one to value the benefits and compare them to the inputs of medical research, namely the investment in research. The benefits, in this case improvement in health, must be directly related to the output of research, which can be difficult in relation to all the other forces that impact health care in the United States. CBA can thus be useful in isolating and examining the economic impacts of medical research.

Placing a Value on Health

The benefits of medical research can be found in the improvement of the health of people suffering from disease or disorders. In order to measure the economic benefits of

medical research, one must place a value on those benefits, i.e. the improvement in health. A valuation of health can be measured in two ways. One takes the approach of human capital, measuring the discounted value of the potential output of a person over time. The second takes the approach of health capital, the discounted value of the utility one receives from health over time. In this research, both methods are used in the valuation of the economic benefits of diabetes research.

In human capital methodology, economic value is estimated for a person who is able to work and be economically productive. Examples of measures of indirect cost, then, include lost workdays due to worker absenteeism (not only of patient, but also of caregiver, e.g. parent of sick child), and lost productivity due to impaired inability or incapacity to work. Thus, little intrinsic value is placed on health improvements of those outside the workforce, such as the retired or children. Furthermore, values placed on an individual's contributions to the economy vary widely over the course of a single career. Thus, a wage earner at the beginning of his or her career is likely to make a fraction of his earnings near the end of that career.

Human capital uses as its guiding principle the economic worth of a person over time. This worth can be most easily measured by estimating the net present value or salary of a person. For example, a person in good health can be expected to earn a certain amount, X, over the course of his or her career. Society has valued the worth of that individual at a given level using as a surrogate the economic value of his or her productivity. The average of these individual values of productivity will give an estimate of the economic

value of any one person. If the person suffers from a disease such as diabetes such that he or she must take time from work for recuperation or rehabilitation, then his or her lifetime salary will be $X - X_1$, where X_1 is the amount of salary lost due to absences or early retirement. Calculation of X_1 is a relatively simple matter by estimating the number of lost days or years and multiplying by the average salary per year or day. This method enjoys a large degree of flexibility in calculating the willingness to pay for improved health over varying periods of time, e.g. from days to years.

With human capital methodology, we experience a distance between the patient and society's valuation of health outcomes, a distance that mirrors that between worker and society's value of his or her contribution to the economy. Therefore, from a societal perspective, it may seem reasonable to rely on average wage earnings to determine the value of additional life-years gained. On the other hand, measurement of human capital negates the intrinsic value of a person and his or her quality of life. As a result, if a person is not a wage earner, e.g. a stay-at-home mother or father, a retiree, or a student, his or her value to society is completely ignored.

A more cumbersome but perhaps more accurate approach is health capital, i.e. the valuation of a year's good health. A person's health capital is the product of the number of quality adjusted life years (QALY), and the value of those years in dollars, discounted to present value. Pioneered by Richard Zeckhauser in 1976, QALYs refer to a measure placed on the quality of life enjoyed by a person over the course of year. Perfect health is given a measure of one, while death is equivalent to zero. Imperfect health is somewhere

in between. QALY weights are based on individual preferences over health states, as revealed in surveys, rating scales and other instruments. Because the determination of QALY weights involve much speculation (i.e. one must "imagine" life with and without a specific disease or disability) revealed preferences vary greatly from person to person and depending on the methodology. Sources of these weights can come from patients, the general public and medical experts who have experience working with the affected populations and thus are knowledgeable about their limitations and capabilities. Using an approach comparing self-reported health of people with and without particular disabilities, Cutler and Richardson (1997) came up with their own estimate of the QALY weights and studied how these have varied over time. For diabetes, the weight is 0.65, thus in their estimation, a person with diabetes has a quality of life that is 65 percent of a person in perfect health. In their research, this weight has been fairly constant over time.

An important consideration is the interaction between diseases and their affect on weighting. For example, one should not assume that if a person has both heart disease (QALY weight of 0.71) and diabetes (0.65) that his or her quality of life is weighted at 0.36 (the linear combination of the two weights). Rather, it should be somewhat higher, although no higher than 0.65, due to the similarities in the implications on quality of life that both diseases have. Diabetes is particularly problematic in this sense, since it is associated strongly with other diseases, such as cardiovascular disease, neuropathy, renal disease, and retinopathy.

Recalling the studies of Testa and Simonson described earlier in Chapter 2, the results of their studies would ideally be translated into refinements of the weighting given to QALY ratings. Cutler and Richardson conclude that an appropriate QALY weighting for diabetes is 0.65, with no distinction between different types of diabetes or what sort of treatment is undertaken. However, as demonstrated above, people with diabetes who have chosen one of the two types of interventions or therapies have experienced significantly different levels of quality of life. Thus, it would seem reasonable to assign these two sets of people with different QALY weightings. However, without more expert evaluations, for the purposes of this research, these differences are regrettably ignored.

With accepted QALY weights, one can then begin to combine these with estimates of the value of health. One set of methods estimates the value for health and health consequences based on willingness to pay for reductions on risk, and on premiums paid to those who willingly take on riskier occupations. Wage-risk tradeoffs are a major way of valuing health risks. A popular approach is to compare wage differentials to job characteristics that reflect on a job's inherent risks, such as working with chemicals or other hazardous situations. Using these differentials, economists have estimated the wage premium workers receive for risk. In a number of studies, Kip Viscusi has found that on average the rate of tradeoff varies from $3 million to $7 million per statistical life in 1990 prices. (Viscusi 1992 and 1993). This figure is irrespective of mode of death or stage of life in which death occurs. Furthermore, these estimations are applicable only in the United States. In other nations, particularly in the developing world, wage-risk tradeoffs will vary tremendously.

Surveys have also been used to determine wage-risk tradeoffs or willingness-to-pay. Surveys of workers in hazardous and non-hazardous positions, asking them to value different risk levels to determine individual utility functions, have yielded a wider variety of estimations of the value of life, from $100,000 to over $15 million, as summarized by Viscusi (1993) again in 1990 figures. A variation of these types of estimates is to use wage-risk reduction tradeoffs, i.e. what discounts on wages would workers accept in order to achieve less risk.

Alternatively, one may use contingent valuation (Cutler and Richardson 1997). Several studies have been used to calculate the value of life and life-years and have concluded that a range of $70-175,000 *per life year* is reasonable (Tolley, et al., 1994).[23]

"Life year" is a somewhat more manageable unit for economic analyses expressing the life expectancy of an individual in units of one year. While many proposed or real health policy interventions have as its impact the saving of a life, e.g. a food regulation that prevent a person from falling ill due to food poisoning. However, many other interventions have a different type of impact, such as the lengthening of life. Recent advances in diabetes or AIDS research, for example, do not cure or prevent the disease but merely allow people with the disease to live longer and healthier lives. Thus, in order to monetize the value of this lengthening of life, it is important to have a unit of

[23] Tolley, George S., Donald Scott Kenkel, and Robert G. Fabian, eds. 1994, *Valuing Health for Policy: An Economic Approach*, University of Chicago Press. See also Zarkin, Gary A., N. Dean, J.S. Mauskopf, and R. Williams, "Potential Health Benefits of Nutrition Label Changes," *American Journal of Public Health*, 1983, pp. 717-724.

measurement that captures the incremental benefit of additional years of life lived. The life year is also amenable to adjustment using the QALY weighting described earlier.

Several evaluations conducted by the FDA also came up with similar measures of the value of a life year. In 1999, FDA concluded in a nutrition labeling regulation that the value of life year was $100,000.[24] Cutler and Richardson (1997) also conclude that $100,000 is an appropriate value for a life year and that this value does not vary across age groups, socioeconomic strata, nor over time.

Translation of wage-risk tradeoffs, which focus on risk of death or harm to an individual, to health outcomes and their economic value is obvious on its face, but has some complications which make them unwieldy when considering economic benefits of biomedical research. Namely in the United States and in most developed countries health costs are borne indirectly by the consumer. Most people in the United States have some form of health insurance, whereby they pay a third party a regular premium in order to avoid the risk of sudden large bills. In contrast, wage-risk tradeoffs force a consumer to face directly the choice of life and death. As a result, Weisbrod (1983) notes that to many, willingness to pay is an ambiguous or even irrelevant conceptual basis for placing a value on health and medical care. First, the value of life depends on the perspective of the person being surveyed, whether the sum is in compensation or as substitution. Second, demand depends on the distribution of money income, and thus whether good

[24] U.S. Food and Drug Administration, "Food Labeling: Trans Fatty Acids in Nutrition Labeling, Nutrition Content Claims, and Health Claims; Proposed Rule," Federal Register, November 17, 1999.

health is viewed as a privilege or a right. This would be especially true if one is comparing equivalent health care in developed and developing world circumstances.

With a standard value for a life year, combined with the concept of QALY, one can now begin to estimate the value of extending life through health interventions such as improved treatments or cures for disease, or alternatively the value of a life lost due to disease or injury. For example, in the analysis provided by the FDA (1999), the FDA estimates that the average victim of coronary heart disease loses 13 years of life, which discounted at 7 percent becomes 8.4 years. Thus, the value of each life lost to coronary heart disease is $840,000 (8.4 discounted years X $100,000/year).

The discount rate used in the above example was 7 percent, as mandated by the Office of Management and Budget in all cost-benefit analyses of regulations. This is closer to a market interest rate rather than a utility discount rate used by most economists who generally use discount rates between 0 and 6 percent, with 3 percent being most popular. For example, at the NIH, the discount rate commonly used in their economic analyses is 3 percent. In this research, a range of 3-7 percent is used. The use of a particular discount rate is important since whichever rate one chooses to use can make a large impact on the results. What might seem like a great return at a low rate may diminish or even disappear when a higher rate is employed.

Previous studies evaluating the social returns of scientific research have focused on non-health related research endeavors, particularly those that lead eventually to commercial

products. Examples include studies of private sector and government research by Mansfield, Link, Terleckyj, and Griliches cited previously. The advantage of studies in these sectors is that one can point eventually to comparatively straightforward productivity increases in the overall economy in determining the benefits of that research.

Unfortunately, the same methods cannot be used in estimating the social returns of medical research, since many of the productivity increases must be measured by examining the effects of the research on the health of the relevant population. Furthermore, because health is multiattribute, research is but one of several factors that improve or impact on a person's health. Other stronger factors include access to health care, affordability, quality of health care received, and social and environmental conditions. Teasing out the impact of research amongst these other variables is not trivial.

On the other hand, the evaluation of returns on medical research does share some analogous issues with scientific research. One is the distance between the original research and the eventual consumer. Due to the unpredictability of research, whether medical or basic science in nature, one cannot say with certainty which scientific investments will bear fruit. Similarly, with the distance between the scientific bench and the patient's bedside, one has difficulty attributing specific research findings to overall improvements in health. Finally, due to the incremental nature of research, i.e. the slow accretion of knowledge, and the constant adaptation of new knowledge to old techniques,

we often see a continuum of improvement in many cases, rather than a wholesale change in methodology.

Chapter 5: Cost-Effectiveness Analysis and Cost-Utility Analysis of Diabetes Research

The goals of this chapter are to develop the conceptual and actual basis for conducting both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) of diabetes research. The CEA and CUA described in this chapter expands on previous CEA of intensive treatment versus conventional treatment conducted by researchers associated with the Diabetes Control and Complications Trial (DCCT) and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Essentially, the CEA/CUA described here builds on the initial results, expanding the population base to the entire United States and adding costs associated with diabetes research, in order to analyze the impact of diabetes research investment on the lengthening the life of those with diabetes.

Conceptual Design of the CEA and CUA

As stated previously, in CEA, one examines the costs to society as a whole when considering a policy or program and compares them to the benefits, in this case additional years of life gained. CUA compares these same costs to benefits that are expressed in standardized units of utility, such as QALYs. In this study, we are trying to determine

whether or not a concerted effort by the United States to invest in diabetes research over a period of time had or will have a measurable impact on people with diabetes. In order to conduct this examination, one must first identify the relevant costs and impacts. The identification of costs and benefits described in this chapter will also be relevant to the next chapter detailing the results of a cost-benefit analysis (CBA) of diabetes research.

The conceptual parameters of a CEA or CUA are fairly simple. On one side of the equation we have the costs, in this case the costs of the initial research investment. Additionally, we should add the incremental costs of intensive treatment instead of conventional treatment. As discussed earlier, using the simulation models, researchers determined that intensive treatment costs more than conventional treatment, regardless of whether or not the person has type 1 or type 2 diabetes.

On the other side, we have the impact or the effectiveness, due strictly to the research investment. In the studies used in this research, these impacts are expressed primarily in additional years of life gained due to use of this newer treatment. Additionally, as found by Testa and Simonson, people with diabetes can experience a higher quality of life due to their use of intensive treatment instead of conventional treatment. However, the impact is limited in that not all people with diabetes are eligible to use the intensive treatment. Thus, the CEA/CUA should reflect this limited eligibility.

Costs

In this study, regardless of whether one is conducting a CEA, a CUA, or a CBA, the costs are fairly self-evident, that is the resources devoted by Congress to diabetes research plus the incremental costs of intensive treatment. Building on previous studies of the cost-effectiveness of intensive treatment, this research adds in the elements of the diabetes research investment, plus expands the results of the original studies to the entire U.S. population.

Costs of Diabetes Research

For purposes of this research, only research investments borne by Congress and placed in the National Institutes of Health (NIH) were utilized. While the diabetes research community does receive support from other sources of funding, NIH provides the vast majority of funding. This study was limited to the U.S. Government's investment in diabetes research since this research considered the rationale of diabetes research investment within the budget of the U.S. Government.[25] Understandably, when making allocation decisions Congress must and should consider first and foremost the benefits to U.S. taxpayers of additional investment in diabetes research. Thus, it is appropriate to include only costs borne by U.S. society, i.e. research investments made by the NIH at the direction of the U.S. Congress.

[25] While this study is limited to the U.S. Government's *investment* in research, some of the research funded by the NIH and other USG agencies may have taken place outside of the United States. Furthermore, the diabetes research community has benefited from research supported by other governments, although the U.S. is by far the largest funder of diabetes research.

A necessary question then is which costs of diabetes research to include. The diabetes research costs associated with period of 1975-2000 were chosen after reviewing the medical literature for this period. A transition occurred over the course the 1970s in the treatment of diabetes research, specifically the introduction of oral hypoglycemic agents, which substantially altered the practices of physicians treating people with diabetes. Practitioners began to develop what is known as conventional therapy. This transition is akin to the type of transition taking place at the turn of the century with the changeover from conventional therapy to intensive therapy. Thus, the period of 1975-2000 represents an "era" in diabetes research beginning with the introduction and ending with the eventual phase-out of conventional therapy as the therapy of choice. The year 1975 was chosen as a representative year in the middle of this transition. Note that there is no specific or extraordinarily significant event in the history of diabetes research associated with this year. Rather, during the ten years of the 1970s, we saw a gradual transition from one type of therapy to another, with 1975 being the half-way point. Coincidentally, 1975 marked the time when Congress first began to take on the issue of diabetes in America and focused on diabetes research.

Since that time, significant gains have been made in all areas of diabetes research, including the increased understanding of diabetes at the cellular level, the development of new drug leads, behavioral studies of health practices, studies of diet and nutrition and its relation to diabetes prevention, and finally the clinical studies that synthesized much of the previous studies into one or more central questions. Of course, results from each of these areas of research raised even more questions to be pursued.

As outlined in the previous chapter, budget data were collected from the National Institute of Diabetes and Digestive and Kidney Diseases for the years 1975-2000. For comparison purposes, these figures were converted from current dollars to 1975 dollars. Thus, the total amount of funding for diabetes research from 1975-2000 was $2.87 billion in 1975 dollars. Appendix A provides a table of these expenditures in current and 1975 dollars.

Incremental Costs of Intensive Treatment

Each year, approximately 658,000 people are newly diagnosed with either type 1 or type 2 diabetes. Each year, these 658,000 are put on a regimen as prescribed by their physician which they will adhere to for the rest of their lives, assuming no outright cure is found. The simulations developed by the DCCT Research Group and described in the previous chapter modeled the impacts of the two therapies throughout the lifetimes of the people in the cohort.

As part of this research, the results of the simulations have been extrapolated to the entire U.S. population of people with diabetes, using these new models as the basis for estimating the marginal benefits between intensive and conventional therapy from the perspective of the U.S. population as a whole. In order to extend the results of the original simulations, two models have been created to reflect the transition from conventional to intensive therapy—one to estimate the benefits to people with type 1 diabetes and a second to estimate the benefits to people with type 2 diabetes. Model 1

describes the increases in longevity within the population of people with type 1 diabetes due to the shift from conventional therapy to intensive therapy. Model 2 describes the same shift in people with type 2 diabetes. Significant differences in the two models include a major difference in the cost of therapy for type 1 vs. type 2, and the much larger number of people in the United States with type 2 diabetes.

The beginning point for both models is the numbers of people with diabetes, whether type 1 or 2. The new therapy is best applied to people soon after their diagnosis; this allows the intensive therapy to have its maximum impact in delaying onset of complications. Every year in the United States, approximately 658,000 people are diagnosed with type 1 (10% of the total diagnosed) or type 2 diabetes (90% of the total diagnosed). As the DCCT researchers found, some people used to conventional therapy have difficulty in complying with the relatively burdensome intensive therapy. The DCCT enrolled cohorts of persons aged 13 to 39 years of age with type 1 diabetes. These enrollees had to meet certain criteria for enrollment based on the progression of their disease. The researchers then determined the proportion of the U.S. population with type 1 diabetes who met these criteria. Approximately 17% of the U.S. population with type 1 diabetes met those criteria. Similar analyses showed that 85% of the U.S. population with type 2 diabetes met the enrollment criteria. For these reasons, in this analysis, Model 1 is limited to 17% of newly diagnosed type 1 patients and Model 2 is limited to 85% of type 2 patients. For example, in year 2001, approximately 65,800 people are presumed to be diagnosed with type 1 diabetes, of which 17% or approximately 11,200 are eligible for intensive treatment. Similarly, 592,000 people are diagnosed each year

with type 2 diabetes of which 85% or 503,000 are eligible. Thus, Model 1 estimates the impact of intensive vs. conventional treatment on 11,200 people per year and Model 2 estimates a similar impact on 503,000 people per year, representing the number of people diagnosed each year who are eligible for the newer treatment.

Models 1 and 2 each are run for 25 years (2001-2025). Each "year" of the model, a new hypothetical set of patients representing a portion of the people diagnosed with diabetes that year begin their treatment and the incremental costs and marginal impact of intensive versus conventional therapies are calculated. Note that there is an assumption that there will be no change in the numbers of people diagnosed annually with diabetes. While there may be a slight growth in the number of people at risk for diabetes in the coming 25 years, due to the aging baby boomer population, other factors may mitigate that growth, such as the successful application of diabetes prevention programs. Thus, given the uncertainties, it was deemed better to stay with the more conservative assumption of the status quo.

Costs of Treatment

The lifetime cost of each of these therapies comes next. As stated earlier, when conducting a CEA or CUA of the impacts of disease-based research, one should look not only at the simple costs of the research investment, but also the marginal costs of the treatment that came about as a result of the research and match them ultimately against the appropriate medical and economic benefits.

The simulation models developed by the DCCT Research Group calculated the lifetime direct costs of disease using the various therapies. These included not only the cost of the therapy, i.e. medications and health care costs directly related to diabetes, but also costs of treating subsequent complications, such as kidney failure and diabetic retinopathy. Not included were a calculation of the benefits of additional years of sight, freedom from kidney disease, amputation, or other complications.[26] Out-of-pocket expenses not already covered by insurance were also not included, nor were the benefits of additional years of life expressed in monetary terms. Finally, the DCCT Research Group did not incorporate short-term benefits of one therapy versus the other, such as improved quality of life. In the models developed as part of this research, neither out-of-pocket expenses, nor short-term quality of life, were included.

The table below outlines the lifetime costs of the two therapies. This table can also be found in Chapter 2 and is repeated here for the reader's convenience.

Table 5-A: Lifetime Costs (1994 dollars)

Therapy	Type 1 Diabetes	Type 2 Diabetes
Conventional treatment	$66,076	$62,769
Intensive Treatment	$99,822	$76,691
Incremental Lifetime Cost	$33,746	$13,922

Source: DCCT Research Group, "Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trials," JAMA, v. 276, n. 17, 6 November 1996, pp. 1409-15, and Eastman, RC, et al., "Model of Complications of NIDDM," Diabetes Care, v. 20, n. 5, May 1997, pp. 735-744.

Note that costs of treatment, i.e. direct costs, were lower when using conventional therapy. These figures, of course, do not reflect the productivity losses due to absenteeism and shortened lifespan.

[26] For example, a person with type 1 diabetes using intensive therapy will on average experience 56.8 years

The nationwide incremental cost of using intensive treatment is the product of the number of eligible people with diabetes multiplied by the incremental cost per person with diabetes. Each year, 11,200 people in the United States are newly diagnosed with type 1 diabetes and are eligible for intensive treatment. Nationally, the additional cost of using intensive treatment is approximately $378,000,000 per year (the product of the 11,200 per year and the incremental cost of treatment for people with type 1 diabetes). For the 593,000 Americans diagnosed each year with type 2 diabetes and eligible for intensive treatment, the nationwide incremental cost is approximately $7,016,688,000 per year (the product of the number of people with the type 2 diabetes and the incremental cost of treatment). Note that these cost figures are in 1994 dollars and are undiscounted.

Thus, over a 25-year period (2001-2025), the incremental costs of the intensive treatment relative to the conventional treatment are $16.47 trillion in 1994 dollars. These figures were discounted back to 1975, using a range of discount rates (3%, 5%, and 7%) and added to the research costs described above. At a 3% discount rate, the total cost of both treatment and research is approximately $63.4 billion; at 5% discount rate, the total cost is approximately $32.3 billion; and at 7% discount rate, the total cost is approximately $17.1 billion. Additional details are given below.

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of sight versus 49.1 years of sight using conventional therapy. See *JAMA* v. 276, n. 17, p. 1412 for details.

Table 5-B: Total Costs Discounted to 1975

Cost	3% discount rate	5% discount rate	7% discount rate
Treatment Costs (Years 2001-2025)			
Type 1 Diabetes	$3,143,282,869	$1,573,029,553	$811,524,878
Type 2 Diabetes	$58,354,628,242	$29,203,084,359	$15,065,851,380
Research Costs (Years 1975-2000)			
Diabetes Research	$1,914,046,879	$1,507,964,615	$1,216,185,861
Total Costs (Years 1975-2025)	$63,411,957,990	$32,284,078,527	$17,093,562,119

Estimating Effectiveness or Impact

The original simulation models of the DCCT showed that the average number of years a person with type 1 diabetes will survive after diagnosis with intensive therapy is 61.6 years, while the average survival of a person with type 1 diabetes using conventional therapy is 56.5 years, thus the differential is 5.1 years. Similarly, using results from with the WESDR study, researchers found that the average person diagnosed with type 2 diabetes is expected to survive after diagnosis for 17.05 years with conventional therapy and 18.37 years with intensive therapy, with a differential of 1.32 years. Recall, the QALY weighting for people with diabetes is 0.65. Adjusting for QALYs, the figures become 3.32 years and 0.86 years for type 1 and type 2 diabetes respectively. These figures were discounted to reflect better the value of these years at the beginning of a person's therapy. The table below reflects the discounted value using several discount rates. The discounting shown below factors in the initial periods of 56.5 years and 17.05 years accordingly.

Table 5-C: Number of Additional Years of Life: Intensive vs. Conventional Therapy

		Discount Rate		
	Undiscounted	**3 %**	**5%**	**7%**
Type 1 Diabetes	5.1	0.96	0.32	0.11
Type 2 Diabetes	1.32	0.80	0.57	0.42
QALY-Adjusted Additional Years of Life				
Type 1 Diabetes	3.32	0.62	0.21	0.07
Type 2 Diabetes	0.86	0.52	0.37	0.27

These differences were multiplied by the number of people with diabetes eligible to receive intensive treatment and a discount factor to discount the number of years to 1975 levels. The product is the number of discounted additional years gained in the United States as a result of widespread use of intensive treatment. Despite the relatively modest gains, due to the great number of people, particularly those with type 2 diabetes, the impact of these additional years is substantial.

Table 5-D: Nationwide Increase in the Numbers of Years of Life Lived

		Discount Rate		
	Undiscounted	**3%**	**5%**	**7%**
Type 1 Diabetes	1,428,000	89,420	14,917	2,645
Type 2 Diabetes	16,631,868	3,353,233	1,195,644	454,508
Total	**18,059,868**	**3,442,653**	**1,210,561**	**457,153**
QALY-Adjusted Additional Years of Life				
Type 1 Diabetes	928,200	58,123	9,696	1,719
Type 2 Diabetes	10,810,714	2,179,602	777,169	295,430
Total	**11,738,914**	**2,237,725**	**786,865**	**297,150**

Cost Per Additional Year of Life Gained

To determine the cost-effectiveness of diabetes research investments made during the period of 1975-2000, we must divide the total cost by the total number of additional years gained as a result of this research, using the appropriate discount rates. Note that the table below uses the non-QALY adjusted additional years of life figures.

Table 5-E: Cost Per Additional Year of Life Gained

	Discount Rate		
	3%	5%	7%
Total Cost	$63,412,457,165	$32,284,328,335	$17,093,690,995
Additional Years of Life Gained	3,442,653	1,210,561	457,153
Cost Per Additional Year of Life Gained	$18,420	$26,669	$37,392

Using this calculation, we find that the cost-effectiveness of diabetes research and implementation (i.e. use of the new research advances) ranges from $18,400 per additional year of life gained to $37,400 per additional year of life gained, depending on the discount rate used.

For comparison, recall in the previous chapter, in the discussion of the CEA performed by the DCCT researchers, they estimated the cost-effectiveness of the new therapy to be

$28,661 per year of life gained for people with type 1 diabetes.[27] These earlier calculations by the DCCT Research Group do not incorporate the cost of the underlying research as the present analysis does.

Cost Per Discounted Years of Life Gained

As discussed before, the primary difference between CEA and CUA is that CUA attempts to compare costs to benefits that are expressed in standardized units of utility, such as QALYs. Thus, for the CUA, the costs are compared to the QALY-discounted years of life gained and we must divide the total cost by the total number of QALY-discounted years gained as a result of this research.

Table 5-F: Cost Per Discounted Life Year

	Discount Rate		
	3%	5%	7%
Total Cost	$63,412,457,165	$32,284,328,335	$17,093,690,995
QALY-Discounted Additional Years of Life Gained	2,237,725	786,865	297,150
Cost Per Discounted Year of Life Gained	$28,338	$41,029	$57,526

As with the CEA, the results of the CUA show that the cost per discounted life year is rather low. The range is $28,300 to $57,500 per discounted and QALY-weighted life

[27] DCCT Research Group, "Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trial," JAMA, v. 276, n. 17, Nov. 6, 1996, p. 1409-1415.

year depending on the discount rate (3% and 7% respectively). This compares to $16,002 per QALY gained for people with type 2 diabetes derived by Eastman, et al. in previous studies. Again, these earlier studies did not incorporate research costs nor did they discount, preferring to keep all figures in 1994 dollars.[28]

Sensitivity Analysis

As demonstrated above, the cost of diabetes research, in terms of its effectiveness and impact, seems quite low. Further analysis has been completed to determine how sensitive the cost-benefit models are to changes in the variables and assumptions used in developing the models. These analyses demonstrate that the results are in general not dependent on any one variable or assumption. Rather, changes of even fifty percent plus or minus in the major assumptions, including average number of additional years of life, treatment costs, QALY weighting, and number of people with diabetes, do not change substantially the overall result.

Even varying the number of people with diabetes willing or able to take on the intensive therapy did not substantially change the result. The high and low estimates are fifty percent greater and fifty percent lower than the best estimates. The percentage of the number of people eligible to implement intensive therapy has also been varied, in addition to varying the number of people implementing intensive therapy. Note that changing the treatment costs by fifty percent and the number of people by fifty percent

[28] Eastman, RC, et al., "Model of Complications of NIDDM." Diabetes Care, v. 20, n. 5, May 1997, pp. 735-744.

have identical effects on the outcomes. The table below provides details of the sensitivity analyses. Further information can be found in Appendix D .

Table 5-G: Results of Sensitivity Analyses for the Cost-Effectiveness and Cost-Utility Analyses

CEA/CUA	Treatment Costs		Number of People	
OUTCOMES	+50%	-50%	+50%	-50%
NPV of Costs				
3%	$ 94,161,662,308	$ 32,663,252,022	$ 94,161,662,308	$ 32,663,252,022
7%	$ 25,032,443,561	$ 9,154,938,428	$ 25,032,443,561	$ 9,154,938,428
Cost Per additional Year of Life				
3%	$ 27,351	$ 9,488	$ 27,351	$ 9,488
7%	$ 54,757	$ 20,026	$ 54,757	$ 20,026
Cost Per additional QALY-adjusted Year of Life				
3%	$ 42,079	$ 14,597	$ 42,079	$ 14,597
7%	$ 84,242	$ 30,809	$ 84,242	$ 30,809

CEA/CUA	Mix of Type 1 and Type 2		Eligibility of Type 1 (Type 2 is unchanged)	
OUTCOMES	+50%	-50%	+50%	-50%
NPV of Costs				
3%	$ 60,071,393,276	$ 65,082,289,944	$ 64,984,111,357	$ 61,840,802,974
7%	$ 16,231,103,510	$ 17,524,804,228	$ 17,499,456,727	$ 16,687,925,262
Cost Per additional Year of Life				
3%	$ 17,449	$ 18,905	$ 18,876	$ 17,963
7%	$ 35,505	$ 38,335	$ 38,279	$ 36,504
Cost Per additional QALY-Adjusted Year of Life				
3%	$ 26,845	$ 29,084	$ 29,040	$ 27,636
7%	$ 54,623	$ 58,976	$ 58,891	$ 56,160

CEA/CUA	Eligibility of Type 2 (Type 1 is unchanged)		QALY Weights	
OUTCOMES	+50%	-50%	+50%	-50%
NPV of Costs				
3%	$ 73,709,816,972	$ 34,234,674,646	$ 63,412,457,165	$ 63,412,457,165
7%	$ 19,752,237,491	$ 9,560,644,375	$ 17,093,690,995	$ 17,093,690,995
Cost Per additional Year of Life				
3%	$ 21,411	$ 9,944	$ 18,420	$ 18,420
7%	$ 43,207	$ 20,913	$ 37,392	$ 37,392
Cost Per additional QALY-adjusted Year of Life				
3%	$ 32,940	$ 15,299	$ 22,327	$ 38,778
7%	$ 66,472	$ 32,175	$ 45,323	$ 78,719

Chapter 6: Cost-Benefit Analysis of Diabetes Research

As stated previously, in CBA, one examines the costs and benefits to society as a whole when considering a policy or program. In contrast to CEA and CUA, CBA monetizes all costs and benefits, allowing one to compare directly the costs against the benefits and determine whether the outcome is positive or negative. Furthermore, CBA allows us to compare alternatives against one another, providing information about the relative efficiency of the competing alternatives. In this study, we are trying to determine whether or not a concerted effort by the United States to invest in diabetes research over a period of time had or will have a measurable impact on people with diabetes.

Conceptual Design of the Cost-Benefit Analysis

To conduct this analysis, the benefits and costs of diabetes research within the United States were examined. In essence, do the benefits of diabetes research outweigh the costs of the inputs of research? In order to conduct this examination, one must first identify the relevant costs and benefits.

In contrast to the CEA and CUA described in the previous chapter, the costs are simply the resources devoted by Congress to diabetes research.[29] Again, for purposes of this research, only the cost of research investments borne by Congress and placed in the National Institutes of Health (NIH) was utilized. While the diabetes research community does receive support from other sources of funding, NIH provides the vast majority of funding. As before, the costs were limited to the U.S. Government's investment in diabetes research since this research considered the rationale of diabetes research investment within the context and the budget of the U.S. Government.

Less straightforward are the benefits of diabetes research. Undoubtedly, the health of people with diabetes has improved over the last few decades. People with diabetes are living longer and more comfortably than ever before. At the same time, costs of treating diabetes have also increased, as evidenced by the cost-of-illness studies mentioned previously. The reasons behind both the overall improvement in health and the increased costs are complex. Greater access to health care, particularly by the elderly through Medicare, have led to larger numbers of people with diabetes living longer. Since they are living longer, that segment of the population has seen rising health care costs related to diabetes treatment. Similarly, screening for diabetes among the general population has increased over the years, leading to more diagnoses of diabetes in the U.S. earlier in life. This has also added to overall health care costs and to improved health of those who received treatment for their diabetes. Finally and most importantly, not all the improvements in health can be attributed to research. While a portion of their

[29] The treatment costs previously calculated in the CEA and CUA are now incorporated into the calculation of benefits of research, i.e. the implementation of the research.

improvement can legitimately be associated with research findings, it is difficult, if not impossible, to assign a weighting or percentage to research supported by the NIH.[30]

If it is not feasible to examine the improvements in health of the overall population of people with diabetes and determine which portion to attribute to diabetes research, what are the alternatives? One alternative would be to examine the corpus of diabetes research over a period of time and trace the research results from the basic science to the clinical applications. Theoretically, it should be possible to follow specific findings from the bench to the bedside and estimate the impact of those findings. Conversely, it should be possible to identify key clinical findings and trace back to the appropriate basic research activities. However, again the problem of attribution appears. For example, since only a portion of research investments is successful in leading to improvements in health, how does one account for the investments in research that did not lead to new discoveries? Furthermore, since most research improvements are incremental in nature, the actual improvements in health attributed to a specific finding may be quite small, but when taken with other research findings over decades, may be quite significant. Again, this approach is awkward and insufficient in helping one perform a cost-benefit analysis.

A third approach, the one used in this analysis, looked at the history of diabetes research over a period of time and examined the evolution of the field. This history is summarized in Appendix C, while the major research findings and their relevance to this study are

[30] Recall that in the Mushkin analysis, the researcher measured all the improvements to health, subtracted all known factors such as improvements in public health, and attributed the rest to biomedical research writ large. Due to the complexity of today's American society and biomedical research, performing such an analysis would likely be quite flawed.

outlined in Chapter 2. Upon examination, one can see that the Diabetes Control and Complications Trial (DCCT) was a major turning point in the field of diabetes. The DCCT compared conventional treatment to intensive treatment in patients with type 1 diabetes. The trial demonstrated that a regimen of intensive therapy aimed at maintaining near-normal blood glucose values markedly reduced the risk of development of type 1 diabetes when compared to a conventional treatment regimen. A similar trial, the Wisconsin Epidemiological Study of Diabetic Retinopathy, found equally compelling results among people with type 2 diabetes.

As described in the previous chapter, these two studies were relevant for this analysis because they represented the culmination of research over the previous 25 years. The trials represent in essence the product of the past 25 years of diabetes research performed primarily by the NIH and other public sector biomedical research support organizations. In other words, 25 years of research into new drugs, therapeutic techniques, and educational measures led up to that trial, thus is appropriate to consider the marginal benefits of adopting the techniques studied in these two trials as being a surrogate measure of the marginal benefits of the entire corpus of diabetes research over the past 25 years.

Measuring the Costs and Benefits of Diabetes Research

In essence, this study estimates the marginal benefits of people with diabetes due to diabetes research over the past fifty years net of treatment costs, and subtracts the costs of

diabetes research from those gains in order to arrive at a final answer. A theoretical model for analyzing costs and benefits of diabetes research is given below:

The net benefits of diabetes research to society are characterized by increases in the marginal benefits of people with diabetes attributable to advances in diabetes research minus the cost of diabetes research.

Net Benefits (or Costs) of Diabetes Research	=	**Marginal Benefits of People with diabetes due to R&D**	-	**Costs of Diabetes Research**

Costs of Diabetes Research

A necessary question then is which costs of diabetes research to include. The diabetes research costs associated with period of 1975-2000 was chosen after reviewing the medical literature for this period. A transition occurred over the course the 1970s in the treatment of diabetes research, specifically the introduction of oral hypoglycemic agents, which substantially altered the practices of physicians treating people with diabetes. Practitioners began to develop what is known as conventional therapy. This transition is akin to the type of transition currently taking place with the changeover from conventional therapy to intensive therapy. Thus, the period of 1975-2000 represents an "era" in diabetes research beginning with the introduction and ending with the eventual phase-out of conventional therapy as the therapy of choice. The year 1975 was chosen as a representative year in the middle of this transition. Note that there is no specific or extraordinarily significant event in the history of diabetes research associated with this

year. Rather, during the ten years of the 1970s, we saw a gradual transition from one type of therapy to another, with 1975 being the half-way point. Coincidentally, 1975 marked the first time when Congress first began to take on seriously the issue of diabetes in America and focused on diabetes research as a means of improving the health of those Americans with diabetes.

Since that time, significant gains have been made in all areas of diabetes research, including the increased understanding of diabetes at the cellular level, the development of new drug leads, behavioral studies of health practices, studies of diet and nutrition and its relation to diabetes prevention, and finally the clinical studies that synthesized much of the previous studies into one or more central questions. Of course, results from each of these areas of research raised even more questions to be pursued.

As outlined in the previous chapter, budget data were collected from the National Institute of Diabetes and Digestive and Kidney Diseases for the years 1975-2000. For comparison purposes, these figures were converted from current dollars to 1975 dollars. Thus, the total amount of funding for diabetes research from 1975-2000 was $2.87 billion in 1975 dollars.

Benefits of Diabetes Research

This cost-benefit analysis is built on the assumption that the benefits of research investments made from 1975 to 2000 as described above will accrue in the years 2001 to 2025. Ideally, it should be possible to isolate the substantive role that biomedical

research played in the improvement of the health of people with diabetes research. In order to identify and isolate that role in practice, it is necessary to use the Diabetes Control and Complications Trial (DCCT), which does allow us a mechanism for viewing the impact of medical research on the management of diabetes net of treatment costs without the confounding factors of access to and affordability of health care.

The DCCT ended in 1993 and the analysis of the trial continues today. For a variety of medical reasons, not all physicians treating people with diabetes have universally translated the results into everyday practice, however the ADA in January 1999 incorporated these findings and the associated treatment goals into their official position statement regarding diabetes treatment. Thus, this segment of the research is based on an estimate of prospective benefits over the next 25 years (years 2001-2025) taking advantage of research investments made from 1975-2000. By 2025, that is, after another 25 years, it can be reasonably forecast that the next generation of treatment, developed as a result of ongoing as well as earlier research, will be evaluated and put into practice.

To assist in isolating the impacts of diabetes research, researchers in the DCCT Research Group compared the health benefits of intensive therapy versus conventional therapy in Monte Carlo/Markov simulations described in the previous chapter. With the aid of the simulations, the DCCT Research Group was able to compare two identical cohorts of people with diabetes, the first without the benefit of the past 25 years of research (those receiving conventional therapy) and the second with the benefit of the past 25 years of research (those receiving intensive therapy).

It is also important to reemphasize that the shift from conventional therapy to intensive therapy does not represent a major introduction of new drugs or technologies. Indeed, the patients and their physicians in the original trials had access to the same drugs and technologies. Rather, intensive therapy consists primarily of a different approach to the management of the diseases using essentially the same tools, i.e. drugs and devices, available to the patient and physician as before. Nonetheless, as was noted in the CEA/CUA, there are costs of treatment, or rather implementation, associated with the new therapy which must be taken into account when evaluating the cost of research.

As in the CEA/CUA in the previous chapter, the two simulations described above were used as the basis for calculating the marginal benefits between intensive and conventional therapy by expanding the results of the simulations to the entire U.S. population of people with diabetes. For convenience, the salient points are repeated below.

Each year, approximately 658,000 people are diagnosed with either type 1 or type 2 diabetes. Each year, these 658,000 are put on a regimen as prescribed by their physician which they will adhere to for the rest of their lives, assuming no outright cure is found. The simulations developed by the DCCT Research Group modeled the impacts of the two therapies throughout the lifetimes of the people in the cohort.

The impacts of the two therapies were represented in two manners. First was a calculation of the total costs of the two therapies over the lifetimes of the individuals in

the cohorts. This cost incorporated not only the direct cost of treating the disease, but also the costs of treating the complications associated with diabetes, e.g. retinopathy, neuropathy, renal disease, and cardiovascular disease. It did not however try to measure the indirect costs of lost productivity to individuals in the cohorts. Thus, it is possible to compare the two therapies to see which is more costly to implement. For both type 1 and type 2 diabetes, intensive therapy costs more than conventional therapy.

The second manner was an estimation of the impact of the two therapies on the longevity of individuals, i.e., which of the two therapies would on average allow one to live longer and by how much. In the simulations, intensive therapy allowed individuals on average to live longer than did conventional therapy. A later study by Testa and Simonson showed that individuals utilizing intensive therapy also experienced better quality of life, exemplified by lower number of absences from work.

These three calculations (additional cost, increased longevity and lower rate of absences) were the basis of the modeling of the marginal benefits of intensive therapy over conventional therapy, spread over the entire U.S. population and over the course of 25 years. In doing so, this research expands the two original cohorts developed by the DCCT Research Group to reflect the benefits and costs to the entire U.S. population of people with type 1 and 2 diabetes, and by extension the entire United States. Finally, the important long and short-term benefits of additional years of life and improvements to everyday quality of life have been incorporated.

In essence, the original contribution of this research is the development of an economic model for comparing costs and benefits of biomedical research, specifically diabetes research, including in the model both the costs of research, the implementation costs, and the benefits associated with the research.

The next section outlines the basic model for estimating the marginal benefits of intensive treatment versus conventional treatment, including the health capital and human capital methods for valuing those benefits in economic terms.

Estimating the Marginal Benefits

Two models were created to reflect the transition from conventional to intensive therapy—one to estimate the benefits to people with type 1 diabetes and a second to estimate the benefits to people with type 2 diabetes. See Figure below.

Figure 6-A: Simulation Models

Model 1—*Type 1 Diabetes*	**Model 2**—*Type 2 Diabetes*
Conventional Therapy ⇒ Intensive Therapy	Conventional Therapy ⇒ Intensive Therapy

Model 1 describes the increases in productivity within the population of people with type 1 diabetes due to the shift from conventional therapy to intensive therapy. Model 2 describes the same shift in people with type 2 diabetes. Significant differences in the two models include a major difference in the cost of therapy for type 1 vs. type 2, and the much larger number of people in the United States with type 2 diabetes.

As with the CEA/CUA, the beginning point for both models is the numbers of people with diabetes, whether type 1 or 2. Since the rationale for the CEA/CUA is similar to the CBA, the description below is abbreviated. Further details can also be found in Appendix A.

As described in the previous chapter, the new therapy is best applied to people soon after their diagnosis; this allows the intensive therapy to have its maximum impact in delaying onset of complications. Thus, Model 1 estimates the impact of intensive vs. conventional treatment on 11,200 people per year and Model 2 estimates a similar impact on 503,000 people per year.

Recall that the DCCT-generated benefits were expressed in number of additional years of life. Both models ran for 25 years (2001-2025). Each "year" of the model, a new hypothetical set of patients representing a portion of the people diagnosed with diabetes that year began their treatment and lifetime costs and the medical benefits of intensive versus conventional therapies were calculated. Refer to the Appendix A for a fuller discussion of the costs and benefits.

Estimating Changes in Lifespan and Productivity

In order to estimate the marginal benefits of intensive treatment over conventional treatment and eventually to conduct a cost-benefit analysis of diabetes research, one must calculate and then value these changes in lifespan and additional work productivity. There are two major elements in estimating the marginal benefits. Each of these two

elements demonstrates the value of one type of treatment over the other. The first major element in the estimation of marginal benefits is a valuing of the benefits due to the expected increase in life span when using intensive therapy instead of conventional therapy. The second major element is a valuing of the benefits of fewer absences in the workplace as a result of using intensive therapy instead of conventional therapy.

Increased Lifespan: The average number of years a person with type 1 diabetes will survive after diagnosis with intensive therapy is 61.6 years, while the average survival of a person with type 1 diabetes using conventional therapy is 56.5 years, thus the differential is 5.1 years. Similarly, the average person diagnosed with type 2 diabetes is expected to survive 17.05 years after diagnosis with conventional therapy and 18.37 years with intensive therapy, with a differential of 1.32 years. Adjusting for QALYs, the figures become 3.32 years and 0.86 years for type 1 and type 2 diabetes respectively. These figures were further discounted to reflect the value of these years in 1975. The table below reflects the discounted value using several discount rates. The discounting shown below factors in this initial period of 56.5 years for people with type 1 diabetes and 17.05 years for people with type 2 diabetes. Note that the table below can also be found in Chapter 5 and is repeated here for the convenience of the reader.

Table 6-A: Nationwide Increase in the Numbers of Years of Life Lived

		Discount Rate		
	Undiscounted	**3 %**	**5%**	**7%**
Type 1 Diabetes	5.1	0.96	0.32	0.11
Type 2 Diabetes	1.32	0.80	0.57	0.42
QALY-Adjusted Additional Years of Life				
Type 1 Diabetes	3.32	0.62	0.21	0.07
Type 2 Diabetes	0.86	0.52	0.37	0.27

These differences were multiplied by the number of people diagnosed with diabetes annually and by the value of those additional years of life. Despite the modest gains, due to the much greater number of people with type 2 diabetes, the economic impact of that subgroup is substantial.

Decreased Absences: The next major element in the cost-benefit models was the relative gains or losses in short-term productivity, namely absenteeism, i.e. missed workdays. The degree of absenteeism is a measure of the short-term quality of life of the person with diabetes. A person with relatively lower quality of life will experience more days when she is forced to stay at home, or enter the hospital. In the long-term, her quality of life may suffer to the extent that she may decide to retire earlier than otherwise expected, again adversely affecting productivity as well as her sense of well-being. Data on absenteeism came from Testa and Simonson.

Table 6-B: Absenteeism

Therapy	Workdays Missed per Year[31]
Conventional treatment (10% HbA1C)	12
Intensive Treatment (7.2% HbA1C)	2.5

[31] Testa MA, Simonson DC, "Health Economic Benefits and Quality of Life During Improved Glycemic Control in Patients with Type 2 Diabetes Mellitus," JAMA, v. 280, n. 17, 4 November 1998, p. 1490-96.

After understanding the differences between the two types of treatments in the population, one may begin to value these differences and make an estimate of the marginal benefits.

In order to make estimates of the marginal benefits, two approaches have been used. One approach estimates the benefits of the newer treatment using a health capital method to estimate the value of a year of life based on how much individuals are willing to pay for that additional year of life. The second approach estimates the benefits using a human capital method, estimating the discounted future earnings of an individual over the additional years of life gained by virtue of using the newer treatment. The two methods are described in detail below.

Human Capital Methodology

The first methodology is used in this analysis is Discounted Future Earnings (DFE). DFE allows one to infer the value of life and what people are willing to pay for additional years of life by estimating their expected income. People can be expected to earn a stream of income over their working lives equivalent to their productivity or human capital. This stream of income can be estimated and the discounted present value of their income can be used to calculate changes in productivity, in this case due to diabetes research.[32]

[32] Cordes, Joseph, personal communication, November 2002.

To calculate the projected changes in DFE, it is necessary to determine any expected changes in the quality of life of people with diabetes over the time period due specifically to diabetes research. As described above, there are two major elements that can be used in calculating marginal benefits. The first major element comes from the increase in expected life span when using intensive therapy instead of conventional therapy. The second major element is expected decrease in absenteeism in the workplace. Each of these elements required separate calculations to determine the additional DFE as a result of using intensive treatment. Costs used in this study were based on Current Population Survey and Bureau of Labor Statistics data from 1994. It should be noted that historically the real value of human productivity has increased over time. However, no attempt has been made in this study to develop a formula that estimates and incorporates this increase in value. Thus, the calculations described below can be viewed as a conservative estimate of the value of human productivity during the years 2001-2025. Actual values may in fact be slightly larger.

Value of Additional Days Worked: The average value of a day of work in 1994 is estimated to be $88.91 per day. This value was multiplied by the expected additional number of days worked per year as a result of using intensive treatment (9.5 days per year) over the remaining years of life of the person with diabetes (18.37 years for people with diabetes type 2 and 61.6 years for people with diabetes type 1).

Value of Additional Years of Life Lived: For the average person with diabetes, whether type 1 or type 2, the value of one year of work in 1994 is estimated to be $22,774. The

annual income figure was calculated by weighting the average values of one year of work by the comparable income levels of the population of people with diabetes stratified by age groups. In other words, the annual income levels in 1994 matched the age distribution of people with diabetes. Note that 80% of the people with diabetes are 45 years of age and above, the age range which is generally viewed as the most economically productive years, particularly the period from 45 to 54 years of age. See table below for more details. Further details on the calculation of the weighted annual income figure are given in Appendix A.

Table 6-C: Mean Annual Income by Age Distribution

Age Groups	Percentage of People with Diabetes Type 1 and 2	Mean Annual Income (current 1994 dollars)
15 to 44 year olds	18%	$21,724
45 to 54 year olds	38%	$30,769
55 to 64 year olds	26%	$17,952
65 to 74 year olds	17%	$14,971
Weighted Mean Income	**99%***	**$22,774**

*does not equal 100% due to rounding differences.
Sources: Current Population Survey and *Diabetes in America*, 2nd edition.

These two sources of increased productivity (decreased absences and additional years of work using the human capital method) were combined and multiplied by the number of people in each cohort to estimate the value of the additional years of life lived and the additional days worked. As will be described later, the additional costs of treatment will be subtracted from this figure.

Health Capital Methodology

In order to estimate the value for health and health consequences, some economists and policy analysts use a system based on willingness to pay (WTP) for reductions on risk,

and on premiums paid to those who willingly take on riskier occupations. As noted in Chapter 4, several studies have been used to calculate the value of a statistical life and life-years and have concluded that a range of $70-175,000 per life year is reasonable (Tolley, et al., 1994). In 1999, FDA concluded that the value of a year of life was $100,000.[33] Cutler and Richardson (1997) also concluded that $100,000 is an appropriate value for a life year and that this value does not vary across age groups, socioeconomic strata, nor over time. As a result, this analysis also uses $100,000 as an appropriate expression of willingness to pay for a year of life in perfect health.

In brief, this value was multiplied by the discounted and QALY-adjusted number of years of life gained through use of the intensive therapy instead of conventional therapy. Thus, for example, the value of extending the life of a single person with type 1 diabetes, discounted at 3% and QALY-adjusted becomes $62,000. The corresponding value for extending the life of a single person with type 2 diabetes would be $52,000. Multiplying this value by each person in the cohort gives a value for the additional years of life across the United States as a result of using intensive therapy instead of conventional therapy.

Finally, for each person in the cohort and for each year 2001 to 2025, the marginal treatment cost of intensive versus conventional therapy was subtracted from the value of the additional years of life lived, calculated using both the human capital and health capital methods. To maintain consistency, costs and benefits were aggregated by year and the net present value taken based on the year 1975. Costs of research during the

[33] U.S. Food and Drug Administration, "Food Labeling: Trans Fatty Acids in Nutrition Labeling, Nutrition Content Claims, and Health Claims; Proposed Rule," Federal Register, November 17, 1999.

period 1975 to 2000 were then subtracted, again after the net present value based on the year 1975 was calculated. The next section details the results of these models.

Results

Human Capital Methodology

The gross and net benefits of intensive treatment versus conventional treatment using the human capital method are summarized in the table below. Note that the annual figures refer to entire cohorts of people diagnosed with diabetes, both type 1 and type 2, in one year. Gross benefits refer to the benefits of intensive treatment in an annual cohort net of treatment costs. Thus, in one year, there is a loss of $98 million in the cohort of people with type 1 diabetes when matching the additional treatment costs ($378 million) against the discounted future earnings ($280 million). This loss to society from those with type 1 diabetes is more than made up by the $10.6 billion gain from those people with type 2 diabetes ($17.6 billion in discounted future earnings minus $7 billion in additional treatment costs). Combining the 25 annual cohorts for type 1 and type 2 for the years 2001-2025 and subtracting the net present value of the cost of research from 1975-2000 gives a net present value of benefits of $85 billion.

Table 6-D: Discounted Future Earnings (Human Capital Methodology)

Model	Type 1	Type 2
Number of Newly Diagnosed (type 1 or type 2) annually	11,200	504,000
Difference in Lifetime Costs annually	$377,955,200	$7,016,688,000
Value of Additional Years annually	$149,901,561	$5,907,430,972
Value of Additional Days annually	$130,047,319	$11,700,616,993
Gross Annual Benefits (or Costs) of Improved Therapy	($98,006,320)	$10,591,359,965
Total NPV of Gross Benefits (or Costs) of Improved Therapy in Year 1975	($815,080,962)	$88,084,277,093
NPV of Cost of Diabetes Research in 1975	$1,914,046,879	
NPV of Net Benefits (1975)	$85,355,149,252	
Cost-Benefit Ratio	45.59	

Note: Unless noted otherwise, all costs are in 1994 dollars. Discount rate used in calculations of net present value is 3 percent.

The net present value of benefits is roughly 45 times the initial investment in Federal diabetes research over the period from 1975 to 2000. These calculations assume a 3% discount rate. At a 7% discount rate, the net benefit drops to only $2.86 billion in 1975 dollars, with a benefit-cost ratio of 3.35. See the table below for a summary. Full details on the calculations can be found in Appendix A and in the spreadsheets. Clearly, the selection of a discount rate affects the valuation of diabetes research. Note that taken alone, there is a loss when looking exclusively at those with type 1 diabetes, but that these loses are more than made up by the much larger number of people with type 2 diabetes.

Table 6-E: Benefits and Costs Discounted to 1975 (Human Capital Methodology)

Benefits and Costs	3% discount rate	5% discount rate	7% discount rate
Benefits for Type 1	($815,080,962)	($902,744,126)	($565,746,258)
Benefits for Type 2	$88,084,277,093	$22,220,603,997	$4,645,070,398
Costs of Diabetes Research	$1,914,046,879	$1,507,964,615	$1,216,185,861
Net Benefits	$85,355,149,252	$19,809,895,257	$2,863,138,279
Benefit-Cost Ratio	45.59	14.14	3.35

Health Capital Methodology

Similar to the calculations using the human capital method, the gross and net benefits of intensive treatment versus conventional treatment using the human capital method are summarized in the table below. Note again that the annual figures refer to entire cohorts of people diagnosed with diabetes, both type 1 and type 2, in one year. Gross benefits refer to the benefits of intensive treatment in an annual cohort net of treatment costs. Thus, in one year, there is a gain of $280 million in the cohort of people with type 1 diabetes when matching the additional treatment costs ($378 million) against the willingness to pay ($658 million). This gain to society from those with type 1 diabetes is combined with the $18.9 billion gain from those people with type 2 diabetes ($25.9 billion in discounted future earnings minus $7 billion in additional treatment costs). Combining the 25 annual cohorts for type 1 and type 2 for the years 2001-2025 and subtracting the net present value of the cost of research from 1975-2000 gives a net present value of benefits of $157.8 billion.

Table 6-F: Willingness to Pay (Health Capital Methodology)

Model	Type 1	Type 2
Number of Newly Diagnosed (type 1 or type 2) annually	11,200	504,000
Difference in Lifetime Treatment Costs annually	$377,955,200	$7,016,688,000
Value of Statistical Life Gained Annually	$658,223,306	$25,939,748,178
Gross Benefits Annually (before discounting)	$280,268,106	$18,923,060,178
Total Net Benefits Discounted Back to 1975	$2,330,882,305	$157,375,831,020
Total NPV of Cost of Diabetes Research in 1975	$1,914,046,879	
Total NPV of Benefits (1975)	$157,792,666,446	
Benefit-Cost Ratio	83.44	

Note: Unless noted otherwise, all costs are in 1994 dollars. Discount rate used in calculations of net present value is 3 percent.

Using health capital methodology, based on willingness-to-pay, the projected value of net benefits of Federally-supported diabetes research is roughly 83 times the investment from 1975 to 2000. Again, these calculations assume a 3% discount rate. At a 7% discount rate, the value of net benefits drops to $11.9 billion or approximately 10 times the investment. See the table below for a summary. Full details can be found in Appendix A and in the spreadsheets.

Table 6-G: Benefits and Costs Discounted to 1975 (Health Capital Methodology)

Benefits and Costs	3% discount rate	5% discount rate	7% discount rate
Benefits for Type 1	$ 2,330,882,305	$ (683,262,898)	$ (659,125,238)
Benefits for Type 2	$157,375,831,020	$ 48,224,616,720	$ 13,764,152,588
Costs of Diabetes Research	$ 1,914,046,879	$ 1,507,964,615	$ 1,216,185,861
Net Benefits	$157,792,666,446	$ 46,033,389,207	$ 11,888,841,489
Benefit-Cost Ratio	83.44	31.53	10.78

Social Rate of Return

For both methods of calculating benefits (human capital and health capital) a social rate of return (SRR) was calculated. The SRR is essentially the rate at which benefits equal the cost or the discount rate at which the net present value equals zero. Using the human capital methodology, the SRR was 8.04%; using the health capital methodology, the SRR was 9.06%.[34]

While direct comparisons are difficult given differing methods of calculating benefits, the SRR for this period of diabetes research was considerably lower than the rate of return found by Mushkin in her analysis of all biomedical research. In that study, Mushkin found a return of $145-167 billion on an investment of only $30 billion or an internal rate of return of 46 percent. Note that Mushkin in her analysis used estimates of $76,000 per premature death averted and $12,250 for each work-year gained when illness averted.[35] It is not known what, if any, discount rate Mushkin used, but the value of statistical life and the value of a year of work are considerably more conservative than those used in this study.

In contrast, the social rates of return found in this study are in the same range as Weisbrod's analysis of poliomyelitis research. In his analysis, Weisbrod estimated the internal rate of return is to be between 11 and 12 percent, depending on the time horizon selected. In this analysis, Weisbrod used a human capital approach, calculating benefits

[34] The calculation of the SRR discounts all values at the same rate, including the cost of research.
[35] Mushkin, Selma, *Biomedical Research: Costs and Benefits*, (Ballinger Publishing, Cambridge: 1979).

per case of polio prevented using estimates of productivity loss due to mortality, morbidity, treatment and rehabilitation of polio victims.[36]

Finally, for comparisons to other types of scientific research, the studies by Terleckyj (1977) and Griliches (1975) of research-based industries found internal rates of return of 28% and 17% respectively.

As seen above, the annualized marginal benefits of the improved treatment outpace the annual expense of diabetes research, when using discount rates of 3-5%. These benefits extend into perpetuity, regardless of whether additional resources are put into diabetes research. It is important to remember that the results reported here reflect the assumption that each person received the appropriate treatment for their complication, in other words, universal health care. This assumption ignores the possibility that someone did not receive appropriate health care, and thus as long as health care is not accessible to all, these results should be considered theoretical, not actual.

In the human capital calculations the bulk of the gains for people with type 1 diabetes is in the value of the additional years of life gained as a result of the intensive therapy. These gains are valued at roughly 3.8 times the value of the additional workdays during the year.[37] For those with type 2 diabetes, these values are roughly the same. Even though the actual gains are modest when using intensive therapy instead of conventional therapy, 5.1 years for people with type 1 diabetes (undiscounted), and 1.32 years of

[36] Weisbrod, BA, *Economics and Medical Research*, AEI Studies, American Enterprise Institute, Washington, D.C., 1983.

additional life for people with type 2 diabetes (undiscounted), given the numbers of people with this disease, these savings add up to $662 million per year for people with type 1 diabetes and $7.7 billion for people with type 2 diabetes (3% discount rate, human capital method).

Sensitivity Analysis

As demonstrated in the analysis, the economic benefits to society of recently conducted diabetes research are projected to be quite substantial. Further analyses have been undertaken to determine how sensitive the cost-benefit models are to changes in the variables and assumptions used in developing the models. These analyses demonstrate that the results are not dependent on any one variable or assumption. Rather, changes of even fifty percent plus or minus in the major assumptions, including treatment costs, number of people with diabetes, eligibility and QALY weights do not change substantially the overall result. One noteworthy comment is that a 50% increase in treatment costs yields a net loss when using a 7% discount rate. This is the only instance where the social rate of return drops below 7%, in this case to 5.53%. The table below gives further details.

[37] These comments assume a 3% discount rate.

Table 6-H: Sensitivity Analyses of Discounted Future Earnings and Willingness to Pay

Human Capital (Discounted Future Earnings)	Treatment Costs		Number of People	
OUTCOMES	+50%	-50%	+50%	-50%
SRR	5.53%	11.86%	8.26%	7.52%
NPV of Benefits				
3%	$54,605,944,109	$116,104,354,395	$128,989,747,317	$41,720,551,186
7%	$ (5,075,614,288)	$10,801,890,845	$4,902,800,348	$823,476,209
Cost-Benefit Ratio				
3%	29.53	61.66	68.39	22.80
7%	(3.17)	9.88	5.03	1.68

Human Capital	Mix of Type 1 and Type 2		Eligibility of Type 1 (Type 2 is unchanged)	
OUTCOMES	+50%	-50%	+50%	-50%
SRR	7.69%	8.20%	7.93%	8.16%
NPV of Benefits				
3%	$74,752,227,308	$90,655,561,601	$84,947,608,770	$85,762,689,733
7%	$1,781,236,222	$3,404,034,008	$2,580,265,150	$3,146,011,408
Cost-Benefit Ratio				
3%	40.05	48.36	45.38	45.81
7%	2.46	3.80	3.12	3.59

Human Capital	Eligibility of Type 2 (Type 1 is unchanged)		QALY Weights	
OUTCOMES	+50%	-50%	+50%	-50%
SRR	8.17%	7.34%	8.60%	7.42%
NPV of Benefits				
3%	$100,898,528,751	$41,312,661,164	$98,918,055,945	$71,792,242,558
7%	$3,682,808,876	$540,584,647	$4,640,164,856	$1,086,111,701
Cost-Benefit Ratio				
3%	53.71	22.58	52.68	38.51
7%	4.03	1.44	4.82	1.89

Health Capital (Willingness to Pay)	Treatment Costs		Number of People	
OUTCOMES	+50%	-50%	+50%	-50%
SRR	7.84%	12.56%	10.15%	9.32%
NPV of Benefits				
3%	$127,043,461,303	$188,541,871,589	$237,646,023,108	$77,939,309,783
7%	$3,950,088,922	$19,827,594,056	$18,441,355,164	$5,336,327,814
Cost-Benefit Ratio				
3%	67.37	99.50	125.16	41.72
7%	4.25	17.30	16.16	5.39

Health Capital	Mix of Type 1 and Type 2		Eligibility of Type 1 (Type 2 is unchanged)	
OUTCOMES	+50%	-50%	+50%	-50%
SRR	9.55%	10.07%	9.79%	10.02%
NPV of Benefits				
3%	$142,636,096,290	$165,369,078,002	$158,958,107,598	$156,627,225,293
7%	$9,700,256,724	$12,982,970,013	$11,559,278,870	$12,218,404,108
Cost-Benefit Ratio				
3%	75.52	87.40	84.05	82.83
7%	8.98	11.68	10.50	11.05

Health Capital	Eligibility of Type 2 (Type 1 is unchanged)		QALY Weights	
OUTCOMES	+50%	-50%	+50%	-50%
SRR	10.05%	9.14%	11.18%	8.19%
NPV of Benefits				
3%	$185,563,255,548	$79,104,126,429	$217,347,892,033	$98,237,440,858
7%	$14,317,668,224	$5,006,710,575	$19,691,831,004	$4,085,851,974
Cost-Benefit Ratio				
3%	97.95	42.33	114.55	52.32
7%	12.77	5.12	17.19	4.36

Breakeven points for several variables were also calculated for both human capital and health capital methods. In most circumstances, these variables had to be lowered dramatically in order to reach a breakeven point, where the benefits equaled approximately the costs of research. Recall that using the discounted future earnings (DFE) method, for those with type 1 diabetes, the net incremental cost of intensive treatment is negative, i.e. that society has a net loss if only benefits accruing to people with type 1 diabetes are accounted. Since those people are only 2% of those who benefit from intensive treatment, their losses are far more than made up for by the benefits associated with those with diabetes type 2. Thus, when using the human capital method, the breakeven point for the number of people with type 2 diabetes must drop to 15,600 people with diabetes type 2 enrolled per year at a 3% discount rate before costs of research and keeping the number of people with type 1 diabetes steady. This number

increases to 193,000 enrollees per year when a 7% discount rate is used. This number is approximately 38% of the total number of enrollees estimated to be eligible for intensive treatment. In other words, assuming a 7% discount rate, only two-fifths of the population of people with diabetes type 2 needs to take advantage of the newer therapy for the country's research investment to be worthwhile. At a 3% discount rate, this fraction drops to 3.1% of the population of people with type 2 diabetes and eligible to use intensive treatment.

When considering the health capital method (willingness to pay), the minimum number of people with type 2 diabetes who would utilize intensive therapy is 68,700 when using a 7% discount rate. When using a 3% discount rate, the minimum number of people with type 2 diabetes can drop to zero and there still would be a positive gain. Only by dropping the number of type 2 people to zero and dropping the number of people with type 1 diabetes to 9,200 do we reach a breakeven point. In other words, when using a 3% discount rate, the entire population of people with type 2 diabetes could ignore the newer method of treatment, and only 14% of the entire population of people with type 1 diabetes (including both those eligible and ineligible) would need to utilize intensive therapy in order to make this research investment worthwhile.

Table 6-1: Breakeven points

	DFE	WTP
Cost of Treatment at 3% for Type 2 diabetes	$ 34,285	$51,567
Cost of Treatment at 7% for Type 2 diabetes	$16,566	$24,908
Number of People with Type 2 diabetes at 3%	15,616	0
Number of People with Type 2 diabetes at 7%	193,344	68,668

Note: for WTP, the breakeven point for number of people was zero for all people with type 2 diabetes and 9,198 people with type 1 diabetes.

Finally, an examination of the components underlying the calculation of research costs was undertaken. The methodology for calculating research costs was developed by NIH scientific administrators and outlined in the previous chapter. Possible errors in calculating these costs include both false positives, i.e. inclusion of costs related to research activities not associated with diabetes research, or false negatives, the exclusion of appropriate research activity costs. Without a strict examination of each project over the past forty years, it is impossible to verify the appropriateness of the research activities, however it is possible to vary the best estimate for research costs. Given that research costs are only a fraction of the benefits of that research, even doubling the cost of research does not change substantially the overall result of the analysis.

Threats to Validity

Measurement validity: The biggest potential threats to validity are the measurement of the costs and benefits, particularly the value placed on work productivity and thus, the major benefits of diabetes research. There are a number of accepted methods for valuing cost-of-illness and work productivity. The method chosen here measures the loss in terms of human capital, i.e. productivity, due to sickness and disability. To minimize this threat, standard databases and surveys prepared by government sources have been used as much as possible. Also, standard measurements of human capital, worker productivity and others were used.

Throughout the analyses, direct ties were made between HbA_{1C} status and work productivity, for example additional years of life with diabetes, and missed workdays.

Because different studies were used to gather the necessary data, some measurement discrepancies exist in the different data sources. Furthermore, small differences may exist in the treatment of patients with diabetes, which manifested themselves in the results. Extensive efforts were made by DCCT-affiliated researchers to ensure standardization of treatment outcomes (through use of HbA_{1C} levels) and thus assure that economic measures were also appropriate. Testa and Simonson used slightly different standards for intensive and conventional therapy in their quality of life studies, but the slight discrepancies only served to understate the benefits and thus were left as is.

External validity: No attempt has been made to generalize the results of this research to other diseases, or to other countries. The objective of this research is to test the feasibility of this approach to valuing research benefits, not to develop a definitive rate of return for all biomedical research. Furthermore, because of the use of economic models created solely for this type of analysis, direct application of this study to all fields of biomedical research will lead to difficulties in appropriately assigning research and research funding to specific diseases. Finally, many other diseases have not been studied in the manner of and as extensively as diabetes has been, thus potentially leading to incomplete information and faulty analyses when trying to replicate this study using other diseases. For example, researchers may have not reached the point where a massive trial like the DCCT would be appropriate or desirable. Nonetheless, the success of applying this type of analysis to diabetes research may lead others to study other diseases and disease-based research in a similar manner.

Internal validity: Greater attempts have been made to maintain internal validity. Only improvements in the health status of people ascribed to advances in diabetes research, in particular the DCCT, were used. It was important to isolate the research advances because of several contradictory trends, including the increasing number of people with diabetes due to better screening and diagnosis, better treatment and greater access to health care, and finally the growing U.S. population, which have resulted in ever increasing amounts devoted to treatment of diabetes in the United States. Thus, while we are spending more than ever on diabetes treatment, we are also at the same time reaping the benefits of diabetes research, primarily through enhanced work productivity.

Chapter 7: Conclusion and Implications for Policy

The analyses conducted as part of this research are considered *ex post* analyses, in that the investments being studied have already been committed and the results are either made public or can be forecast with some accuracy. Since it is not possible to alter the terms of the initial investment, i.e. we cannot change decisions that have already been implemented, policymakers cannot use the results of this analysis to influence the direction of the current program of research. However, this type of analysis does have value in that it allows to us examine what has transpired and draw some lessons from the experience. By examining the process and the results, we may be able to influence future decisions regarding the allocation of scarce resources. Furthermore, by combining this study with studies of other disease-based research investments, we may be able to provide valuable guidance to policymakers and research advocates about the impact generally of medical research and its translation into clinical practice throughout society.

Another important reason for research of this nature is to allow researchers and those in the research community to appreciate the role of both direct and indirect costs in the development of treatments. For example, it may be immediately obvious to many,

including patients, physicians, and insurance companies, that a treatment that involves more active health care, through increased checkups with physicians, greater involvement of allied health workers such as dieticians and physical therapists, and more frequent monitoring of blood glucose would naturally be more expensive to maintain. These are all direct costs that are borne ultimately by the consumer and society at large. That knowledge may in fact influence the purchase and practice of health care. What might not be so obvious are the indirect gains due to this more active health care. These are measured quite readily in the research cited in this study, such as increased longevity, increased quality of life and a significant delay in complications. However, without a translation into monetary terms, policymakers may never match up these benefits against the additional costs. While the gains may be modest on a personal level, e.g. a gain of a few months or years in the lives of individuals, when summed across the nation, these benefits become quite substantial, depending on the method used for valuing human life. Conversely, if the population base of affected people is small, the payoffs must be large in order to justify the costs from an economic perspective.[38]

Most importantly from the perspective of this study, no connection is ever made to the upfront research costs, i.e. the initial investment made by the Federal Government to address the overall problem of ill health. Thus, society does not have the benefit of knowing how a certain portion of their taxes set aside for medical research has indeed paid off in terms of their well-being, in some cases handsomely.

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[38] This is not to imply that research on a disease affecting a small number of people is not without merit. Indeed, numerous benefits of a scientific nature may accrue from this type of research. Additionally, Congress has recognized the plight of so-called "orphan diseases" and has enacted tax breaks to ensure that the pharmaceutical industry does pay attention to these diseases.

Another insight is the role of access in realizing the benefits of medical research. The study described herein assumes that there is a single payer of health care and that health care is not restricted due to income level or geographic location. As we know, this country has many pockets or areas where people do not have adequate access to health care. The United States has several medically underserved areas, both in rural locations and in urban environments, where clinics and hospitals are scarce. Even if health care is located geographically nearby, access to health care is not guaranteed. The majority of Americans pay for their medical care through health insurance schemes provided by their employers. A large number, unfortunately, have no or limited health insurance from their employers, or have no employer at all. Although the purpose of the research was not to document the economic benefits of improved health care access, it is nonetheless interesting to note that the benefits of diabetes research do depend heavily on the ability of Americans to have access to improved medical treatments. Otherwise, the benefits that would have otherwise accrued to society are lost.

Finally, it should be noted that this type of study has an additional benefit. By focusing on the Federal role in biomedical R&D, it sharpens the argument for the continued role of the Federal Government in the support of R&D. Through this research, we can appreciate the long-term view of the NIH in making a 25-year commitment to diabetes research and seeing how that research has evolved over time. This is a commitment that the private sector, particularly the pharmaceutical industry, cannot afford to make. It must focus their resources primarily on short-term goals, chasing down leads that

developed either in their own laboratories or those that they have purchased from others, and funding the clinical trials to evaluate those leads. The pharmaceutical industry also cannot justify support for trials like the DCCT simply because the DCCT did not focus on any one drug but instead focused on evaluating a method of addressing a disease that is not drug-specific. In this manner, the DCCT approached diabetes treatment from a holistic perspective, managing the disease using whatever drugs were at the researchers' disposal.

This holistic approach included behavioral changes, more frequent monitoring of diet, exercise and lifestyle, and a conscious effort to educate the patient about the causal links between their lifestyle and their health. No drug company would be interested in evaluating such a holistic approach unless they were convinced beforehand that their company would be a significant beneficiary.

It would be to state the obvious that the goal of NIH's research program on diabetes is to find a cure for diabetes. Other goals are to find methods for preventing the onset of diabetes and better treatment methods, such as intensive therapy. An interesting insight however is that these goals are not necessarily consonant with the pharmaceutical and medical device industry. Diabetes is presently a chronic disease, meaning that once a person is diagnosed with diabetes, he or she has recurring costs of treatment, including hospital visits, drugs and medical supplies such as blood testing equipment. These costs are recurring throughout the remainder of the person's life, constituting rents that are collected by industry. A cure for diabetes would impact the collection of those rents such

that unless the cure for diabetes is priced at a figure equivalent to or greater than the net present value of those recurring costs, the pharmaceutical and device industry will experience a net loss. This realization may in fact be guiding in part their research investment decisions. If so, this could demonstrate a situation where industry's objectives are not the same as society's objectives. Again, this further strengthens the argument for continued Federal involvement in biomedical R&D.

One unexpected outcome of this study was the realization that from society's perspective, there is a net loss in the research investment if one considers only people with type 1 diabetes, when using the human capital approach, i.e. when considering discounted future earnings. If taken alone, i.e. if type 2 diabetes did not exist, the research investment in diabetes research would not have been justified from a societal perspective. The same is not the case when using the health capital approach, i.e. using willingness to pay.

Nonetheless, even using the human capital approach, these losses are more than made up by the gains of people with type 2 diabetes, of which there are nine times more in the general population. When one considers that research on type 1 diabetes is often seen as the motivating force in overall diabetes research, this result is doubly interesting. Much of the research focus is on type 1 diabetes and results specific to type 1 diabetes are often applied afterwards to type 2 diabetes. For example, the DCCT focused initially on people with type 1 diabetes. Only after the results of the trial became evident did researchers begin a similar trial, the United Kingdom Prospective Diabetes Study, to test the same therapy on people with type 2 diabetes. If the initial results of the DCCT had not been

promising from a scientific perspective—depending on the reasons for the failure—it is a possibility that the same method would not have been tried in those with type 2 diabetes. Note that this rationale would not necessarily hold in all types of diabetes research; rather it depends on what makes sense from a scientific perspective and whether a trial that fails in one population would fail in a different population either for the same or different reasons.

Reasons behind this sequence may be historical and/or scientific. For example, in the past, type 1 diabetes was a much more tragic problem, affecting young children and causing much premature death. With the advent of insulin in the early to middle 20th Century, we saw those children and young adults with type 1 diabetes living longer lives, although they still suffered greatly. During that same time period, type 2 diabetes was a silent killer, undiagnosed, unacknowledged, and thus untreated. People who had the disease often perished due to one of the complicating conditions, further obscuring the underlying reason behind their premature death.

Only recently have we seen a surge in the number of people with type 2 diabetes, as the overall rates in this country and globally have increased due to greater incidence of obesity and sedentary lifestyles, and greater efforts to screen for the disease early on. Importantly, greater access to health care by the elderly through Medicare has also been a factor. Senior citizens with access to health care now are able to spot earlier the onset of diabetes, they are also able to treat the complications earlier and more effectively, thus lengthening their overall lifespan and adding to the greater prevalence of the disease

throughout the United States. As a result, the 1 to 10 ratio of type 1 to type 2 diabetes will likely drop to 1 to 20 in the near future, further increasing the value of this research investment. Already, as a result of these changing demographics, we are seeing increased attention and resources on the problem of type 2 diabetes, focusing on both the basic science and behavioral studies.

Besides cost-benefit analysis, this study also examined the appropriateness of using cost-effectiveness and cost-utility analysis in evaluating diabetes research. As noted before, CEA and CUA are widely used in evaluating health outcomes, such as the outcomes of two different therapies. In their most common use, CEA and CUA examine the costs from either the patient's perspective or a single payer perspective. In other words, they do not normally allow for the identification and integration of indirect costs to society. Thus, society cannot evaluate how well those health dollars were spent.

CEA is additionally limited in that it can be used only when comparing therapies that are mutually exclusive and achieve the same goal. For example, intensive and conventional therapies treat the same condition, diabetes, and have the same objective in mind, control of diabetes. One cannot simultaneously use both conventional and intensive therapy, thus a choice must be made between the two. CUA at least allows one to value the achievements in standardized units which allows one to compare across treatments and to a lesser degree across objectives. Even then, not all costs to society are accounted for.

With an arsenal of CUA studies of the sort described in this study—all expressing outcomes in terms of QALYs saved—it is conceivable that one could begin to evaluate the value of different avenues of biomedical research, however, then one is forced to compare one disease-based research program against another, which could lead to a zero-sum game and would ultimately be unproductive. One should not be forced to compare diabetes research to cardiovascular disease research, for example. To do so would deny or compromise the potential gains made through research in diabetes which ultimately benefit the patient with cardiovascular disease, or vice versa.

Given the interrelatedness of biomedical and behavioral research, what would be much more desirable is an ability to evaluate the entire portfolio of NIH research (or at least significant parts of it) and demonstrate its value against other forms of Federal Government spending, whether in health care, national security, other types of scientific research, or in land and resource management.

Thus, we begin to see the value of cost-benefit analysis (CBA). While more complicated to design and implement, it does allow one to factor in all the costs and benefits to society and to compare those net benefits or costs across the spectrum, even to different fields of investment or government spending. In that sense, CBA is much more flexible and ultimately valuable as a tool of the policy analyst.

This analysis attempts to achieve an understanding of biomedical research in terms of its economic impact. It attempts to measure research benefits in a manner that is useful to

policymakers without causing undue administrative burdens and without unduly biasing one type of medical research over another. This research also attempts to answer some basic questions, such as how much return in the medical research investment are we as a society receiving. Is this research investment justified and should we be investing more or less in research? Should we ask our scientific administrators, those entrusted with the actual disbursement of research funds, to make their annual appeals for funding in terms of economic returns, numerical goals, and lives to be saved? Does it make sense to perform cost-benefit or cost-effectiveness studies of medical research investments, and is this type of analysis useful in GPRA reports?

The results of this research show that the investment in diabetes research is substantial, and compares well to many private sector investments. Therefore, the nation's investment in diabetes research is well justified. Because diabetes is a widespread disease, affecting a relatively large component of the population, the benefits extend to practically all segments of the population, whether personally through increased quality of life, within the workplace due to less absenteeism and fewer complications, or society at large due to increased productivity and contributions to the overall economy.

However, the analysis has its limitations, particularly in its applicability to the yearly process for determining how much Congress should invest in NIH, and where those investments should be placed. For example, while the results can be expressed as net benefits per year or cost per life saved, no direct correlation to inputs (research costs) for any one year can be made, because the actual benefits are spread out over a wide time

horizon. To apply the results of this analysis on a year-by-year basis would be futile, due to the general inability to assign research results to any single year's funding level.

As mentioned before, the DCCT and related trials were multi-year commitments. Furthermore, the consensus decision to undertake the DCCT and other trials was dependent on the outcome of many years of research undertaken by numerous researchers in different locations, including outside the United States, and in some cases supported by sources other than the NIH. Therefore, Congress cannot modulate the amount of NIH research dollars invested in any one year and expect to have an identifiable impact on future net benefits. By the same token, one cannot assess the impact of sudden dips or increases in research funding by looking at later research results. Of course, in extreme circumstances, a sudden decrease will negatively impact the ability of the NIH to fund major ongoing research initiatives, e.g. a multi-year clinical trial. In cases of sudden downward shifts, ongoing funding commitments would have the highest priority and new projects would be given a lower priority. A dip or increase would merely delay or advance by one or more years the commencement of worthy research projects.

Furthermore, while this analysis shows that there are substantial returns over a twenty-five year period to diabetes research, this particular analysis does not allow one to compare an investment in diabetes research to other fields of medical research, such as cancer, cardiovascular disease, AIDS or asthma research. In order to do so, one would need to conduct similarly designed studies on those other areas of research. Thus, we

cannot yet say whether diabetes research is a good investment in relation to other areas of medical research, or even non-medical research.

It may be possible to perform a similar type of analysis to subgroups, such as research into the genetic basis of diabetes, however such an analysis would suffer from problems with internal validity and other measurement problems due to the difficulty in assigning the relevant research projects to the correct subgroups. For example, it is entirely conceivable that progress in a specific subgroup would benefit greatly due to research conducted in a separate, but related, subgroup. Finally, the economic impact of such subgroups would be murky at best, since the application of the results—for example, identification of the genetic mutation (assuming one or more mutations exist) responsible for type 1 or 2 diabetes—would be dependent on knowledge gained in other research subgroups, e.g. nutrition research, prevention research, or drug development.

A further limitation, as acknowledged earlier, is that actual net benefits, i.e. those experienced by society, are heavily dependent on access to health care. While the DCCT researchers took special care to include in the study and subsequent simulation models only the fraction of people with diabetes most likely to respond well to intensive treatment, and while these calculations are reflected in this study's calculation, no attempt was made to estimate what portion of those with diabetes actually have access to health care. Thus, we cannot know with certainty how these benefits will actually accrue over the next 25 years. Much of the success of the diabetes research program is dependent on this country's ability to deliver health care. Nonetheless, the value of this research still

exists in that it does enable us to make comparisons of other research investments, particularly if assessments of those investments also make similar assumptions, creating a baseline with which to compare. Thus, this study can be seen as having more value as a research policy tool than a health policy tool.

One should also note that these results—and in particular the methodology used—are specific to diabetes research, which benefited from the availability of appropriate data from clinical trials and analyses of results from the economic perspective. Other broad areas of biomedical research, e.g. cancer or cardiovascular research, may have similar data available. But many other diseases have not been studied in the same manner and as extensively as diabetes has been, thus potentially leading to incomplete information and faulty analyses when trying to study other diseases using this model. Timing should also be considered. For example, researchers may have not reached the point where a massive trial like the DCCT would be appropriate or desirable. Furthermore, researchers may not have chosen to conduct the sorts of cost-effectiveness research that would allow one to determine lifetime costs and medical benefits.

Diabetes research has benefited from sustained Congressional interest, which has resulted in the creation of a number of commissions, advisory groups, and task forces all of which have examined the body of research in detail, catalogued and accounted for all research expenditures, and recommended areas for new inquiry. As a result of this attention, a plethora of information is available. This same information is not necessarily available in other medical research areas, particularly those areas that have not caught the interest of

Congress. Two countervailing trends are the increasing interest in GPRA and separately the interest in tying biomedical research expenditures to burden of disease. While researchers and research administrators may be concerned, and justly so, about non-scientific experts micro-managing their research portfolios, these developments do have the unintentional benefit of refining and expanding our categorization of research into disease areas, making more studies of this nature conceivable.

As part of this development, the success of applying cost-benefit analysis techniques to diabetes research may lead others to study other subsets of medical research in a similar manner. Indeed, perhaps the most compelling aspect of this analysis is the dramatic benefits derived from a sustained commitment to diabetes research over the course of two twenty-five year periods. This example can be used by NIH scientific administrators and research advocates as part of their yearly Congressional justification process. To echo the cautionary statements of the finance industry, past performance is never a guarantee of future success. Nonetheless, the scientific community can justifiably claim these successes as further validation of their ability to select specific research activities and to make progress against disease. Furthermore, they can credibly claim substantial benefits from incremental increases in medical research investment.

If applied on a selective basis to other diseases and other large areas of research, for example, prevention research, then policymakers may begin to use these and similar results as part of the yearly GPRA presentation. The objective of the GPRA legislation was to establish parameters for execution of an agency's responsibilities—in the case of

NIH, that would be the support and conduct of biomedical and behavioral research. The performance objectives and measurements designed by the agency should indicate whether or not that agency was making progress towards its mission. For NIH, that mission includes the improvement of the health of the nation through science.

As discussed earlier, NIH has chosen in its GPRA reporting not to focus on quantitative outputs but more qualitative descriptions of their progress. They have divided their performance goals into three broad areas: research programs; research training programs; and research facilities programs. It would be difficult at best to fit analyses such the one undertaken in this study into this paradigm. For example, under the goal of Research Programs, the goals are divided into four "functional areas": research outcomes, communication of results, technology transfer and research leadership and administration. Of those of some relevance perhaps to cost-benefit analysis, research outcomes refer to specific scientific endeavors with a general goal of creating new scientific knowledge and research leadership and administration refers to goals such as streamlining administrative functions and ensuring financial accountability. Econometric measures such as cost-benefit analyses or cost-effectiveness analyses are not currently being considered, although this is not to suggest that if the case for cost-benefit analysis was made that NIH leadership not be in favor of presenting their results in this manner.

The types of analyses described in this research were not particularly burdensome or costly. These analyses built on studies previously conducted for other purposes, i.e. the search for improvements in diabetes therapy. Keeping in mind that not all areas of

medicine have been studied as extensively as diabetes, it is nonetheless conceivable that other areas of biomedical and behavioral research could be analyzed in a similar manner. If NIH wished to use cost-benefit analyses to demonstrate the accomplishment of its mission, staff could analyze data from a variety of research areas, using different time periods as appropriate to the field of research.

Because these analyses should not be expected to change dramatically from year to year, not all areas of research need to be re-analyzed or updated each year. A more reasonable period would be every five to ten years. In this manner, the administrative burden on NIH staff would not be great, as long as the data were available for analysis. To ensure that these data were available, the NIH may wish to develop a systematic approach to collection of the necessary statistics, such as the regular solicitation of proposals to conduct cost-benefit studies. Indeed, in certain circumstances, the NIH or research advocacy groups may wish to use cost-benefit studies to highlight areas of research that have not received significant Congressional attention in the past, but could substantially benefit from increased investment.

Once a body of *ex post* studies like this study has been completed, we may begin to amass information regarding the nature of economic returns to medical research and to note certain trends. For example, in this study of diabetes research, we learned that although the gains in life expectancy are rather modest on a personal scale, with the large number of people with diabetes in the United States, society reaped substantial gains, in some calculations far outweighing the initial investment costs. If enough *ex post* studies

of this nature were done, one could make some reasonable guesses, *ex ante*, that is, before the research program began, what economic returns could be reasonably expected.

Care should be taken, however, that this and related analyses not be the sole criterion for determining the appropriate level of resources to devote to medical research. While cost-benefit analyses hold the promise of estimating the economic impact of certain types of research, we should insist that future investments in medical research not be made on economic impact alone. Furthermore, with increasing use, these analyses will be subjected to greater criticism, particularly of the assumptions made as part of the analyses. Because of the arbitrary nature of valuing lost human potential and human pain and suffering, different constituencies may value the same costs and benefits differently. While both willingness-to-pay and human capital methodologies were used to value the economic benefits of diabetes research, different groups may prefer one over the other.

Economic impact should instead be part of a basket of parameters and performance measures used by NIH and Congress in evaluating past achievements and allocating new funding. Scientific research is unpredictable in the timing and nature of results. We can never know where insights into the biological processes and behavior of humans will come next. Therefore, we must rely on the best judgment of scientific experts to judge the results that are available, and make recommendations on worthwhile investments.

While it may not seem necessary to determine the benefits of specific areas of research when one knows that the overall effort is beneficial, lawmakers often exercise a

prerogative to allocate funds at the programmatic level, often at the urging of outside groups. Thus, administrators within the technical agency could consider foreknowledge of the benefits at this level of detail useful. However, measures of this type must be developed and used with caution. Just like any other measures of the epidemiological dimensions of a disease such as diabetes, measures of cost-benefit ratios and other econometric tools are only based on past performance without necessarily pointing to possible solutions for the future. These tools only enable us to understand the context in which we are making decisions, in other words, the proverbial "big picture." Their use in determining specific funding needs have the potential for misallocating resources, particularly by those with narrow agendas such as advocacy groups seeking to increase funding in a specific area of medical research.

One cannot stress enough that because of the uncertainty of scientific research, we can never know where the next breakthrough will come. Research breakthroughs or new ways of studying the mechanisms of the human body may come from any number of sources, including outside the field of biomedical and behavioral research. Thus, we must continue to rely on experts to evaluate the research results of the scientific community and make recommendations on where next to invest limited resources.

Information such as cost-benefit analyses helps to assure us that we are making wise investments, and in general, allows us to argue for additional overall funding, but we cannot allow these analyses to be used to determine exact funding levels for specific

diseases or areas of research. We must continue to make those judgments based on the advice of those who are aware of the scientific achievements and opportunities.

Summary

This research has allowed us to say that the nation's investment in medical research can be evaluated using cost-benefit analysis in a reliable, unbiased, and reasonably accurate manner. Cost-effectiveness analysis and cost-utility analysis, while somewhat more limited, are also useful techniques. Furthermore, this research has given us an idea of the amount of work necessary to carry out such an analysis, and what results may show. The research will not give absolute figures for the rate of return on the science and technology investment in aggregate, or in specific subsets.

It has been the intention of this study to test the feasibility of these approaches to determining the benefits of research. In addition, this research adds to the general body of knowledge regarding cost analyses and economic evaluation of research investments, particularly because of its focus on the relatively unexplored area of medical research. With a validated and reliable method for determining benefits, science agencies can more effectively make their case to Congress for greater investment in science and technology, particularly in an era of constrained resources and a need to justify investments in a quantified manner. Furthermore, science administrators can determine which aspects of their investment make the greatest impact, based on criteria they deem important. If R&D is to be seen as both a public good and an investment for all Americans, then the public should know what return on their investment they are getting.

Appendix A

This appendix provides additional details of the steps taken in the analyses described in Chapters 5 and 6. It also includes the spreadsheets where the data can be examined firsthand. As stated numerous times before, the purpose of this research is to estimate the economic impact of diabetes research and whether cost-benefit and cost-effectiveness/cost-utility analyses can and should be applied to disease-specific research. To complete this analysis, the benefits and costs of diabetes research within the United States were modeled.

As outlined in Chapter 6, the proposed research estimates the marginal benefits to people with diabetes due to diabetes research over the past fifty years, and subtracts the costs of diabetes research from those benefits in order to arrive at a final net result. A theoretical model for analyzing costs and benefits of diabetes research is given below:

> *The net benefits of diabetes research to society are characterized by the marginal benefits people with diabetes attributable to advances in diabetes research minus the cost of diabetes research.*

Net Benefits (or Costs) of Diabetes Research	=	Marginal Benefits to People with diabetes due to R&D	-	Costs of Diabetes Research

Costs of Diabetes Research

As discussed previously, it is appropriate to incorporate an expansive view of the diabetes research portfolio, including all diabetes-related research funded by NIH. The rationale was that basic research does not flow in simple lines, with one research activity leading to another and so on until the clinical trial. Rather, we see multiple feedback loops with researchers absorbing and borrowing ideas from many others in their search for clues enabling them to understand how the body works. Data for the cost-of-research component from Fiscal Years 1975 to 2000 came from the budget records of National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) which tracks all diabetes-related research funded by NIH. Again, it should be noted that the perspective used in this cost-benefit analysis is the perspective of U.S. society. Table A below gives the funding levels for NIH diabetes research, as determined by the scientific program directors of NIH. For the purpose of this analysis, the "Trans-NIH" figures were used. These figures reflected the total amount of diabetes-related research funded by NIH, regardless of the individual institute funding the research. Thus, it captures all diabetes-related research, for example, research on retinopathy due to diabetes funded by the National Eye Institute. These figures, given in current dollars, were translated first into constant 1996 dollars (for which deflator values were known), then into constant 1975 dollars. Deflator values were taken from the price indices provided by Bureau of Economic Analysis, *GDP tables: 1940 to 1999*. Thus, we see that the cumulative value

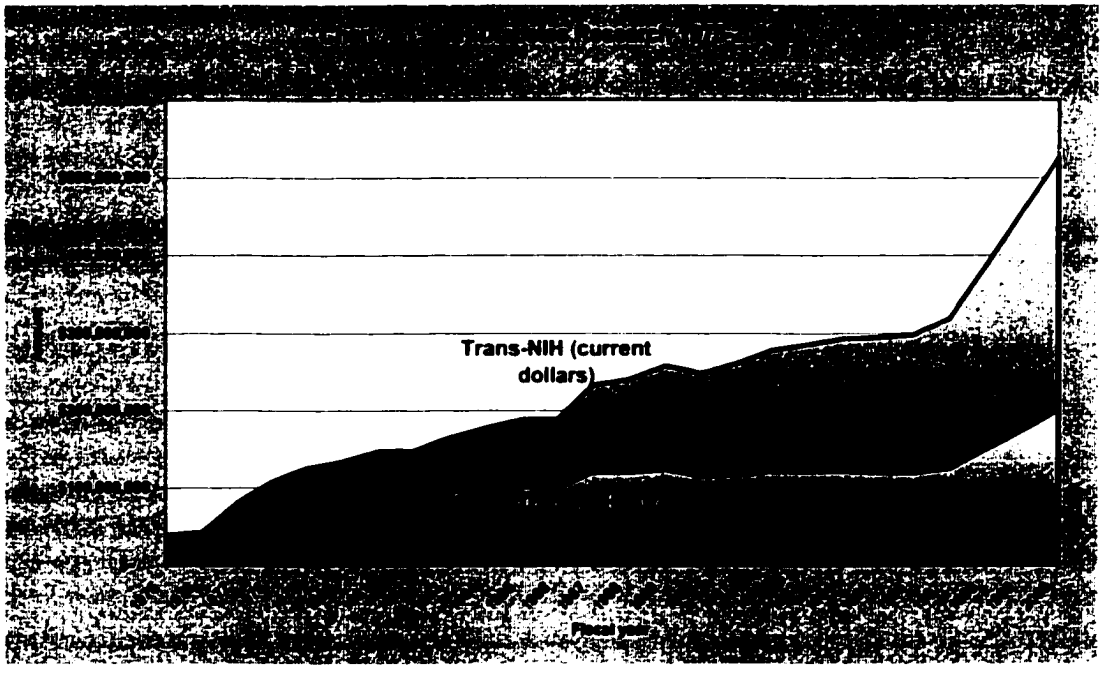
in 1975 of all NIH-funded diabetes research was approximately $2.87 billion. Note that Table A-1 can also be found in Chapter 2.

Table A-1: NIH Diabetes Research Investment

Fiscal Year	Trans-NIH (current dollars)	Trans-NIH (1975 dollars)
1975	$39,100,000	$ 39,100,000
1976	$42,700,000	$ 40,408,534
1977	$81,500,000	$ 72,466,570
1978	$108,400,000	$ 89,969,977
1979	$125,900,000	$ 96,455,062
1980	$134,200,000	$ 94,179,979
1981	$147,800,000	$ 94,860,253
1982	$148,400,000	$ 89,667,200
1983	$165,200,000	$ 96,006,911
1984	$177,900,000	$ 99,682,769
1985	$188,900,000	$ 102,614,561
1986	$189,100,000	$ 100,513,517
1987	$234,100,000	$ 120,791,738
1988	$240,800,000	$ 120,174,841
1989	$258,800,000	$ 124,411,721
1990	$249,200,000	$ 115,310,091
1991	$261,500,000	$ 116,750,446
1992	$278,400,000	$ 121,345,296
1993	$285,800,000	$ 121,643,530
1994	$293,600,000	$ 122,412,332
1995	$295,100,000	$ 120,416,442
1996	$298,900,000	$ 119,649,670
1997	$319,500,000	$ 125,449,583
1998	$387,200,000	$ 150,160,977
1999	$457,600,000	$ 174,837,530
2000	$525,100,000	$ 200,627,594
TOTAL	**$5,934,700,000**	**$ 2,869,907,125**

Source: NIH National Institute of Diabetes and Digestive and Kidney Diseases Budget Office and Bureau of Economic Analysis, GDP tables: 1940 to 1999

Chart A-1 is a graph charting the NIH diabetes research investment from 1975 to 2000, giving both the current dollars and the value in 1975 dollars.



Benefits of Research

In the cost-benefit analysis, two methods were used to determine the marginal benefits of intensive versus comprehensive therapy. The health capital method utilized willingness-to-pay measures to estimate the value to people of the additional years of life due to intensive therapy, and the human capital method utilized estimates of the increases to worker productivity from both the additional years of life and the decreased number of absences from work. Either estimate can be used when comparing the benefits to the costs.

Both estimates used essentially the same model to estimate the benefits of intensive therapy over conventional therapy. The model was first applied to people with type 1 diabetes and then, with minor modifications, was applied to people with type 2 diabetes.

Recall, in the original research by the DCCT Research Group, simulated cohorts of people with type 1 and 2 diabetes were subjected to differing standards of treatment, each standard reflecting the state-of-the-art treatment at different periods of time corresponding roughly to the years of 1975 (conventional therapy) and 2000 (intensive therapy). Each state-of-the-art treatment was developed with the benefit of research carried out and knowledge gained over the previous 25 years.

Starting from the work of the DCCT Research Group, a new model (Model 1) was created to reflect the transition from conventional to intensive therapy among people with type 1 diabetes. Model 1 includes the marginal costs of intensive therapy over conventional therapy within a cohort of people with type 1 diabetes. This cohort represents the number of people in the U.S. newly diagnosed with type 1 diabetes every year and eligible for intensive therapy. This cohort was replicated 25 times, once for each year from 2001 to 2025. To this model were columns incorporating the additional number of years gained by using intensive therapy instead of conventional therapy and estimates of either the increases in productivity or the willingness to pay for the additional years of life, as described below.

A similar procedure was used to develop Model 2, which estimates the marginal benefits of those with type 2 diabetes. Below are more complete descriptions of the individual components of Model 1 and 2.

Numbers of eligible people with diabetes

Each year, approximately 658,000 Americans are diagnosed with some form of diabetes.[39] Approximately 10% of this cohort is diagnosed with type 1 diabetes, and 90% is diagnosed with type 2 diabetes. Table A-2 below gives the three-year averages from 1980-1992 of newly diagnosed cases per year. An average of these figures was used in the analyses. This average is used in projecting the number of people diagnosed with diabetes over the next 25 years. This may be a conservative figure given better screening techniques and the aging of the "baby boomer" population.

Table A-2: Newly Diagnosed Cases per Year, 1980-1992, Three Year Averages

	All types	Type 1	Percent Eligible (17%)	Type 2	Percent Eligible (85%)
1	601,000	60,100		540,900	
2	647,000	64,700		582,300	
3	696,000	69,600		626,400	
4	685,000	68,500		616,500	
5	669,000	66,900		602,100	
6	693,000	69,300		623,700	
7	691,000	69,100		621,900	
8	701,000	70,100		630,900	
9	633,000	63,300		569,700	
10	607,000	60,700		546,300	
11	624,000	62,400		561,600	
Average	658,818	65,882	11,200	592,936	503,996

Source: *Diabetes in America*, 2nd edition, p. 236.

Of the 65,882 people every year diagnosed with type 1 diabetes, only 17% or 11,200 of this group were eligible for intensive treatment, using the criteria of the DCCT Research

[39] In the model, the number of newly diagnosed people with diabetes was kept constant at 658,000 per year, although the U.S. population is predicted to rise and the number of people with diabetes is also predicted to rise. The nature of this increase is difficult to predict accurately, particularly given the eligibility requirements described later, thus, a conservative estimate of the status quo was assumed in the analysis.

Group. Of the 592,936 people diagnosed with type 2 diabetes, approximately 85% or 503,996 per year were eligible. As stated previously, the new therapy is best applied to people soon after their diagnosis; this allows the intensive therapy to have its maximum impact in delaying onset of complications. Furthermore, some people used to conventional therapy have difficulty in complying with the relatively burdensome intensive therapy, thus do not successfully shift from conventional to intensive therapy.

Cost of Treatment

Basic costs of the two types of therapies to treat type 2 diabetes are given below in Table A-3. These figures were the basis of later calculations comparing the two therapies.

Table A-3: Average Lifetime Cost of Treatment, Effectiveness, and Incremental Cost-Effectiveness under Conventional and Intensive Therapy for Type 2 Diabetes (Present Value costs (3% discount rate) in 1994 dollars)

	Conventional Therapy	Intensive Therapy	Difference
Cost of general and diabetes-related medical care	$32,365	$58,312	$25,947
Cost of eye disease	3,128	1,536	(1,592)
Cost of renal disease	9,437	960	(8,477)
Cost of neuropathy/lower extremity amputation	4,381	1,469	(2,912)
Cost of new coronary heart disease	13,458	14,414	956
Total Costs	$62,769	$76,691	$13,922
QALY (undiscounted)	16.04	18.03	1.99
QALY (discounted 3%)	11.43	12.3	0.87
Life years (undiscounted)	17.05	18.37	1.32
Incremental costs/QALY gained			$16,002

Source: *Diabetes Care*, v. 20, n. 5, may 1997, p. 739

Similar differences existed between the costs of therapies to treat type 1 diabetes. A summary comparing these cost differences (conventional vs. intensive, type 1 vs. type 2) is given in Table A-4 below.

Table A-4: Cost of Diabetes Types 1 & 2: Intensive vs. Conventional Treatment

using a 3% discount rate, the expected ***lifetime cost per patient*** (1994 prices) was:

	Type 1 Diabetes	Type 2 Diabetes
Intensive Treatment	$99,822	$76,691
Conventional Treatment	$66,076	$62,769
Difference	$33,746	$13,922
Difference per QALY gained	$19,987	$16,002

Source: DCCT Research Group, "Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trial," *JAMA*, v. 276, n. 17, Nov. 6, 1996, p. 1409-1415 and *Diabetes Care*, v. 20, n. 5, may 1997, p. 739.

Note that the figures above do not incorporate a calculation of the benefits of additional years of sight, freedom from kidney disease, amputation, or other complications.[40] Out-of-pocket expenses not already covered by insurance were also not included. Finally, the DCCT Research Group did not incorporate short-term benefits of one therapy versus the other, such as improved quality of life.

Additional Years of Life Gained

Recall that the DCCT-generated benefits were expressed in additional years of life. Both models ran for 25 years (2001-2025). Each "year" of the model, a new hypothetical set of patients representing a portion of the people diagnosed with diabetes that year began

[40] For example, a person with type 1 diabetes using intensive therapy will on average experience 56.8 years of sight versus 49.1 years of sight using conventional therapy. See *JAMA* v. 276, n. 17, p. 1412 for details.

their treatment and the incremental costs and benefits of intensive versus conventional therapies were calculated over the course of their lifetime. In other words, someone who began their treatment for type 1 diabetes in the year 2001 would expect to spend approximately $99,822 for intensive treatment or $66,076 for conventional treatment over the course of his or her remaining life. If the person chose intensive treatment, he or she can expect to live 5.1 years longer for an average of 61.6 years after diagnosis.

Similarly, in Model 2, people with type 2 diabetes could expect to live 1.32 additional years of life more than the average of 17.05 years after diagnosis if they used intensive therapy instead of conventional therapy.

A person with diabetes is estimated to have a quality of life approximately 65% of a person in perfect health. Adjusting for QALYs and discounting at 3% to the beginning of diagnosis, the additional number of years become 0.62 years and 0.52 years for type 1 and type 2 diabetes respectively. Table A-5 below gives details with discounting also at 5% and 7%.

Table A-5: Number of Additional Years of Life: Intensive vs. Conventional Therapy

		Discount Rate		
	Undiscounted	3 %	5%	7%
Type 1 Diabetes	5.1	0.96	0.32	0.11
Type 2 Diabetes	1.32	0.80	0.57	0.42
QALY-Adjusted Additional Years of Life				
Type 1 Diabetes	3.32	0.62	0.21	0.07
Type 2 Diabetes	0.86	0.52	0.37	0.27

Willingness to Pay

Cutler and Richardson (1997) estimate the value to a person for an additional year of life to be $100,000, regardless of the year, health and socioeconomic condition of the person. Among people with type 1 diabetes, utilizing intensive therapy instead of conventional therapy adds 5.1 years of life to the average life expectancy of 56.5 years after diagnosis. Discounted to the beginning of the diagnosis at 3%, this becomes approximately 0.96 years of life. Thus, the value of utilizing intensive therapy for people with type 1 diabetes becomes approximately $96,000 (discounted number of years multiplied by the value of a year of life). Among people with type 2 diabetes, utilizing intensive therapy adds 1.32 years of life to the average life expectancy of 17.05 years. When discounted to the beginning of diagnosis at 3%, this becomes approximately 0.80 years and a corresponding value of $79,700. Adjusting for QALYs, the figures become 0.62 years and 0.52 years for type 1 and type 2 diabetes respectively, with corresponding values of $62,000 and $52,000.

The additional costs of treatment were then subtracted from these values to calculate the net benefits of intensive treatment over conventional treatment. For type 1, each person in each cohort had a net benefit of $28,700; and for type 2, each person in each cohort had a net benefit of $37,900. This assumes a discount rate of 3% and QALY adjustments. See Table A-6 for details.

Table A-6: Diabetes Types 1 & 2: Net Benefits of Intensive vs. Conventional Therapy			
	Value of Years of Additional Life*	Additional Cost of Intensive Therapy	Net Benefits
Type 1	$62,409	$33,746	$28,663
Type 2	$51,834	$13,922	$37,912

*includes both discounting at 3% and QALY adjustments.

Changes in Productivity

While intensive treatment generally results in higher direct costs than conventional treatment, the indirect benefits of intensive treatment are considerably greater, particularly for people with diabetes type 2. To calculate these indirect benefits using the human capital method, the benefits of intensive treatment were compared to the benefits of conventional treatment, looking at the differences in remaining years of life and the changes in absenteeism, i.e. missed days from work. Intensive treatment enabled people to live longer and miss fewer days from work due to complications related to their diabetes.

The next step was to calculate the dollar value of these additional days worked and years lived. Costs used in this study were based on Current Population Survey and Bureau of Labor Statistics data from 1994. The average value of a day of work was estimated to be $88.91, and the average value of one year of work was $22,774. The annual income figure was calculated by weighting the average values of one year of work by the comparable income levels of the population of people with diabetes stratified by age groups. Tables A-7 and A-8 give further information.

Table A-7: Average Number of People with Diabetes (Type 1 and 2 Combined)

Age	No.	Percentage
18-44	1,345,000	17.97%
45-64	2,835,000	37.88%
65-74	1,966,000	26.27%
>75	1,249,000	16.69%

Table A-8: Income in 1994

(current dollars)	Mean Income	Number with Income	Percentage (1st 3 and 2nd 2)	Weighted Mean Income (by age group)
15 to 24 years old	$ 8,764	27,026	25.33%	
25 to 34 years old	$ 22,296	39,150	36.69%	
				$ 21,724
35 to 44 years old	$ 29,817	40,517	37.98%	(15-44 years)
45 to 54 years old	$ 33,381	29,380	59.92%	
				$ 30,769
55 to 64 years old	$ 26,863	19,652	40.08%	(45-64 years)
				$ 17,952
65 to 74 years old	$ 17,952	17,886		(65-74 years)
				$ 14,971
75 years old and over	$ 14,971	12,791		(>75 year))
Mean Income of all people with diabetes weighted by age distribution				**$ 22,774 (all ages)**

Increases to productivity in utilizing intensive therapy were the sum of the values for the additional years of life and the additional workdays over the course of the remaining years of a person's life. Both the number of additional years of life and the value of the additional workdays over the course of the remaining years of life were discounted. Table A-9 gives details utilizing a 3% discount rate. The attached spreadsheets give further details on the calculations used.

Table A-9: Summary Calculations		
	Type 1 Diabetes	Type 2 Diabetes
Discounted Number of Years of Additional Life*	0.62	0.52
Mean Income per Year	$22,774	$22,774
Discounted Value of Additional Years of Life*	$14,120	$11,842
Number of Additional Workdays per Year	9.08	9.08
Value of Each Workday	$88.91	$88.91
Discounted Number of Years After Diagnosis	14.4	28.8
Discounted Value of Additional Workdays Over Lifetime*	$11,611	$23,216
Total Value of Increase in Productivity	$25,731	$35,058

*utilizes a 3% discount rate and QALY adjustments. Attached spreadsheets provide results using a 5% and 7% discount rate

The additional cost of the intensive versus conventional treatment was subtracted from the total value of increase in productivity to give the net benefits of intensive treatment per individual ($20,301 for people with type 1 diabetes; $10,235 for people with type 2 diabetes). See Table A-10.

Table A-10: Net Costs or Benefits per Person with Diabetes			
	Value of Increased Productivity*	Additional Cost of Intensive Therapy	Net Costs or Benefits
Type 1	$25,731	$33,746	($8,015)
Type 2	$35,058	$13,922	$21,136

*utilizes a 3% discount rate. Attached spreadsheets provide results using a 5% and 7% discount rate

These figures were then multiplied by the numbers of individuals in each cohort to arrive at a final figure of the total benefits to the United States of using intensive treatment. Discounting was then used to reflect these values in 1975, for comparison with the costs of diabetes research. Summary tables can be found in Chapter 5.

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Appendix C: A Brief History of Diabetes Research

Why Diabetes?

Diabetes research is a suitable subject of study because it is a reasonably well-defined field of study, with an identifiable constituency of people with diabetes. It has benefited from a long and consistent source of funding, with some improvements in treatment, although no cure or preventive measure has yet been found. Diabetes is one of the most prevalent diseases and one of the leading causes of disability in the United States and in the world. Estimates based on the 1993 National Health Interview Survey (NHIS) indicate that diabetes is diagnosed in 1% of the U.S. population under age of 45, 6.2% in those aged 45-64 years, and 10.4% of those 65 and older. In absolute numbers, an estimated 7.8 million persons in the U.S. were reported to have this chronic condition. The same survey reported that 625,000 new cases of diabetes are diagnosed every year.[41]

The Disease: Diabetes is a metabolic disorder primarily characterized by elevated blood glucose levels and by microvascular and cardiovascular complications that substantially increase the morbidity and mortality associated with the disease and reduce the quality of

life. There are two generally known types of diabetes, type 1 and type 2. Type 1 diabetes occurs in about 10 percent of all cases of diabetes. It generally afflicts the young and is characterized by a reliance on insulin for survival. Type 2 diabetes occurs in about 90 percent of all cases and generally occurs late in life. Insulin deficiency and/or insulin resistance characterizes type 2 diabetes.

The causes of diabetes are not precisely know, but both genetic and environmental factors play a role. The disease is marked by an inability to produce and properly use insulin—a hormone that is necessary to convert glucose into energy, leading to elevated blood glucose levels. An association between the complications of diabetes and elevated blood glucose has been postulated since the early part of the century.

The first major milestone in the control of diabetes was the discovery of insulin by Banting and Best made in 1921. However, only in the last three decades has a substantial body of evidence developed that directly linked hyperglycemia (the presence of too much sugar or glucose in the blood) to the development of diabetic complications such as nephropathy (liver failure leading to end stage renal disease and death), diabetic retinopathy (blindness), neuropathy (often leading to amputation of lower extremities), and cardiovascular disease. Some of the studies of the 1990s have demonstrated that strict control of blood glucose levels reduces the risks of diabetic retinopathy, neuropathy and nephropathy.[42]

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[41] National Center for Health Statistics, CDC: Current estimates from the NHIS 1993, *Vital and Health Statistics*, Series 10, no. 190, 1994.

[42] American Diabetes Association. "Position Statement: Implications of the United Kingdom Prospective Diabetes Study," Diabetes Care, v. 21, n. 12, December 1998, p. 2180.

The People: Of the many diseases that afflict Americans, few are as common and as complicated as diabetes. Despite the years of investment and the commitment of numerous scientists and physicians, there has been a steady increase in diabetes prevalence over the past 40 years, as well as a steady rise in the cost of the disease. Results of epidemiological surveys show that the prevalence of diagnosed diabetes in the U.S. has increased dramatically and now affects about 10.5 million people in 1998. These studies of representative samples of U.S. adults also found that as many as five million more people have undiagnosed type 2 diabetes and that African Americans, Mexican Americans, and Native Americans are more severely affected.[43] As a cause of death, diabetes ranks seventh, with 61,600 deaths occurring annually.[44] This number is an underestimate since many people die of complications of diabetes, such as cardiovascular disease, without diabetes being listed as a cause of death.

The Costs: The American Diabetes Association estimated the economic consequences of diabetes to be $98.2 billion in 1997. This included direct medical expenditures of $44.1 billion and indirect costs from premature mortality and disability of $54.1 billion. It also estimated that total medical expenditures incurred by people with diabetes was $10,071 per capita in 1997, compared with $2,669 per capita for people without diabetes. A 1992 study by ADA showed a total cost of $91.8 billion ($45.2 billion in direct costs and $46.6

[43] Harris, Maureen I., "Diabetes in America: Epidemiology and Scope of the Problem," *Diabetes Care*, v. 21, supplement 3, December 1998, p. C11.
[44] NCHS, Monthly Vital Statistics Report, vol. 46, no. 1, Supplement, 1996.

billion in indirect costs).[45] Note that, as calculated by the ADA, the increase in costs from 1992 to 1997, particularly direct costs, had more to do with changes in hospitalization rates and practices, and less to do with changes in treatment.

While it may be possible to approximate health care costs of diabetes within a specific time frame, the appropriateness of doing so for the purposes of this study is not apparent. Factors unrelated to research advances, such as changing health care financing conditions, serve to confound any attempt to link directly research advances to health care costs. For example, with the help of Medicare, greater numbers of seniors, the sector of the population most likely to be afflicted with type 2 diabetes, now have regular access to health care, thus their health status as a group has been more closely monitored and their overall health has improved. This in turn has led to increased longevity for those with diabetes. As a result, we have a higher prevalence of diabetes, i.e. a greater number of people with diabetes, in the general population. This greater prevalence, in turn, has led to an overall increase in health care costs. Thus, we have the apparent paradox of greater direct health care costs despite, or even as a result of, increased diabetes-related research and improved diabetes treatment.

Appropriateness as a Research Topic: During the past four decades, since significant NIH investment in diabetes began, much has been learned about the basic etiology and pathophysiology of diabetes. Many assessment and treatment options are now available to help people affected by diabetes, and scientific evidence supports both the efficacy and

[45] American Diabetes Association, "Economic Consequences of Diabetes Mellitus in the U.S. in 1997", *Diabetes Care*, v. 21, n. 2, p.296.

cost-effectiveness of programs directed at improving glycemic control as well as detecting and treating the complications of diabetes.[46]

Diabetes is an interesting and appropriate subject for a study of the costs and benefits associated with medical research into a particular disease. Diabetes afflicts a large, discrete population in the U.S. and thus is of broad interest. The disease is also a topic of intense study, both by academic health researchers as well as the private pharmaceutical industry, and well funded by NIH. In Fiscal Year 2000, NIH placed approximately $400 million into diabetes-related research. The NIH supports a remarkably wide range of research in its diabetes portfolio, from genetics and molecular and cellular biology, clinical and epidemiological research, to training and education programs for physicians and patients. One of its newest large-scale endeavors is a Diabetes Prevention Study that is enrolling people who are at risk of developing diabetes later in life to identify ways of preventing the disease, or at least to diagnose the disease at an earlier stage.

Diabetes is a chronic disease. Once a person is diagnosed—in the case of type 2 diabetes, usually 10 years or so after the onset of the disease —he or she will likely be under treatment for the rest of his or her life. Thus, a lifetime of costs is incurred. This is in contrast to many acute diseases, such as most infectious diseases, which have a relatively short course of treatment. Furthermore, as of yet, there is no cure for diabetes, nor is there an effective prevention system, adding to the urgency of additional investment. Thus, diabetes is broadly representative of most chronic diseases, such as asthma or

[46] Vinicor, Frank, "The Public Health Burden of Diabetes and the Reality of Limits", Diabetes Care, v. 21, supplement 3, December 1998, p. c15.

arthritis. Yet, because of its discrete nature and because major research funding for the disease comes from a single source, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the NIH, the bulk of research costs can be easily identified.

At the same time, diabetes is a contributory factor to a number of diseases, such as cardiovascular disease, blindness and end-stage renal disease. Research into the direct causes and treatment of these diseases is not included in the following analysis, although cost savings through control of diabetes do include savings associated with lowered prevalence of these diseases.

The past few decades have marked a period of rapid change in the understanding of diabetes and a greater appreciation of its natural history and of the benefits to be derived from systematic treatment of its preventable complications. Thirty years ago, diabetes was viewed as a condition resulting from abnormal glucose metabolism. It was known to be associated with a number of complications enumerated above, yet these complications were not viewed as manageable or preventable. As a result of research supported by NIDDK, culminating in the Diabetes Control and Complications Trial (DCCT), a link was established between the maintenance of near normal blood glucose levels and the mitigation of complications in persons with Type 1 diabetes. Likewise, similar benefits were found with patients with Type 2 diabetes.[47]

[47] McDonald, Robert C, "Diabetes and the Promise of Managed Care," Diabetes Care, v. 21, supplement 3, December 1998, p. C25.

In spite of these encouraging findings, there is evidence that the clinical practices promulgated as a result of DCCT and other related research have not been widely adopted.[48] In addition, surveys gives us strong evidence that there are a great many people with diabetes whose conditions are undiagnosed.[49] This evidence shows the difficulty in realizing the cost savings associated with new treatments and reduced incidence of costly complications. Simply conducting biomedical research into the causes and treatment of disease is not enough to effect substantial savings in the economy. The health care community must also work to provide new information to physicians and to ensure that new treatment methodologies are adopted. Beyond that, persons with undiagnosed diabetes must be encouraged to undergo screening and treatment and when diagnosed, placed as soon as possible on the new regimens to maintain blood glucose levels. Any cost-benefit models constructed to value the benefits of medical research must contain sensitivity analyses to consider compliance rates.

A Brief History of Diabetes Research

Diabetes mellitus is an ancient disease whose symptoms were first described over 3,500 years ago in a collection of medical diseases found in Luxor. This compendium was found by the Egyptologist George Ebers, and is known as the *Papyrus Ebers*. In 10 A.D., the Roman physician Celsus described diabetes mellitus as a disease of excess urination and wasting. The word diabetes comes from the Greek word meaning "siphon" or "going through." Mellitus is Latin for honey or sweet. Throughout written history several

[48] Vinicor, Frank, "The Public Health Burden of Diabetes and the Reality of Limits". Diabetes Care, v. 21, supplement 3, December 1998, p. c15.

mentions are made of the disease. For most of the last 2,000 years, diabetes mellitus was believed to be a disease of the kidney or bladder (urine of patients with diabetes when evaporated was found to contain sugar). (Goldfine and Youngren, 1998)

The source of that sugar was unknown. In 1857, Claude Bernard described glycogen as a product of glucose metabolism in the liver. Thus, he concluded that an alteration in this process produced the condition known as diabetes. In 1869, Paul Langerhans discovered the cells now referred to as the Islets of Langerhans within the pancreas. In patients with diabetes, these islets and pancreatic cells were abnormal, leading to the deduction that their secretions held the key to diabetes. Soon after, Oskar Minkowski and Joseph von Mering, by removing the pancreas of a dog and causing diabetes to appear, provided experimental proof that the pancreas was the key to diabetes mellitus, not the kidney or bladder. However, isolating the exact secretion of the pancreas that presumably prevented diabetes from occurring would prove to be very difficult. (Peterson, 1982).

Part of the difficulty in isolating the substance responsible for controlling diabetes lay in the lack of sophisticated equipment and methods for analyzing the components of body fluids, such as blood sugar or glycosuria (sugar in the urine). The equipment available at the turn of the century was primitive by today's' standards. For the next twenty years, scientists at that time used a variety of pancreatic extracts on pancreatized dogs (dogs whose pancreas was removed to model diabetes in humans) to see if the effects of diabetes were reversed. Some had promising results, but also toxic side effects, primarily

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[49] Harris, Maureen I., Eastman, Richard C., "Early Detection of undiagnosed non-insulin dependent Diabetes Mellitus," JAMA v. 276, Month 1996, pp. 1261-2.

due to the methods for isolating and extracting the active substance. Also, delivery of the extracts proved to be problematic. The extracts could not be administered orally, for they would decompose in the digestive tract. Thus, they had to be administered by injection. One promising line of research ten years before the discovery of insulin, by E.L. Scott, a graduate student in physiology, was dropped prematurely due to lack of interest by his advisors. Another investigator, a Romanian physiologist, N.C. Paulesco, also came very close. Unfortunately, World War I and the German invasion of Romania halted his work at a crucial stage. After the war, Paulesco was unable to pick up where he left due to lack of equipment and funds. Many have felt that he should have been nominated for the Nobel Prize along with those who would eventually be hailed as the discoverers of insulin. (Peterson, 1982)

Clinical treatment of diabetes during this period before the discovery of insulin reached its peak between 1910 and 1920 with the techniques employed by Frederick Allen. Allen's technique consisted of treating patients by fasting until their glycosuria disappeared. Then caloric intake was gradually increased until the sugar began to appear again in the urine. This level of calories was recorded and used as the basis for devising a diet with a maximum caloric intake. Although marked by severe weight loss and weakness, patients did manage to survive under these extreme conditions. In addition to working with humans, Allen also worked with partially pancreatized dogs to determine the effects of other conditions, such as cold, fever, infections and intoxication, on the clinical manifestations of diabetes. This harsh treatment was immediately rendered obsolete with the discovery of insulin. (Goldfine and Youngren, 1998) Nonetheless, the

close monitoring of diet and weight reduction, have been mainstays of modern diabetes treatment.

After the Great War ended, in 1920, Frederick Banting, a 22-year old surgeon attempted to launch a general practice in the small Canadian city of London, Ontario. Having some time on his hands, he also agreed to teach surgery and anatomy at Western University in London. In preparing for class one day, he came upon an idea for approaching the problem of isolating the internal secretion of the pancreas. Eager to pursue his idea, but unable to do so at Western University, Banting approached J.J.R. MacLeod of the University of Toronto, Banting's alma mater. While skeptical, MacLeod nonetheless agreed to provide lab space and dogs for Banting's experiments while MacLeod was on summer sabbatical, and even provided a graduate student, Charles Best, to be his assistant. (Bliss, 1993)

Within 18 months, with the assistance of MacLeod and later J.B. Collip, they had isolated the pancreatic extract, known as insulin, and had successfully administered it, first in dogs, and later in a 14-year old boy. Success here meant that metabolic problems associated with diabetes were mitigated or eliminated. While the Nobel committee named only Banting and MacLeod in 1923, both shared their prize money—Banting with Best and MacLeod with Collip, who had played a crucial role in refining the extract, thus producing one of the breakthroughs. Their association, while extraordinarily fruitful, was also marked by acrimony and accusations of stealing credit. (Peterson, 1982)

The next steps were to purify the extract, in order to reduce the side effects, and to produce larger quantities for other researchers. In 1922, the investigators began working with the Eli Lilly and Company of Indiana and Novo Nordisk of Scandinavia. Purification would remain an issue throughout the years until the 1970s when chromatography (and later recombinant DNA techniques) would be used. (Bliss, 1993) The wide-scale availability of insulin to researchers opened up vast new areas of research.

The Post-Insulin Era

Treatment of diabetes with insulin also made a tremendous difference in the lives of those with diabetes. Instead of the diabetes death that was to be expected, many could now consider a life with diabetes. The goals of treatment had to be revised. Death avoidance could be expected and the focus would now shift to long-term complications—chronic morbidity instead of mortality. The goal of treatment was to "mimic" the body's own secretion of insulin under normal conditions.

One of the first issues to be tackled was standardization of the insulin product. The first Toronto patients received one injection of extremely impure insulin. It was not until the mid-1970s could relatively pure quantities be prepared. Various committees over the years have worked throughout the years to define a standard unit of insulin, finally deciding that a "unit" was the activity contained in 0.04167 mg of the Fourth International Standard Zinc Insulin Preparation, as defined by the World Health Organization.

Part of the problem was also determining what was a normal amount of insulin found in the body. Further study went into determining when insulin output by the pancreas occurred, both throughout the day, and during and immediately after meals, when output peaked. Total insulin production appeared to be about 0.6 units/kg/24 hours.

As "regular" bovine and porcine insulin was increasingly purified in the early years of manufacture, patients complained of the inconvenience of taking multiple injections in a single day. Over the years, from 1920 to present day, combining insulin with other substances made improvements in its action. These substances, zinc and protamine, would serve to prolong the action of the insulin, thus eliminating the need for multiple daily injections in some patients. (Bliss, 1993 and Peterson, 1982)

After the discovery of insulin, research in diabetes exploded in different directions. Clinical treatment and preparation of insulin was one track. Another track lay in the investigation of the biochemical pathways of endocrinology and metabolism. These pathways regulated the disposition of body fuels, such as glucose and proteins. New methods, such as radioimmunoassays, were developed to quantitate and analyze body fluids and laid the ground work for understanding fluid composition and electrolyte homeostasis. These developments led, in turn, to a greater knowledge of insulin action and the maintenance of equilibrium in the patient with diabetes. (Tepperman)

It is important to point out that at this stage, discoveries and developments in areas of research not directly in the field of diabetes had its greatest impact. As biochemistry began to mature as a field, endocrinology, i.e. the study of hormonal action in the body, was being investigated from a variety of angles, not all with a specific long-term goal in mind. At times, breakthroughs pertinent to diabetes were made when experiments were designed to answer other questions. One such breakthrough led to the discovery of insulin-binding antibodies—leading eventually to the conclusion that diabetes type 1 was an autoimmune disease. (Tepperman)

The next major event in diabetes research was the elucidation of the structure of insulin by Frederick Sanger in 1953. While acknowledged as a protein only in the late 1920s its composition would not be deduced for 30 more years, despite exhaustive studies—many of which contributed greatly to the field of protein chemistry. Sanger's demonstration in turn paved the way to the elucidation of hundreds of other biologically important proteins and peptides. (Bliss, 1993 and Tepperman)

Sanger's feat led to another major milestone, the synthesis of insulin by Donald Steiner in 1967. This led eventually to recombinant DNA technology. Insulin was one of two substances to be first manufactured using this new methodology. Recombinant DNA technology allowed for the manufacture of insulin from pure substances, severing the link since the 1920s between the slaughterhouse and the patient. (Tepperman)

In 1971, fifty years after insulin's discovery, Dorothy Hodgkins unveiled a three-dimensional model of the protein. Again, this feat led to remarkable discoveries in areas of research seemingly far afield of diabetes. Other major achievements were made in understanding insulin secretion, the way the islets were designed and how they work, and what stimulated and inhibited them. Also when and how insulin synthesis was turned off and on. (Tepperman) In doing so, researchers discovered both short-term rapid effects of the presence of insulin in the blood, medium-term metabolic reactions, and even a long-term effect on growth. (Rasmussen and Schwartz)

The Search for Normalcy

Ever since the discovery of insulin in 1922, the eventual goal of diabetes treatment was the subject of debate among clinicians. Should the physician work simply to relieve symptoms or try to achieve a more difficult objective of near-physiological normality, i.e. the absence of sugar in the urine and normal blood sugar levels? Additionally, what combination of diet, exercise, and insulin was most beneficial?

In the early years of insulin use, two schools of thought began to emerge. One placed its faith in tight control of sugar levels in the blood and urine, i.e. that blood sugar should be within normal limits if the patient was to remain in good health. High sugar levels (hyperglycemia) overtaxed the islets of Langerhans and contributed to the patient's overall decline. Early proponents of this goal felt that the Langerhans must be rested in order for them to work properly, thus minimizing the need for additional doses of insulin taken from artificial sources.

These principles were well accepted by physicians with strong backgrounds in physiology and/or biochemistry. Others felt it was unrealistic to put patients to the expense (and pain) of so many blood sugar tests. The cost of one test could pay for a week's supply of insulin. Furthermore, patients found it difficult to keep sugar-free at all time, due to normal variations in diet and exercise. Additionally, there was the very real danger of hypoglycemia (less than optimal levels of blood sugar), which could lead to sleep, coma, and even death.

Beginning in the 1930's, a new trend began to emerge, that of liberalized diets. These liberalized diets were introduced to improve the quality of life of patients who were not satisfied with the limited diets allowed. Proponents of liberalized diets maintained that normal blood sugar levels were possible even with a generous allowance of carbohydrates as long as fat content was minimized. This led to patients who felt more normal, since they were not hungry all the time, and complied with their diet better.

These diets did lead to presence of sugar in the urine, however. The dangers of this phenomenon were discounted as long as recognized diabetic complications were not present. Complications now associated with diabetes, such as cardiovascular disease and retinopathy, were not commonly linked to diabetes. In part, this linkage was not made due to the shortened lifespan of people, particularly children, with diabetes. It was not common for those children, even with good glycemic control, to live only to 35 years of

age. It was after the age of 30 that retinopathy and other complications of diabetes could also be seen in large numbers.

The debate between strict and liberalized diets continued past the half-century mark. Various small trials were initiated to watch for the development of complications under varying conditions of diet and glycemic control (using various definitions of what "good" control meant). Quality of life was a large part of the issue. Some felt that maintenance of a strict diet was deleterious to the mental and physical development of children. Edward Tolstoi of New York, the most outspoken of those who favored liberalized diets, claimed that a life saved by insulin must be a life worth living. Others, such as Elliot Proctor Joslin, the most preeminent authority on diabetes in the United States, represented the "chemical school" maintaining that poor glycemic control was a recipe for destruction. (Tattersall, 1994)

In the decades of the 1950s and 1960s, most physicians began to agree that patients with poor glycemic control developed complications earlier than those with good glycemic control. Yet, it was hard to understand when and why exceptions to the general rules occurred.

The first major attempt to resolve this question was the University Group Diabetes Program (UGDP), a collaborative study involving 12 university clinics in the United States and supported by the NIH. Enrollment in the study began in 1960, four years after the introduction of the first sulphonylurea (tolbutamide in 1956). Tolbutamide was the

first non-insulin drug used to treat people with diabetes. The study set up four arms or cohorts of patients with newly diagnosed type 2 diabetes. Each arm would be treated with a different treatment methodology—variable and fixed doses of insulin, tolbutamide, and a placebo. In 1962, a fifth arm was created treated with a fixed dose of phenformin, a second type of oral hypoglycemic agent.

Initial analyses of the results in 1970 of this highly controversial trial indicated that a combined diet and insulin treatment was more desirable than use of tolbutamide and phenformin. However, every aspect of this trial, from its design, to its execution and analysis, was severely criticized by clinicians and statisticians. Nonetheless, statements in support of the results made by the American Diabetes Association, the American Medical Association, and the Food and Drug Administation were published in the *New York Times*, the *Washington Post*, and the *Wall Street Journal*, further incurring the ire of the critics who had yet to be given access to the data.

Criticisms of the trial involved several important factors. First was the criteria used to select patients; one quarter of the patients did not have diabetes according to standard diagnostic criteria. Second was the lack of comparability of patients in the different arms; baseline risk factors were unevenly distributed despite randomization. Third, the different treatment arms had heterogeneous patient populations; some arms had more charity patients, while others had more private patients, leading to differences in nutritional status and compliance to treatment. Fourth was the use of unrealistic treatment methodologies; the use of fixed doses of tolbutamide and phenformin was not

common in practice. Fifth was the treatment of conditions other than diabetes; the treatment of cardiac disease was not followed or controlled. Sixth was the classification of the cause of death; autopsies were not made on all patients who had died during the course of the trial, with wide variations between the arms in the percentage autopsied. If only three deaths per arm were reclassified, the conclusions of the study would have been overturned. Finally, the study was rife with sloppy data management and evidence of patient mismanagement.

The NIH commissioned the Biometric Society, an independent group of biostatisticians, to review the UGDP and its results. The commission ultimately validated the original results which called into question the safety of oral hypoglycemic agents such as tolbutamide and phenformin, and called on the community to produce scientifically valid studies to demonstrate otherwise. The report did little to quell the criticisms on both sides, and in the end, the UGDP did little to answer the original question of whether blood glucose control helped to prevent complications of diabetes. Thus, despite the tremendous basic advances made from the 1920s to the early 1970s, practical everyday management of the diabetes had not changed much. (Tattersall, 1994).

As the medical research community was sorting out the results of the UGDP, the U.S. Congress began to take an interest in the subject. In 1974, it passed the National Diabetes Mellitus Research and Education Act, which mandated the creation by NIH of a National Commission on Diabetes. The commission would formulate a long range plan to combat diabetes. Their report was published in 1975 and described fully the scale of diabetes as

a public health problem. It recommended that the NIH initiate and support a five-year clinical study to assess the effect of treatment on the development of complications in people with type 1 diabetes.

Work began on the design of such a trial to be known as the Diabetes Control and Complications Trial (DCCT). In the meantime, several breakthroughs substantially changed the way that diabetes was diagnosed and monitored. A method for detecting glycosylated hemoglobin (HbA_{1C}) in the blood was devised, enabling clinicians the ability to monitor blood sugar levels more accurately and reliably. Self-monitoring of blood glucose by patients began to take hold, allowing patients to make daily decisions on how much insulin they needed, as well as giving them precise targets with which to work. Finally, quantitative measurements of the progress of complications came into being, including definitive ways of measuring the development of retinopathy. These new developments allowed researchers to focus on two related questions: 1) would intensive treatment delay or prevent the appearance of background retinopathy (primary prevention); and 2) would intensive therapy prevent background retinopathy from progressing to more severe forms of the disease (secondary prevention).

In contrast to the design of the UGDP, extreme care was taken to ensure that the entire scientific community had an opportunity to comment on the research protocol for the DCCT. Planning began in 1982, after the selection by peer review of the study sites, and the first patients were enrolled in the feasibility study in March 1984. In late 1985, the full scale trial was approved.

Since patients could not be assigned to specific HbA_{1C} levels to see how complications progressed, the DCCT investigators instead assigned patients to different treatments, labeling the typical treatment for patients with type 1 diabetes as conventional therapy, and the experimental treatment as intensive therapy. Conventional therapy consisted of seeing a health care provider three or four times a year and treating the diabetes with one or two injections of mixed insulin a day. Urine or self blood glucose monitoring was generally used by the person with diabetes to monitor their disease. The main goal of the treatment was to remain free of symptoms, free of hypoglycemia, and otherwise normal growth and maintenance of ideal body weight. No target values for HbA_{1C} were set.

In the intensive therapy group, patients were given specific targets for blood glucose levels and HbA_{1C} levels. The volunteers could be treated either with subcutaneous insulin infusion, i.e. insulin pumps, or undergo multiple daily injections of insulin. They were seen weekly until their target range was met and then monthly.

A total of 1,411 patients were recruited at 29 sites across the United States from 1983 to 1989. When the trial was terminated in 1993, 99% of the volunteers completed the trial and more than 95% of all scheduled appointments were met, indicating a tremendous accomplishment on the part of both the subjects as well as the investigators. The two groups maintained a statistically significant different in the level of HbA_{1C} throughout the study which translated into significant differences in the occurrence and progression of retinopathy in the two groups. In the primary prevention group, the risk of developing

retinopathy was reduced by 76%, and in the secondary prevention group, the risk of progression of retinopathy was reduced by 54% through use of intensive therapy. However, episodes of severe hypoglycemia was three times more common in the experimental group (this was after screening out participants prone to hypoglycemia), and participants in the intensive group were more prone to weight gain (average weight gain of 10 lbs.). Nonetheless, the investigators recommended that most patients with type 1 diabetes would benefit from "closely monitored intensive regimens, with the goal of maintaining their glycemic status as close to the normal range as safely possible." Further cautions were given to those prone to severe hypoglycemia. (Tattersall, 1994).

Although the DCCT investigators did not enroll patients with type 2 diabetes, a later study, the United Kingdom Prospective Diabetes Study (UKPDS) sponsored by the Government of the United Kingdom, did study whether intensive therapy would result in clinical benefits in patients with type 2 diabetes. The UKPDS ran from 1977 to 1991 involving 5,102 patients in the United Kingdom. A smaller study, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), also found similar results when comparing intensive versus conventional therapy in people with type 2 diabetes. (Klein, 1989)

All three studies described above found that intensive therapy required an expert team of diabetes specialists, nurses, dieticians, and behavioral specialists which can only be supplied at considerable time, effort, and cost. However, the overall treatment programs were not unusually sophisticated or complex, nor did they involve new drugs or devices

not available to patients using conventional therapy. The most important ingredient leading to therapeutic success was persistence.

The Post-DCCT Era

The post-DCCT era has yet to take place. While the American Diabetes Association has accepted and endorsed the results of the DCCT and the UKPDS, thus making intensive therapy the therapy of choice, there is no cure for diabetes.

Researchers around the world are continuing studies to understand and combat type 1 and 2 diabetes. They are working to unlock the mysteries of the beta cell, the mechanisms by which insulin acts in the body, the intricacies of the immune system and why it is triggered in type 1 diabetes, the genetics of diabetes and its complications, and how islet transplantation can be of use.

In addition, researchers have not perfected the management of diabetes. Research continues into new sensors to detect blood glucose with more accuracy and less pain. New systems include implantable sensors and pumps that can detect when the body needs more insulin and provide just enough, mimicking the action of the well-functioning pancreas. Other systems use near-infrared light to detect glucose levels under the skin. Finally, researchers are trying to understand the spread of diabetes within the population, particularly among sub-groups such as minority populations, and new methods for preventing diabetes in at-risk children and adults. Many of these prevention methods

include changes in diet to reduce and prevent obesity, and other behavioral interventions, as well as new medications and exercise.

Appendix D: Selected Spreadsheets

National Institutes of Health Diabetes Research Investment: 1975-2000

Fiscal Year	NIH Diabetes Research Costs (current dollars)	1996 Price deflator	NIH Diabetes Research Costs (1996 dollars)	NIH Diabetes Research Costs (1975 dollars)	Net Present Value in 1975 at 3% discount rate	Net Present Value in 1975 at 5% discount rate	Net Present Value in 1975 at 7% discount rate
1975	$ 39,100,000	40.03	$ 97,676,742	$ 39,100,000	$ 39,100,000	$ 39,100,000	$ 39,100,000
1976	$ 42,700,000	42.3	$ 100,945,626	$ 40,408,534	$ 39,231,587	$ 38,484,318	$ 37,764,985
1977	$ 81,500,000	45.02	$ 181,030,653	$ 72,466,570	$ 68,306,693	$ 65,729,316	$ 63,295,109
1978	$ 108,400,000	48.23	$ 224,756,376	$ 89,969,977	$ 82,335,274	$ 77,719,449	$ 73,442,301
1979	$ 125,900,000	52.25	$ 240,956,938	$ 96,455,062	$ 85,699,073	$ 79,353,818	$ 73,585,105
1980	$ 134,200,000	57.04	$ 235,273,492	$ 94,179,979	$ 81,240,477	$ 73,792,478	$ 67,149,023
1981	$ 147,800,000	62.37	$ 236,972,904	$ 94,860,253	$ 79,443,969	$ 70,786,182	$ 63,209,392
1982	$ 148,400,000	66.25	$ 224,000,000	$ 89,667,200	$ 72,907,639	$ 63,724,805	$ 55,840,226
1983	$ 165,200,000	68.88	$ 239,837,398	$ 96,006,911	$ 75,788,742	$ 64,981,256	$ 55,876,896
1984	$ 177,900,000	71.44	$ 249,020,157	$ 99,682,769	$ 76,398,542	$ 64,256,402	$ 54,220,821
1985	$ 188,900,000	73.69	$ 256,344,144	$ 102,614,561	$ 76,354,870	$ 62,996,439	$ 52,164,039
1986	$ 189,100,000	75.31	$ 251,095,472	$ 100,513,517	$ 72,613,104	$ 58,768,172	$ 47,753,248
1987	$ 234,100,000	77.58	$ 301,753,029	$ 120,791,738	$ 84,720,894	$ 67,261,359	$ 53,632,976
1988	$ 240,800,000	80.21	$ 300,211,944	$ 120,174,841	$ 81,833,219	$ 63,731,284	$ 49,868,287
1989	$ 258,800,000	83.27	$ 310,796,205	$ 124,411,721	$ 82,250,804	$ 62,836,373	$ 48,249,010
1990	$ 249,200,000	86.51	$ 288,059,184	$ 115,310,091	$ 74,013,160	$ 55,466,126	$ 41,793,684
1991	$ 261,500,000	89.66	$ 291,657,372	$ 116,750,446	$ 72,755,018	$ 53,484,725	$ 39,547,415
1992	$ 278,400,000	91.84	$ 303,135,889	$ 121,345,296	$ 73,415,900	$ 52,942,551	$ 38,414,813
1993	$ 285,800,000	94.05	$ 303,880,914	$ 121,643,530	$ 71,452,754	$ 50,545,399	$ 35,989,931
1994	$ 293,600,000	96.01	$ 305,801,479	$ 122,412,332	$ 69,810,042	$ 48,442,717	$ 33,848,030
1995	$ 295,100,000	98.1	$ 300,815,494	$ 120,416,442	$ 66,671,665	$ 45,383,691	$ 31,117,897
1996	$ 298,900,000	100	$ 298,900,000	$ 119,649,670	$ 64,317,593	$ 42,947,335	$ 28,896,961
1997	$ 319,500,000	101.95	$ 313,388,916	$ 125,449,583	$ 65,471,197	$ 42,884,924	$ 28,315,622
1998	$ 387,200,000	103.22	$ 375,121,101	$ 150,160,977	$ 76,085,328	$ 48,888,105	$ 31,675,990
1999	$ 457,600,000	104.77	$ 436,766,250	$ 174,837,530	$ 86,008,479	$ 54,211,508	$ 34,468,628
2000	$ 525,100,000	104.77	$ 501,193,090	$ 200,627,594	$ 95,820,856	$ 59,245,885	$ 36,965,469
TOTAL				**$ 2,869,907,125**	**$ 1,914,046,879**	**$ 1,507,964,615**	**$ 1,216,185,861**

Source: National Institutes of Health and Department of Commerce, Bureau of Economic Analysis.

Discounted Future Earnings (Human Capital Method)

Model 1 Type 1 Diabetes	Year	No. of newly diagnosed Type 1 cases eligible for DCCT^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Discounted Value of Number of Years of Life Gained^^ (3% discount)	Discounted Value of Workdays Gained (3% discount)^^^	Productivity Gains due to Increased Survival and Workdays Gained (3% discount)	Net Benefits of Intensive Treatment over Conventional Treatment	Net Present Value Benefits in 1975 of Intensive Treatment over Conventional Treatment with Discounting (3%)
DISCOUNT RATE = 3%	2001	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($45,445,014)
	2002	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($44,121,373)
	2003	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($42,836,284)
	2004	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($41,588,626)
	2005	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($40,377,306)
	2006	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($39,201,268)
	2007	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($38,059,484)
	2008	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($36,950,955)
	2009	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($35,874,714)
	2010	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($34,829,819)
	2011	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($33,815,358)
	2012	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($32,830,445)
	2013	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($31,874,218)
	2014	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($30,945,843)
	2015	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($30,044,508)
	2016	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($29,169,425)
	2017	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($28,319,830)
	2018	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($27,494,981)
	2019	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($26,694,156)
	2020	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($25,916,656)
	2021	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($25,161,802)
	2022	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($24,428,934)
	2023	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($23,717,412)
	2024	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($23,026,614)
	2025	11,200	$ 377,955,200	$ 149,901,561	$ 130,047,319	$ 279,948,880	$ (98,006,320)	($22,355,936)
Total (w/o discounting)		$ 280,000	$ 9,448,880,000	3,747,539,027	3,251,182,965	$ 6,998,721,992	$ (2,450,158,008)	**($815,080,962)**

Discounted Future Earnings (Human Capital Method)

Model 2 Type 2 Diabetes	Year	No. of newly diagnosed Type 2 cases*	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Discounted Value of Number of Years of Life Gained** (3% discount)	Discounted Value of Workdays Gained (3% discount)***	Productivity Gains due to Increased Survival and Workdays Gained (3% discount)	Net Benefits of Intensive Treatment over Conventional Treatment	Net Present Value of Benefits in 1975 of Intensive Treatment over Conventional Treatment with Discounting (3%)
DISCOUNT RATE = 3%	2001	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$4,911,157,772
	2002	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$4,768,114,342
	2003	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$4,629,237,225
	2004	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$4,494,405,073
	2005	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$4,363,500,071
	2006	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$4,236,407,836
	2007	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$4,113,017,316
	2008	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,993,220,696
	2009	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,876,913,297
	2010	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,763,993,492
	2011	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,654,362,613
	2012	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,547,924,867
	2013	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,444,587,250
	2014	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,344,259,466
	2015	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,246,853,850
	2016	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,152,285,292
	2017	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$3,060,471,157
	2018	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,971,331,220
	2019	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,884,787,593
	2020	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,800,764,653
	2021	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,719,188,984
	2022	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,639,989,304
	2023	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,563,096,412
	2024	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,488,443,118
	2025	504,000	$ 7,016,688,000	$ 5,907,430,972	$ 11,700,616,993	$ 17,608,047,965	$ 10,591,359,965	$2,415,964,193
TOTAL								**$88,084,277,093**

Discounted Future Earnings (Human Capital Method)

Model 1 Type 1 Diabetes	Year	No. of newly diagnosed Type 1 cases eligible for DCCT^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Discounted Value of Number of Years of Life Gained^^ (5% discount)	Discounted Value of Workdays Gained^^^ (5% discount)	Productivity Gains due to Increased Survival and Workdays Gained (5% discount)	Net Benefits of Intensive Treatment over Conventional Treatment	Net Present Value Benefits in 1975 of Intensive Treatment over Conventional Treatment with Discounting (5%)
DISCOUNT RATE = 5%	2001	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($61,001,823)
	2002	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($58,096,974)
	2003	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($55,330,452)
	2004	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($52,695,668)
	2005	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($50,186,351)
	2006	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($47,796,524)
	2007	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($45,520,499)
	2008	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($43,352,857)
	2009	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($41,288,435)
	2010	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($39,322,319)
	2011	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($37,449,828)
	2012	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($35,666,502)
	2013	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($33,968,098)
	2014	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($32,350,569)
	2015	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($30,810,066)
	2016	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($29,342,920)
	2017	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($27,945,638)
	2018	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($26,614,893)
	2019	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($25,347,517)
	2020	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($24,140,493)
	2021	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($22,990,945)
	2022	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($21,896,139)
	2023	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($20,853,465)
	2024	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($19,860,443)
	2025	11,200	$ 377,955,200	$ 48,687,242	$ 112,365,442	$ 161,052,684	$ (216,902,516)	($18,914,708)
Total (w/o discounting)		$ 280,000	$ 9,448,880,000	1,217,181,057	2,809,136,055	$ 4,026,317,111	$ (5,422,562,889)	**($902,744,126)**

Discounted Future Earnings (Human Capital Method)

Model 2 Type 2 Diabetes	Year	No. of newly diagnosed Type 2 cases*	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Discounted Value of Number of Years of Life Gained** (5% discount)	Discounted Value of Workdays Gained*** (5% discount)	Productivity Gains due to Increased Survival and Workdays Gained (5% discount)	Net Benefits of Intensive Treatment over Conventional Treatment	Net Present Value of Benefits in 1975 of Intensive Treatment over Conventional Treatment with Discounting (5%)
DISCOUNT RATE = 5%	2001	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,501,529,958
	2002	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,430,028,532
	2003	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,361,931,935
	2004	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,297,078,033
	2005	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,235,312,413
	2006	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,176,488,012
	2007	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,120,464,773
	2008	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,067,109,308
	2009	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$1,016,294,579
	2010	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$967,899,599
	2011	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$921,809,142
	2012	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$877,913,469
	2013	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$836,108,065
	2014	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$796,293,396
	2015	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$758,374,662
	2016	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$722,261,583
	2017	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$687,868,175
	2018	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$655,112,547
	2019	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$623,916,712
	2020	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$594,206,392
	2021	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$565,910,850
	2022	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$538,962,714
	2023	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$513,297,823
	2024	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$488,855,069
	2025	504,000	$ 7,016,688,000	$ 4,236,727,308	$ 8,118,909,755	$ 12,355,637,063	$ 5,338,949,063	$465,576,256
TOTAL								**$22,220,603,997**

Discounted Future Earnings (Human Capital Method)

Model 1 Type 1 Diabetes	Year	No. of newly diagnosed Type 1 cases eligible for DCCT^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Discounted Value of Number of Years of Life Gained^^ (7% discount)	Discounted Value of Workdays Gained^^^ (7% discount)	Productivity Gains due to Increased Survival and Workdays Gained (7% discount)	Net Benefits of Intensive Treatment over Conventional Treatment	Net Present Value Benefits in 1975 of Intensive Treatment over Conventional Treatment with Discounting (7%)
DISCOUNT RATE = 7%	2001	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($45,371,008)
	2002	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($42,402,812)
	2003	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($39,628,796)
	2004	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($37,036,258)
	2005	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($34,613,325)
	2006	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($32,348,902)
	2007	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($30,232,619)
	2008	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($28,254,784)
	2009	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($26,406,340)
	2010	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($24,678,822)
	2011	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($23,064,320)
	2012	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($21,555,439)
	2013	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($20,145,270)
	2014	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($18,827,355)
	2015	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($17,595,659)
	2016	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($16,444,541)
	2017	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($15,368,730)
	2018	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($14,363,299)
	2019	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($13,423,644)
	2020	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($12,545,462)
	2021	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($11,724,731)
	2022	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($10,957,692)
	2023	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($10,240,834)
	2024	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($9,570,873)
	2025	11,200	$ 377,955,200	$ 16,164,809	$ 98,304,933	$ 114,469,742	$ (263,485,458)	($8,944,741)
Total (w/o discounting)		$ 280,000	$ 9,448,880,000	$ 404,120,221	2,457,623,317	$ 2,861,743,538	$ (6,587,136,462)	**($565,746,258)**

Discounted Future Earnings (Human Capital Method)

Model 2 Type 2 Diabetes	Year	No. of newly diagnosed Type 2 cases*	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Discounted Value of Number of Years of Life Gained** (7% discount)	Discounted Value of Workdays Gained*** (7% discount)	Productivity Gains due to Increased Survival and Workdays Gained (7% discount)	Net Benefits of Intensive Treatment over Conventional Treatment	Net Present Value of Benefits in 1975 of Intensive Treatment over Conventional Treatment with Discounting (7%)
DISCOUNT RATE = 7%	2001	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$372,519,526
	2002	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$348,149,090
	2003	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$325,372,981
	2004	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$304,086,899
	2005	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$284,193,363
	2006	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$265,601,274
	2007	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$248,225,490
	2008	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$231,986,439
	2009	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$216,809,756
	2010	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$202,625,940
	2011	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$189,370,038
	2012	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$176,981,344
	2013	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$165,403,125
	2014	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$154,582,360
	2015	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$144,469,495
	2016	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$135,018,220
	2017	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$126,185,252
	2018	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$117,930,142
	2019	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$110,215,086
	2020	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$103,004,753
	2021	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$96,266,125
	2022	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$89,968,341
	2023	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$84,082,561
	2024	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$78,581,833
	2025	504,000	$ 7,016,688,000	$ 3,057,837,526	$ 6,122,202,835	$ 9,180,040,362	$ 2,163,352,362	$73,440,966
TOTAL								**$4,645,070,398**

Discounted Future Earnings (Human Capital Method)

SUMMARY

	Type 1 (3%)	Type 2 (3%)	Type 1 (5%)	Type 2 (5%)	Type 1 (7%)	Type 2 (7%)
Number of Newly Diagnosed (type 1 or type 2) annually	11,200	504,000	11,200	504,000	11,200	504,000
Difference in Lifetime Costs annually	$ 377,955,200	$ 7,016,688,000	$ 377,955,200	$ 7,016,688,000	$ 377,955,200	$ 7,016,688,000
Value of Additional Years annually	$ 149,901,561	$ 5,907,430,972	$ 48,687,242	$ 4,236,727,308	$ 16,164,809	$ 3,057,837,526
Value of Additional Days annually	$ 130,047,319	$ 11,700,616,993	$ 112,365,442	$ 8,118,909,755	$ 98,304,933	$ 6,122,202,835
Net Annual Benefits of Improved Therapy	$ (98,006,320)	$ 10,591,359,965	$ (216,902,516)	$ 5,338,949,063	$ (263,485,458)	$ 2,163,352,362
Total NPV of Benefits of Improved Therapy in Year 1975	($815,080,962)	$88,084,277,093	($902,744,126)	$22,220,603,997	($565,746,258)	$4,645,070,398
NPV of Cost of Diabetes Research in 1975	$1,914,046,879		$1,507,964,615		$1,216,185,861	
NPV of Benefits (1975)	$85,355,149,252		$19,809,895,257		$2,863,138,279	
Cost-Benefit Ratio	45.59		14.14		3.35	

Sources and Footnotes:

^ JAMA, Nov. 6, 1996, p. 1410 (percentage eligible =17% of all people newly diagnosed with type 1 diabetes in any given year)

^^ JAMA, Nov. 6, 1996, p. 1412 (no. of additional years=61.6-56.5). Average daily productivity taken from Current Population Survey of 1994, Census Bureau. Figure is derived from the baseline number of people multiplied by the QALY-adjusted discounted number of years and by the value of a year's work in 1994.

^^^ Testa, Simon, p. 1494, JAMA Nov. 4, 1998. Average yearly productivity taken from Current Population Survey of 1994. (no. of add'l days=(24-5)/2=9.5 per year, assuming 250 day/year; no. of years is avg life expectancy, 61.6, minus average age of study participant, 58.6 (61.6-58.6=3.0). Final figure is derived by multiplying the no of add'l days of life by the value of a day of work and the number of people newly diagnosed with diabetes. Number of absentee days gained is average number of years with disease left times number of days gained per year times number of patients

*Diab Care, v. 20,n 5, May 1997, p. 725. Assumes that 85% of all people newly diagnosed with type 2 diabetes are eligible.

** Eastman, et al, Diab. Care, May 1997, p. 739. Average age in study is 51 years, avg age at death is 68 years under conventional therapy, plus 1.32 years with intensive treatment. Figure is derived from the baseline number of people multiplied by the QALY-adjusted discounted number of years and by the value of a year's work in 1994.

***Eastman, et al., Diab Care, May 1997, p. 736 Workdays gained taken from Testa, Simonson as above. Final figure is derived by multiplying the no of add'l days of life by the value of a day of work and the number of people newly diagnosed with diabetes.

Willingness to Pay (Health Capital Method)

Year	No. of newly diagnosed Type 1 cases eligible for DCCT^^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Value of Statistical Lives gained (3% discount rate)	Net Benefits	Net Benefits Discounted back to 1975 (3% discount rate)	Value of Statistical Lives gained (5% discount rate)	Net Benefits	N D b (5
2001	11,200	$377,955,200	$658,223,306	$280,268,106	$129,958,843	$213,787,484	-$164,167,716	
2002	11,200	$377,955,200	$658,223,306	$280,268,106	$126,173,634	$213,787,484	-$164,167,716	
2003	11,200	$377,955,200	$658,223,306	$280,268,106	$122,498,674	$213,787,484	-$164,167,716	
2004	11,200	$377,955,200	$658,223,306	$280,268,106	$118,930,751	$213,787,484	-$164,167,716	
2005	11,200	$377,955,200	$658,223,306	$280,268,106	$115,466,749	$213,787,484	-$164,167,716	
2006	11,200	$377,955,200	$658,223,306	$280,268,106	$112,103,640	$213,787,484	-$164,167,716	
2007	11,200	$377,955,200	$658,223,306	$280,268,106	$108,838,485	$213,787,484	-$164,167,716	
2008	11,200	$377,955,200	$658,223,306	$280,268,106	$105,668,432	$213,787,484	-$164,167,716	
2009	11,200	$377,955,200	$658,223,306	$280,268,106	$102,590,711	$213,787,484	-$164,167,716	
2010	11,200	$377,955,200	$658,223,306	$280,268,106	$99,602,632	$213,787,484	-$164,167,716	
2011	11,200	$377,955,200	$658,223,306	$280,268,106	$96,701,584	$213,787,484	-$164,167,716	
2012	11,200	$377,955,200	$658,223,306	$280,268,106	$93,885,033	$213,787,484	-$164,167,716	
2013	11,200	$377,955,200	$658,223,306	$280,268,106	$91,150,518	$213,787,484	-$164,167,716	
2014	11,200	$377,955,200	$658,223,306	$280,268,106	$88,495,648	$213,787,484	-$164,167,716	
2015	11,200	$377,955,200	$658,223,306	$280,268,106	$85,918,105	$213,787,484	-$164,167,716	
2016	11,200	$377,955,200	$658,223,306	$280,268,106	$83,415,636	$213,787,484	-$164,167,716	
2017	11,200	$377,955,200	$658,223,306	$280,268,106	$80,986,055	$213,787,484	-$164,167,716	
2018	11,200	$377,955,200	$658,223,306	$280,268,106	$78,627,237	$213,787,484	-$164,167,716	
2019	11,200	$377,955,200	$658,223,306	$280,268,106	$76,337,124	$213,787,484	-$164,167,716	
2020	11,200	$377,955,200	$658,223,306	$280,268,106	$74,113,712	$213,787,484	-$164,167,716	
2021	11,200	$377,955,200	$658,223,306	$280,268,106	$71,955,060	$213,787,484	-$164,167,716	
2022	11,200	$377,955,200	$658,223,306	$280,268,106	$69,859,282	$213,787,484	-$164,167,716	
2023	11,200	$377,955,200	$658,223,306	$280,268,106	$67,824,546	$213,787,484	-$164,167,716	
2024	11,200	$377,955,200	$658,223,306	$280,268,106	$65,849,073	$213,787,484	-$164,167,716	
2025	11,200	$377,955,200	$658,223,306	$280,268,106	$63,931,139	$213,787,484	-$164,167,716	
	280,000	$9,448,880,000			$2,330,882,305			

l Method)

s	Net Benefits	Net Benefits Discounted back to 1975 (3% discount rate)	Value of Statistical Lives gained (5% discount rate)	Net Benefits	Net Benefits Discounted back to 1975 (5% discount rate)	Value of Statistical Lives gained (7% discount rate)	Net Benefits	Net Benefits Discounted back to 1975 (7% discount rate)
6	$280,268,106	$129,958,843	$213,787,484	-$164,167,716	-$46,170,649	$70,980,274	-$306,974,926	-$52,859,699
6	$280,268,106	$126,173,634	$213,787,484	-$164,167,716	-$43,972,047	$70,980,274	-$306,974,926	-$49,401,588
6	$280,268,106	$122,498,674	$213,787,484	-$164,167,716	-$41,878,140	$70,980,274	-$306,974,926	-$46,169,708
6	$280,268,106	$118,930,751	$213,787,484	-$164,167,716	-$39,883,943	$70,980,274	-$306,974,926	-$43,149,260
6	$280,268,106	$115,466,749	$213,787,484	-$164,167,716	-$37,984,707	$70,980,274	-$306,974,926	-$40,326,411
6	$280,268,106	$112,103,640	$213,787,484	-$164,167,716	-$36,175,912	$70,980,274	-$306,974,926	-$37,688,235
6	$280,268,106	$108,838,485	$213,787,484	-$164,167,716	-$34,453,249	$70,980,274	-$306,974,926	-$35,222,649
6	$280,268,106	$105,668,432	$213,787,484	-$164,167,716	-$32,812,618	$70,980,274	-$306,974,926	-$32,918,364
6	$280,268,106	$102,590,711	$213,787,484	-$164,167,716	-$31,250,113	$70,980,274	-$306,974,926	-$30,764,826
6	$280,268,106	$99,602,632	$213,787,484	-$164,167,716	-$29,762,012	$70,980,274	-$306,974,926	-$28,752,174
6	$280,268,106	$96,701,584	$213,787,484	-$164,167,716	-$28,344,773	$70,980,274	-$306,974,926	-$26,871,190
6	$280,268,106	$93,885,033	$213,787,484	-$164,167,716	-$26,995,022	$70,980,274	-$306,974,926	-$25,113,262
6	$280,268,106	$91,150,518	$213,787,484	-$164,167,716	-$25,709,545	$70,980,274	-$306,974,926	-$23,470,338
6	$280,268,106	$88,495,648	$213,787,484	-$164,167,716	-$24,485,281	$70,980,274	-$306,974,926	-$21,934,896
6	$280,268,106	$85,918,105	$213,787,484	-$164,167,716	-$23,319,315	$70,980,274	-$306,974,926	-$20,499,903
6	$280,268,106	$83,415,636	$213,787,484	-$164,167,716	-$22,208,872	$70,980,274	-$306,974,926	-$19,158,787
6	$280,268,106	$80,986,055	$213,787,484	-$164,167,716	-$21,151,306	$70,980,274	-$306,974,926	-$17,905,409
6	$280,268,106	$78,627,237	$213,787,484	-$164,167,716	-$20,144,101	$70,980,274	-$306,974,926	-$16,734,027
6	$280,268,106	$76,337,124	$213,787,484	-$164,167,716	-$19,184,858	$70,980,274	-$306,974,926	-$15,639,277
6	$280,268,106	$74,113,712	$213,787,484	-$164,167,716	-$18,271,294	$70,980,274	-$306,974,926	-$14,616,147
6	$280,268,106	$71,955,060	$213,787,484	-$164,167,716	-$17,401,232	$70,980,274	-$306,974,926	-$13,659,951
6	$280,268,106	$69,859,282	$213,787,484	-$164,167,716	-$16,572,602	$70,980,274	-$306,974,926	-$12,766,309
6	$280,268,106	$67,824,546	$213,787,484	-$164,167,716	-$15,783,430	$70,980,274	-$306,974,926	-$11,931,130
6	$280,268,106	$65,849,073	$213,787,484	-$164,167,716	-$15,031,839	$70,980,274	-$306,974,926	-$11,150,589
6	$280,268,106	$63,931,139	$213,787,484	-$164,167,716	-$14,316,037	$70,980,274	-$306,974,926	-$10,421,111
		$2,330,882,305			-$683,262,898			-$659,125,238

Willingness to Pay (Health Capital Method)

Year	No. of newly diagnosed Type 2 cases^^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Value of Statistical Lives gained (3% discount rate)	Net Benefits	Net Benefits Discounted back to 1975 (3% discount rate)	Value of Statistical Lives gained (5% discount rate)	Net Benefits	Di
2001	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$8,774,523,232	$18,603,626,514	$11,586,938,514	
2002	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$8,518,954,594	$18,603,626,514	$11,586,938,514	
2003	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$8,270,829,703	$18,603,626,514	$11,586,938,514	
2004	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$8,029,931,750	$18,603,626,514	$11,586,938,514	
2005	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$7,796,050,243	$18,603,626,514	$11,586,938,514	
2006	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$7,568,980,818	$18,603,626,514	$11,586,938,514	
2007	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$7,348,525,066	$18,603,626,514	$11,586,938,514	
2008	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$7,134,490,356	$18,603,626,514	$11,586,938,514	
2009	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$6,926,689,666	$18,603,626,514	$11,586,938,514	
2010	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$6,724,941,423	$18,603,626,514	$11,586,938,514	
2011	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$6,529,069,343	$18,603,626,514	$11,586,938,514	
2012	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$6,338,902,274	$18,603,626,514	$11,586,938,514	
2013	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$6,154,274,053	$18,603,626,514	$11,586,938,514	
2014	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$5,975,023,352	$18,603,626,514	$11,586,938,514	
2015	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$5,800,993,546	$18,603,626,514	$11,586,938,514	
2016	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$5,632,032,569	$18,603,626,514	$11,586,938,514	
2017	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$5,467,992,785	$18,603,626,514	$11,586,938,514	
2018	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$5,308,730,860	$18,603,626,514	$11,586,938,514	
2019	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$5,154,107,631	$18,603,626,514	$11,586,938,514	
2020	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$5,003,987,991	$18,603,626,514	$11,586,938,514	
2021	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$4,858,240,768	$18,603,626,514	$11,586,938,514	
2022	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$4,716,738,610	$18,603,626,514	$11,586,938,514	
2023	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$4,579,357,873	$18,603,626,514	$11,586,938,514	
2024	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$4,445,978,518	$18,603,626,514	$11,586,938,514	
2025	504,000	$7,016,688,000	$25,939,748,178	$18,923,060,178	$4,316,483,998	$18,603,626,514	$11,586,938,514	
					$157,375,831,020			$

ethod)

et Benefits	Net Benefits Discounted back to 1975 (3% discount rate)	Value of Statistical Lives gained (5% discount rate)	Net Benefits	Net Benefits Discounted back to 1975 (5% discount rate)	Value of Statistical Lives gained (7% discount rate)	Net Benefits	Net Benefits Discounted back to 1975 (7% discount rate)
3,923,060,178	$8,774,523,232	$18,603,626,514	$11,586,938,514	$3,258,719,103	$13,427,077,824	$6,410,389,824	$1,103,840,236
3,923,060,178	$8,518,954,594	$18,603,626,514	$11,586,938,514	$3,103,542,003	$13,427,077,824	$6,410,389,824	$1,031,626,389
3,923,060,178	$8,270,829,703	$18,603,626,514	$11,586,938,514	$2,955,754,289	$13,427,077,824	$6,410,389,824	$964,136,812
3,923,060,178	$8,029,931,750	$18,603,626,514	$11,586,938,514	$2,815,004,085	$13,427,077,824	$6,410,389,824	$901,062,441
3,923,060,178	$7,796,050,243	$18,603,626,514	$11,586,938,514	$2,680,956,271	$13,427,077,824	$6,410,389,824	$842,114,431
3,923,060,178	$7,568,980,818	$18,603,626,514	$11,586,938,514	$2,553,291,687	$13,427,077,824	$6,410,389,824	$787,022,833
3,923,060,178	$7,348,525,066	$18,603,626,514	$11,586,938,514	$2,431,706,368	$13,427,077,824	$6,410,389,824	$735,535,358
3,923,060,178	$7,134,490,356	$18,603,626,514	$11,586,938,514	$2,315,910,827	$13,427,077,824	$6,410,389,824	$687,416,222
3,923,060,178	$6,926,689,666	$18,603,626,514	$11,586,938,514	$2,205,629,359	$13,427,077,824	$6,410,389,824	$642,445,067
3,923,060,178	$6,724,941,423	$18,603,626,514	$11,586,938,514	$2,100,599,390	$13,427,077,824	$6,410,389,824	$600,415,951
3,923,060,178	$6,529,069,343	$18,603,626,514	$11,586,938,514	$2,000,570,847	$13,427,077,824	$6,410,389,824	$561,136,403
3,923,060,178	$6,338,902,274	$18,603,626,514	$11,586,938,514	$1,905,305,569	$13,427,077,824	$6,410,389,824	$524,426,545
3,923,060,178	$6,154,274,053	$18,603,626,514	$11,586,938,514	$1,814,576,732	$13,427,077,824	$6,410,389,824	$490,118,266
3,923,060,178	$5,975,023,352	$18,603,626,514	$11,586,938,514	$1,728,168,316	$13,427,077,824	$6,410,389,824	$458,054,454
3,923,060,178	$5,800,993,546	$18,603,626,514	$11,586,938,514	$1,645,874,587	$13,427,077,824	$6,410,389,824	$428,088,275
3,923,060,178	$5,632,032,569	$18,603,626,514	$11,586,938,514	$1,567,499,607	$13,427,077,824	$6,410,389,824	$400,082,500
3,923,060,178	$5,467,992,785	$18,603,626,514	$11,586,938,514	$1,492,856,768	$13,427,077,824	$6,410,389,824	$373,908,878
3,923,060,178	$5,308,730,860	$18,603,626,514	$11,586,938,514	$1,421,768,351	$13,427,077,824	$6,410,389,824	$349,447,550
3,923,060,178	$5,154,107,631	$18,603,626,514	$11,586,938,514	$1,354,065,096	$13,427,077,824	$6,410,389,824	$326,586,495
3,923,060,178	$5,003,987,991	$18,603,626,514	$11,586,938,514	$1,289,585,806	$13,427,077,824	$6,410,389,824	$305,221,024
3,923,060,178	$4,858,240,768	$18,603,626,514	$11,586,938,514	$1,228,176,958	$13,427,077,824	$6,410,389,824	$285,253,293
3,923,060,178	$4,716,738,610	$18,603,626,514	$11,586,938,514	$1,169,692,341	$13,427,077,824	$6,410,389,824	$266,591,863
3,923,060,178	$4,579,357,873	$18,603,626,514	$11,586,938,514	$1,113,992,705	$13,427,077,824	$6,410,389,824	$249,151,274
3,923,060,178	$4,445,978,518	$18,603,626,514	$11,586,938,514	$1,060,945,434	$13,427,077,824	$6,410,389,824	$232,851,658
3,923,060,178	$4,316,483,998	$18,603,626,514	$11,586,938,514	$1,010,424,223	$13,427,077,824	$6,410,389,824	$217,618,372
	$157,375,831,020			$48,224,616,720			$13,764,152,588

Cost-Effectiveness Analysis

Model 1 Type 1 Diabetes	Year	No. of newly diagnosed Type 1 cases eligible for DCCT^		Lifetime Costs of Intensive Treatment minus Conventional Treatment	Net Present Value of Costs in 1975 of Intensive Treatment over Conventional Treatment with Discounting (3%)
DISCOUNT RATE = 3%	2001	11,200	$	377,955,200	$175,255,833
	2002	11,200	$	377,955,200	$170,151,295
	2003	11,200	$	377,955,200	$165,195,432
	2004	11,200	$	377,955,200	$160,383,914
	2005	11,200	$	377,955,200	$155,712,538
	2006	11,200	$	377,955,200	$151,177,221
	2007	11,200	$	377,955,200	$146,774,001
	2008	11,200	$	377,955,200	$142,499,030
	2009	11,200	$	377,955,200	$138,348,573
	2010	11,200	$	377,955,200	$134,319,003
	2011	11,200	$	377,955,200	$130,406,799
	2012	11,200	$	377,955,200	$126,608,543
	2013	11,200	$	377,955,200	$122,920,915
	2014	11,200	$	377,955,200	$119,340,695
	2015	11,200	$	377,955,200	$115,864,752
	2016	11,200	$	377,955,200	$112,490,051
	2017	11,200	$	377,955,200	$109,213,641
	2018	11,200	$	377,955,200	$106,032,661
	2019	11,200	$	377,955,200	$102,944,332
	2020	11,200	$	377,955,200	$99,945,953
	2021	11,200	$	377,955,200	$97,034,906
	2022	11,200	$	377,955,200	$94,208,646
	2023	11,200	$	377,955,200	$91,464,705
	2024	11,200	$	377,955,200	$88,800,685
	2025	11,200	$	377,955,200	$86,214,257
Total (w/o discounting)		280,000	$	9,448,880,000	**$3,143,308,383**

Cost-Effectiveness Analysis

Model 2 Type 2 Diabetes	Year	No. of newly diagnosed Type 2 cases^^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Net Present Value of Costs in 1975 of Intensive Treatment over Conventional Treatment with Discounting (3%)
DISCOUNT RATE = 3%	2001	504,000	$ 7,016,688,000	$3,253,601,230
	2002	504,000	$ 7,016,688,000	$3,158,836,145
	2003	504,000	$ 7,016,688,000	$3,066,831,209
	2004	504,000	$ 7,016,688,000	$2,977,506,028
	2005	504,000	$ 7,016,688,000	$2,890,782,552
	2006	504,000	$ 7,016,688,000	$2,806,585,002
	2007	504,000	$ 7,016,688,000	$2,724,839,807
	2008	504,000	$ 7,016,688,000	$2,645,475,541
	2009	504,000	$ 7,016,688,000	$2,568,422,855
	2010	504,000	$ 7,016,688,000	$2,493,614,423
	2011	504,000	$ 7,016,688,000	$2,420,984,877
	2012	504,000	$ 7,016,688,000	$2,350,470,754
	2013	504,000	$ 7,016,688,000	$2,282,010,441
	2014	504,000	$ 7,016,688,000	$2,215,544,117
	2015	504,000	$ 7,016,688,000	$2,151,013,706
	2016	504,000	$ 7,016,688,000	$2,088,362,821
	2017	504,000	$ 7,016,688,000	$2,027,536,720
	2018	504,000	$ 7,016,688,000	$1,968,482,252
	2019	504,000	$ 7,016,688,000	$1,911,147,818
	2020	504,000	$ 7,016,688,000	$1,855,483,318
	2021	504,000	$ 7,016,688,000	$1,801,440,115
	2022	504,000	$ 7,016,688,000	$1,748,970,985
	2023	504,000	$ 7,016,688,000	$1,698,030,083
	2024	504,000	$ 7,016,688,000	$1,648,572,896
	2025	504,000	$ 7,016,688,000	$1,600,556,209
TOTAL		12,600,000		**$58,355,101,903**

Cost-Effectiveness Analysis

Model 1 Type 1 Diabetes	Year	No. of newly diagnosed Type 1 cases eligible for DCCT^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Net Present Value of COsts in 1975 of Intensive Treatment over Conventional Treatment with Discounting (5%)
DISCOUNT RATE = 5%	2001	11,200	$ 377,955,200	$106,296,398
	2002	11,200	$ 377,955,200	$101,234,665
	2003	11,200	$ 377,955,200	$96,413,967
	2004	11,200	$ 377,955,200	$91,822,825
	2005	11,200	$ 377,955,200	$87,450,310
	2006	11,200	$ 377,955,200	$83,286,009
	2007	11,200	$ 377,955,200	$79,320,009
	2008	11,200	$ 377,955,200	$75,542,866
	2009	11,200	$ 377,955,200	$71,945,586
	2010	11,200	$ 377,955,200	$68,519,606
	2011	11,200	$ 377,955,200	$65,256,768
	2012	11,200	$ 377,955,200	$62,149,303
	2013	11,200	$ 377,955,200	$59,189,812
	2014	11,200	$ 377,955,200	$56,371,249
	2015	11,200	$ 377,955,200	$53,686,904
	2016	11,200	$ 377,955,200	$51,130,385
	2017	11,200	$ 377,955,200	$48,695,605
	2018	11,200	$ 377,955,200	$46,376,766
	2019	11,200	$ 377,955,200	$44,168,349
	2020	11,200	$ 377,955,200	$42,065,094
	2021	11,200	$ 377,955,200	$40,061,995
	2022	11,200	$ 377,955,200	$38,154,281
	2023	11,200	$ 377,955,200	$36,337,410
	2024	11,200	$ 377,955,200	$34,607,057
	2025	11,200	$ 377,955,200	$32,959,102
Total (w/o discounting)		$ 280,000	$ 9,448,880,000	**$1,573,042,321**

Cost-Effectiveness Analysis

Model 2 Type 2 Diabetes	Year	No. of newly diagnosed Type 2 cases^^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Net Present Value of Costs in 1975 of Intensive Treatment over Conventional Treatment with Discounting (5%)
DISCOUNT RATE = 5%	2001	504,000	$ 7,016,688,000	$1,973,378,490
	2002	504,000	$ 7,016,688,000	$1,879,408,086
	2003	504,000	$ 7,016,688,000	$1,789,912,463
	2004	504,000	$ 7,016,688,000	$1,704,678,536
	2005	504,000	$ 7,016,688,000	$1,623,503,367
	2006	504,000	$ 7,016,688,000	$1,546,193,683
	2007	504,000	$ 7,016,688,000	$1,472,565,413
	2008	504,000	$ 7,016,688,000	$1,402,443,250
	2009	504,000	$ 7,016,688,000	$1,335,660,238
	2010	504,000	$ 7,016,688,000	$1,272,057,370
	2011	504,000	$ 7,016,688,000	$1,211,483,209
	2012	504,000	$ 7,016,688,000	$1,153,793,533
	2013	504,000	$ 7,016,688,000	$1,098,850,983
	2014	504,000	$ 7,016,688,000	$1,046,524,746
	2015	504,000	$ 7,016,688,000	$996,690,234
	2016	504,000	$ 7,016,688,000	$949,228,795
	2017	504,000	$ 7,016,688,000	$904,027,424
	2018	504,000	$ 7,016,688,000	$860,978,499
	2019	504,000	$ 7,016,688,000	$819,979,522
	2020	504,000	$ 7,016,688,000	$780,932,879
	2021	504,000	$ 7,016,688,000	$743,745,599
	2022	504,000	$ 7,016,688,000	$708,329,142
	2023	504,000	$ 7,016,688,000	$674,599,182
	2024	504,000	$ 7,016,688,000	$642,475,412
	2025	504,000	$ 7,016,688,000	$611,881,345
TOTAL				$29,203,321,399

Cost-Effectiveness Analysis

Model 1 Type 1 Diabetes	Year	No. of newly diagnosed Type 1 cases eligible for DCCT^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Net Present Value of Costs in 1975 of Intensive Treatment over Conventional Treatment with Discounting (7%)
DISCOUNT RATE = 7%	2001	11,200	$ 377,955,200	$65,082,182
	2002	11,200	$ 377,955,200	$60,824,469
	2003	11,200	$ 377,955,200	$56,845,298
	2004	11,200	$ 377,955,200	$53,126,447
	2005	11,200	$ 377,955,200	$49,650,885
	2006	11,200	$ 377,955,200	$46,402,696
	2007	11,200	$ 377,955,200	$43,367,006
	2008	11,200	$ 377,955,200	$40,529,912
	2009	11,200	$ 377,955,200	$37,878,422
	2010	11,200	$ 377,955,200	$35,400,395
	2011	11,200	$ 377,955,200	$33,084,481
	2012	11,200	$ 377,955,200	$30,920,076
	2013	11,200	$ 377,955,200	$28,897,267
	2014	11,200	$ 377,955,200	$27,006,792
	2015	11,200	$ 377,955,200	$25,239,992
	2016	11,200	$ 377,955,200	$23,588,778
	2017	11,200	$ 377,955,200	$22,045,587
	2018	11,200	$ 377,955,200	$20,603,352
	2019	11,200	$ 377,955,200	$19,255,469
	2020	11,200	$ 377,955,200	$17,995,766
	2021	11,200	$ 377,955,200	$16,818,473
	2022	11,200	$ 377,955,200	$15,718,199
	2023	11,200	$ 377,955,200	$14,689,905
	2024	11,200	$ 377,955,200	$13,728,883
	2025	11,200	$ 377,955,200	$12,830,732
Total (w/o discounting)		$ 280,000	$ 9,448,880,000	**$811,531,465**

Cost-Effectiveness Analysis

Model 2 Type 2 Diabetes	Year	No. of newly diagnosed Type 2 cases^^	Lifetime Costs of Intensive Treatment minus Conventional Treatment	Net Present Value of Costs in 1975 of Intensive Treatment over Conventional Treatment with Discounting (7%)
DISCOUNT RATE = 7%	2001	504,000	$ 7,016,688,000	$1,208,242,049
	2002	504,000	$ 7,016,688,000	$1,129,198,177
	2003	504,000	$ 7,016,688,000	$1,055,325,399
	2004	504,000	$ 7,016,688,000	$986,285,420
	2005	504,000	$ 7,016,688,000	$921,762,075
	2006	504,000	$ 7,016,688,000	$861,459,883
	2007	504,000	$ 7,016,688,000	$805,102,694
	2008	504,000	$ 7,016,688,000	$752,432,424
	2009	504,000	$ 7,016,688,000	$703,207,873
	2010	504,000	$ 7,016,688,000	$657,203,620
	2011	504,000	$ 7,016,688,000	$614,208,991
	2012	504,000	$ 7,016,688,000	$574,027,094
	2013	504,000	$ 7,016,688,000	$536,473,920
	2014	504,000	$ 7,016,688,000	$501,377,495
	2015	504,000	$ 7,016,688,000	$468,577,098
	2016	504,000	$ 7,016,688,000	$437,922,522
	2017	504,000	$ 7,016,688,000	$409,273,385
	2018	504,000	$ 7,016,688,000	$382,498,490
	2019	504,000	$ 7,016,688,000	$357,475,225
	2020	504,000	$ 7,016,688,000	$334,088,995
	2021	504,000	$ 7,016,688,000	$312,232,706
	2022	504,000	$ 7,016,688,000	$291,806,267
	2023	504,000	$ 7,016,688,000	$272,716,137
	2024	504,000	$ 7,016,688,000	$254,874,895
	2025	504,000	$ 7,016,688,000	$238,200,836
TOTAL				**$15,065,973,669**

Cost-Effectiveness Analysis

SUMMARY

Model (Discount Rate)	1 (3%)	2 (3%)	1 (5%)	2 (5%)	1 (7%)	2 (7%)
Number of Newly Diagnosed (type 1 or type 2) annually	11,200	504,000	11,200	504,000	11,200	504,000
Difference in Lifetime Costs annually	$377,955,200	$7,016,688,000	$377,955,200	$7,016,688,000	$377,955,200	$7,016,688,000
Total NPV of Costs of Improved Therapy in Year 1975	$3,143,308,383	$58,355,101,903	$1,573,042,321	$29,203,321,399	$811,531,465	$15,065,973,669
NPV of Cost of Diabetes Research in 1975	$1,914,046,879		$1,507,964,615		$1,216,185,861	
NPV of Costs (1975)	$63,412,457,165		$32,284,328,335		$17,093,690,995	
Additional Number of Years Across the United States	3,442,653		1,210,561		457,153	
QALY-Adjusted No of Years	2,237,725		786,865		297,150	

^ JAMA, Nov. 6, 1996, p. 1410 (percentage eligible =17% of all people newly diagnosed with type 1 diabetes in any given year)
^^Diab Care, v. 20,n 5, May 1997, p. 725. Assumes that 85% of all people newly diagnosed with type 2 diabetes are eligible.

Sensitivity Analyses

	Original Variables	Variables Tested	
Number of People	Best Estimate	Low Estimate	High Estimate
Type 1	11,200	5,600	16,800
Type 2	504,000	252,000	756,000
Cost of Treatment	Best Estimate	Low Estimate	High Estimate
Type 1	$ 33,746	$ 16,873	$ 50,619
Type 2	$ 13,922	$ 6,961	$ 20,883
Mix of Type 1 and 2	Best Estimate	Low Estimate	High Estimate
Ratio	1 to 9	1 to 4	1 to 19
type 1	65,882	131,764	32,941
type 2	592,936	527,055	625,877
Eligibility	Best Estimate	Low Estimate	High Estimate
Type 1	11,200	22,400	5,600
Type 2	503,996	447,996	531,996
Eligibility of Type 1	Best Estimate	Low Estimate	High Estimate
Type 1	11,200	5,600	16,800
Type 2 (unchanged)	503,996	503,996	503,996
Eligibility of Type 2	Best Estimate	Low Estimate	High Estimate
Type 1 (unchanged)	11,200	11,200	11,200
Type 2	503,996	251,998	592,936
QALY Weights	Best Estimate	Low Estimate	High Estimate
	0.65	0.475	0.825

Sensitivity Analyses

Human Capital	Treatment Costs		Number of People	
Outcomes	50%	-50%	50%	-50%
SRR	5.53%	11.86%	8.26%	7.52%
NPV of Benefits				
3%	$ 54,605,944,109	$ 116,104,354,395	$ 128,989,747,317	$ 41,720,551,186
7%	$ (5,075,614,288)	$ 10,801,890,845	$ 4,902,800,348	$ 823,476,209
Cost-Benefit Ratio				
3%	29.53	61.66	68.39	22.80
7%	(3.17)	9.88	5.03	1.68

Human Capital	Mix of Type 1 and Type 2		Eligibility of Type 1 (Type 2 is unchanged)	
Outcomes	50%	-50%	50%	-50%
	1:04	1:19	0.255	0.085
SRR	7.69%	8.20%	7.93%	8.16%
NPV of Benefits				
3%	$ 74,752,227,308	$ 90,655,561,601	$ 84,947,608,770	$ 85,762,689,733
7%	$ 1,781,236,222	$ 3,404,034,008	$ 2,580,265,150	$ 3,146,011,408
Cost-Benefit Ratio				
3%	40.05	48.36	45.38	45.81
7%	2.46	3.80	3.12	3.59

Sensitivity Analyses

Human Capital	Eligibility of Type 2 (Type 1 is unchanged)		QALY Weights	
Outcomes	50%	-50%	50%	-50%
	1.00	0.425	0.825	0.475
SRR	8.17%	7.34%	8.60%	7.42%
NPV of Benefits				
3%	$ 100,898,528,751	$ 41,312,661,164	$ 98,918,055,945	$ 71,792,242,558
7%	$ 3,682,808,876	$ 540,584,647	$ 4,640,164,856	$ 1,086,111,701
Cost-Benefit Ratio				
3%	53.71	22.58	52.68	38.51
7%	4.03	1.44	4.82	1.89

Health Capital	Treatment Costs		Number of People	
Outcomes	50%	-50%	50%	-50%
SRR	7.84%	12.56%	10.15%	9.32%
NPV of Benefits				
3%	$ 127,043,461,303	$ 188,541,871,589	$ 237,646,023,108	$ 77,939,309,783
7%	$ 3,950,088,922	$ 19,827,594,056	$ 18,441,355,164	$ 5,336,327,814
Cost-Benefit Ratio				
3%	67.37	99.50	125.16	41.72
7%	4.25	17.30	16.16	5.39

Sensitivity Analyses

Health Capital	Mix of Type 1 and Type 2		Eligibility of Type 1 (Type 2 is unchanged)	
Outcomes	50%	-50%	50%	-50%
SRR	9.55%	10.07%	9.79%	10.02%
NPV of Benefits				
3%	$ 142,636,096,290	$ 165,369,078,002	$ 158,958,107,598	$ 156,627,225,293
7%	$ 9,700,256,724	$ 12,982,970,013	$ 11,559,278,870	$ 12,218,404,108
Cost-Benefit Ratio				
3%	75.52	87.40	84.05	82.83
7%	8.98	11.68	10.50	11.05

Health Capital	Eligibility of Type 2 (Type 1 is unchanged)		QALY Weights	
Outcomes	50%	-50%	50%	-50%
			0.825	0.475
SRR	10.05%	9.14%	11.18%	8.19%
NPV of Benefits				
3%	$ 185,563,255,548	$ 79,104,126,429	$ 217,347,892,033	$ 98,237,440,858
7%	$ 14,317,668,224	$ 5,006,710,575	$ 19,691,831,004	$ 4,085,851,974
Cost-Benefit Ratio				
3%	97.95	42.33	114.55	52.32
7%	12.77	5.12	17.19	4.36

Sensitivity Analyses

CEA/CUA	Treatment Costs		Number of People	
Outcomes	50%	-50%	50%	-50%
NPV of Costs				
3%	$ 94,161,662,308	$ 32,663,252,022	$ 94,161,662,308	$ 32,663,252,022
7%	$ 25,032,443,561	$ 9,154,938,428	$ 25,032,443,561	$ 9,154,938,428
Cost Per add'l YOL				
3%	$ 27,351	$ 9,488	$ 27,351	$ 9,488
7%	$ 54,757	$ 20,026	$ 54,757	$ 20,026
Cost Per add'l QALY YOL				
3%	$ 42,079	$ 14,597	$ 42,079	$ 14,597
7%	$ 84,242	$ 30,809	$ 84,242	$ 30,809

CEA/CUA	Mix of Type 1 and Type 2		Eligibility of Type 1 (Type 2 is unchanged)	
Outcomes	50%	-50%	50%	-50%
NPV of Costs				
3%	$ 60,071,393,276	$ 65,082,289,944	$ 64,984,111,357	$ 61,840,802,974
7%	$ 16,231,103,510	$ 17,524,804,228	$ 17,499,456,727	$ 16,687,925,262
Cost Per add'l YOL				
3%	$ 17,449	$ 18,905	$ 18,876	$ 17,963
7%	$ 35,505	$ 38,335	$ 38,279	$ 36,504
Cost Per add'l QALY YOL				
3%	$ 26,845	$ 29,084	$ 29,040	$ 27,636
7%	$ 54,623	$ 58,976	$ 58,891	$ 56,160

Sensitivity Analyses

CEA/CUA	Eligibility of Type 2 (Type 1 is unchanged)		QALY Weights	
Outcomes	50%	-50%	50%	-50%
NPV of Costs			0.825	0.475
3%	$ 3,709,816,972	$ 34,234,674,646	$ 63,412,457,165	$ 63,412,457,165
7%	$ 19,752,237,491	$ 9,560,644,375	$ 17,093,690,995	$ 17,093,690,995
Cost Per add'l YOL				
3%	$ 21,411	$ 9,944	$ 18,420	$ 18,420
7%	$ 43,207	$ 20,913	$ 37,392	$ 37,392
Cost Per add'l QALY YOL				
3%	$ 32,940	$ 15,299	$ 22,327	$ 38,778
7%	$ 66,472	$ 32,175	$ 45,323	$ 78,719

Breakeven points	**DFE**	**WTP**
Cost of Treatment at 3% for Type 2 diabetes	$ 34,285	$ 51,567
Cost of Treatment at 7% for Type 2 diabetes	$ 16,566	$ 24,908
Number of People with Type 2 diabetes at 3%	15,616	0*
Number of People with Type 2 diabetes at 7%	193,344	68,668

*number of people with type 1 diabetes must equal 9,198 before breakeven point is reached.

Appendix E: Glossary

Terms in italics are defined elsewhere in the glossary.

benefit-cost ratio The incremental value of obtaining a benefit for every dollar of cost.

clinical trial An study, conducted in a controlled clinical setting, e.g. hospital or clinic, whereby an intervention is evaluated in volunteers against the next best available treatment. A randomized clinical trial is a trial in which the treatments are randomly assigned to the subjects, thereby eliminating bias in the assignment of treatments to patients and establishing the basis for statistical analysis.

cost-benefit analysis (CBA) A systematic categorization of impacts as benefits and costs, valuing in dollars, and then determining the net benefits of the proposal relative to the status quo.

cost-effectiveness analysis (CEA) An analytic tool in which costs and effects of a program or intervention are calculated and presented in a ratio of incremental cost per unit of effect, e.g. additional year of life. See also *cost-utility analysis*.

cost-effectiveness ratio The incremental cost of obtaining a unit of effect, e.g. additional year of life, from a given program or intervention.

cost-of-illness study An analysis of the direct costs incurred by a society due to a specific disease. Cost-of-illness studies may or may not include *indirect costs*, such as lost *productivity*, or *out-of-pocket expenses*.

cost-utility analysis An analytic tool similar to *CEA* in which costs and effects of a program or intervention are calculated and presented in a ratio of incremental cost per standardized unit of effect, e.g. *QALY*-adjusted additional year of life.

direct costs The value of all goods, services, and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.

disability-adjusted life years (DALY) An indicator developed to assess the global burden of disease. DALYs are computed by adjusting age-specific life expectancy for loss of healthy life due to disability. The value of a year of life at each age is weighted, as are decrements to health from disability from specified diseases and injuries.

discounted future earnings A method of measuring the value society places on a good, service, or reduction in risk of death and illness of an individual by estimating the value of the future work output of that individual and *discounting* those future earnings to *present values.*

discounting The process of converting future dollars and future health outcomes to their *present value.*

discount rate The interest rate used to compute *present value*, or the interest rate used in *discounting* future sums.

effectiveness The extent to which medical interventions achieve health improvements in real practice settings.

efficacy The extent to which medical interventions achieve health improvements in ideal circumstances.

ex ante A situation viewed prospectively, before an action has taken place and the outcomes known.

ex post A situation viewed retrospectively, after all action has taken place and after the outcomes are known.

externalities The positive (beneficial) or negative (harmful) effects that market exchanges have on people who do not participate directly in those exchanges

external validity The extent to which one can generalize the study conclusions to populations and settings outside the study.

in media res A situation viewed as the action is taking place, thus while some of the costs may be known, the outcomes are uncertain.

internal validity The extent to which differences in outcomes can be attributed to the particular way in which the outcomes were measured and compared.

hazard function The instantaneous probability of mortality at any point in time.

HbA_{1C} Glycated hemoglobin A_{1C}. A form of hemoglobin, the molecule that carries oxygen in the bloodstream. Researchers have found a strong correlation between glycated hemoglobin and the level of glycemia (sugar) in a person with diabetes, with higher levels of HbA_{1C} indicative of poorer health.

health capital The value of a person's health, as expressed in monetary terms or in life expectancy or years of life in perfect health.

health state The health of an individual at any particular point in time. A health state may be modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or health policy.

human capital The economic worth of a person over time as determined by estimating the *present value* of his or her *discounted future earnings*.

incremental costs The cost of one alternative less the cost of another.

indirect costs The value of time spent or otherwise not utilized due to workplace absences or premature death.

life year A unit for economic analyses used to express life expectancy of an individual in standard units of one year.

marginal benefit The added benefit generated by the next unit consumed.

marginal cost The added cost of producing one additional unit of output.

Markov models A type of mathematical model containing a finite number of mutually exclusive and exhaustive *health states*, having time periods of uniform length, and in which the probability of movement from one state to another depends on the current state and remains constant over time.

Monte Carlo simulation A type of *simulation modeling* that uses random numbers to capture the effects of uncertainty. For example, an event occurs if a random number between 0 and 1 is less than the real-life incidence of that event occurring (e.g. 0.1 or 10%). If greater than the incidence, the event has not taken place and the simulation continues to run until a health state equivalent to death occurs. Multiple simulations simulating additional lives are run, with the results compiled, providing a probability distribution for the overall result.

net present value The value to the decision maker now or some other designated point in time of outcomes occurring in the future.

opportunity costs The other possible uses of funds used in various programs or investments. When pursuing a particular policy or programmatic choice that requires investment of resources, one must forgo other choices where those same resources could be invested.

option pricing approach A technique for justifying various investments *ex ante* whereby small investments are used to gather information about the viability of a larger investment later on.

out-of-pocket expenses In health care, expenses not normally paid for by third-party health insurance or otherwise reimbursed, and thus the responsibility of the patient. These expenses normally include co-payments, transportation and lodging costs, family care, and some drugs and medical supplies. Out-of-pocket expenses do not normally include *indirect costs* such as lost salary due to absences from the workplace.

Pareto efficiency An allocation or distribution of resources such that *social surplus* is maximized and any change in the distribution must make at least one person worse off.

prevalence The proportion of individuals in a population who have a disease or condition at a specific point in time.

productivity The costs or benefits associated with work or the ability to work.

proportional hazards model The hazard function is the instantaneous likelihood of dying at a particular time, from which survival probabilities and survival curves are derived. The proportional hazards model is one algebraic form of the hazard function that assumes the impact of risk factors and other covariates is to multiply the baseline hazard function by some factor; hence their effect can be expressed as being proportional to the baseline hazard. Alternative hazard models such as the additive hazard model (where risk factors add to or subtract from the baseline hazard) are also used in survival analyses.

Proportional hazard rate The risk of an event occurring in time t. See also Box 1 in Chapter 2.

quality-adjusted life years (QALY) A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health related quality of life during that period, where a weight of 1 corresponds to perfect health, while a weight of 0 is equated with death. These weights are independent of time or socioeconomic status.

quality of life A broad construct reflecting subjective or objective judgment concerning all aspects of an individual's existence, including health, economic, political, cultural, environmental, aesthetic, and spiritual aspects.

sensitivity analyses Mathematical calculations that strive to isolate factors involved in an economic analysis to indicate the degree to which each factor influences the outcome of the analysis.

simulation model A model of a complex system or process used to determine how a change in one or more variables affect the rest of the system. Used widely in cases where the problem is difficult to solve by mathematical analysis.

social rate of return The discount rate at which benefits are equal to the costs in a cost-benefit analysis or net present value is equal to zero.

social surplus The sum of consumer and producer surpluses, as determined by supply and demand curves.

societal perspective A viewpoint for conducting cost-benefit or cost-effectiveness analyses that incorporates all costs and all outcomes regardless of who incurs those costs or benefits from the outcomes. This is in contrast to perspectives of the patient, insurer, or provider of health care.

value of statistical life A convenient way to summarize the value of small reductions in mortality risks. This is contrast to "identified lives" whereby the lives of specific individuals are saved, i.e. suddenly changing the risk of mortality from one to zero.

von Neumann-Morgenstern utility A number representing relative desirability that satisfies axioms set forth by von Neumann and Morgenstern stating that one should maximize utility.

welfare economics A normative branch of economics concerned with the development of principles for maximizing social welfare and economic output. It is based on the assumptions that individuals maximize their preferences and that the overall welfare of society is a function of these individual preferences.

willingness to pay A method of measuring the value an individual places on a good, service, or reduction in risk of death and illness by estimating the maximum dollar amount an individual would pay in order to obtain the good, service, or risk reduction.

Source used in development of definitions: Gold, Marthe, et al., ed., *Cost-Effectiveness in Health and Medicine*, Oxford University Press, 1996; Boardman, Anthony, et al., *Cost-Benefit Analysis: Concepts and Practice*, Prentice Hall, 1996; Sloan, Frank A., ed., *Valuing Health Care: Costs, Benefits, and Effectiveness of Pharmaceuticals and Other Medical Technologies*, Cambridge University Press, 1996; Eastman, Richard C, et al., "Model of Complications of NIDDM: Model Construction and Assumptions," *Diabetes Care*, v. 20, n. 5, May 1997, pp. 725-734.

Appendix F: Cost of Illness and NIH Support for Selected Diseases and Conditions

Reprinted from the National Institutes of Health Report on "Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support: Fiscal Year 2000 Update." National Institutes of Health, Bethesda, Maryland, February 2000.

Table 1: Costs of Illness and NIH Support For Selected Diseases and Conditions--Part 1A

February 11, 2000

	Death		Cost Estimate	$ Billions			Estimate Includes					
	Rank	Number					Direct Costs	Indirect Costs				
Diseases/Conditions	Rank by 1998 Death Rates	1998* (1,000s)	Ref. Year of Cost Data	Total Costs	Direct Costs	Indirect Costs	Due to Other Related Non-Health Costs	Due to Mortality of Patient (premature death)	Due to Morbidity Of Patient (lost workdays)	Due to Morbidity of Patient (reduced productivity)	Due to Services of Unpaid Caregivers	Due to Other Related Non-Health Costs
1	2	3	4	5	6	7	8	9	10	11	12	13
Alcohol Abuse and Dependence		110.6*	1998	184.6	50.4	134.2	Yes	Yes	Yes	Yes	No	Yes
Allergic Rhinitis (Hay Fever)			1996	NA	1.9	NA	No	No	No	No	No	No
Alzheimer's Disease and Other Dementia	12	22.8	1997	100.0	15.0	85.0	Yes	Yes	Yes	No	Yes	No
Arthritis			1992	64.8	15.2	49.6	No	Yes	Yes	No	No	No
Asthma			1996	14.0	12.0	2.0	No	Yes	Yes	Yes	No	No
Atherosclerosis	14	15.4	1999	6.2	5.5	0.7	No	Yes	No	No	No	No
Cancer (Malignant neoplasms, including neoplasm of												
lymphatic and hematopoietic tissues) #	2	538.9	1990	96.1	27.5	68.7	No	Yes	Yes	No	No	No
Cancer--(Breast)			1990	12.7	6.6	6.2	No	Yes	Yes	No	No	No
Cancer--(Cervical)			1990	NA	0.6	NA	No	No	No	No	No	No
Cancer--(Colorectal)			1990	NA	6.5	NA	No	No	No	No	No	No
Cancer--(Lung)			1990	NA	5.1	NA	No	No	No	No	No	No
Cancer--(Ovarian)			1990	NA	0.9	NA	No	No	No	No	No	No
Cancer--(Prostate)			1990	NA	4.7	NA	No	No	No	No	No	No
Cerebrovascular Disease (Stroke)	3	158.1	1998	43.3	28.3	15.0	No	Yes	Yes	No	No	No
Chronic Liver Disease and Cirrhosis	10	24.9	1985	3.2	1.2	2.1	No	Yes	Yes	No	No	No
Chronic Obstruct. Pulmonary Diseases & Allied Condition	4	114.4	1998	37.3	21.6	16.2	No	Yes	Yes	No	No	No
Dental/Oral Diseases			1997	NA	50.6	NA	No	No	No	No	No	No
Diabetes	7	64.6	1997	98.2	44.1	54.1	No	Yes	Yes	Yes	No	Yes
Digestive Diseases #			1985	56.2	41.5	14.7	No	Yes	Yes	No	No	No
Digest--(Gallbladder Disease)			1985	4.7	4.4	0.4	Yes	Yes	Yes	No	No	No
Digest--(Peptic Ulcer)			1989	4.9	3.6	1.4	Yes	Yes	Yes	No	No	No
Disability (Rehabilitation Research)			1986	169.4	82.1	87.3	Yes	No	Yes	No	No	No
Drug Abuse (Including AIDS due to IV Drug Use)		26.3*	1995	109.8	32.0	77.6	Yes	Yes	Yes	Yes	No	Yes
Epilepsy			1992	NA	3.0	NA	No	No	No	No	No	No
Eye Diseases and Disorders of Vision #			1991	38.4	22.3	16.1	Yes	NA	Yes	Yes	NA	NA
Eye Diseases--Diabetic Retinopathy			1992	2.8	0.6	2.2	Yes	NA	Yes	Yes	NA	NA
Heart Diseases #	1	724.3	1999	183.1	101.8	81.3	No	Yes	Yes	No	No	No
Heart Diseases--Coronary Heart Disease			1999	99.8	53.1	46.7	No	Yes	Yes	No	No	No
HIV/AIDS Infections	16	13.2	1999	28.9	13.4	15.5	No	Yes	Yes	No	No	No
Homicide and Legal Interventions	13	17.4	1989	33.7	10.4	23.3	Yes	Yes	Yes	Yes	No	Yes
Infertility			1987	NA	1.0	NA	No	No	No	No	No	No

Table 1: Costs of Illness and NIH Support For Selected Diseases and Conditions--Part 1B

February 11, 2000

		Estimate Includes Costs			Scope of Estimate	ICD		NIH Support $ Billions
Diseases/Conditions	Discount Rate	Of Related Conditions Beyond Primary ICD-9-CM Codes**	Attributable As A Secondary Diagnosis	Of Underlying Causes of Other Conditions	Total U.S. Population or Subset	Identifying Cost Data	Quoted By ICD	FY 1999 Spending***
1	14	15	16	17	18	19	20	21
Alcohol Abuse and Dependence	6%	Yes	Yes	Yes	Total	NIAAA	Yes	0.3465
Allergic Rhinitis (Hay Fever)		No	No	No	Total	NIAID		0.0017
Alzheimer's Disease and Other Dementia	NA	No	Yes	Yes	Age65+	NIA,NINDS	Yes	0.4065
Arthritis	4%	No	No	No	Total	NIAMS		0.2388
Asthma	NA	No	No	No	Total	NIAID	Yes	0.1404
Atherosclerosis	6%	No	No	No	Total	NHLBI		0.2108
Cancer (Malignant neoplasms, including neoplasm of								-
lymphatic and hematopoietic tissues) #	4%	No	No	No	Total	NCI	Yes	3.3773
Cancer--(Breast)	4%	No	No	No	Total	NCI	Yes	0.4747
Cancer--(Cervical)		No	No	No	Total	NCI	Yes	0.0752
Cancer--(Colorectal)		No	No	No	Total	NCI	Yes	0.1759
Cancer--(Lung)		No	No	No	Total	NCI	Yes	0.1631
Cancer--(Ovarian)		No	No	No	Total	NCI	Yes	0.0654
Cancer--(Prostate)		No	No	No	Total	NCI	Yes	0.1775
Cerebrovascular Disease (Stroke)	6%	No	No	No	Total	NINDS	Yes	0.1860
Chronic Liver Disease and Cirrhosis	4%	Yes	Yes	No	Total	NIDDK		0.1984
Chronic Obstruct. Pulmonary Diseases & Allied Conditions	6%	No	No	No	Total	NHLBI	Yes	0.0997
Dental/Oral Diseases		No	No	No	Total	NIDCR	Yes	0.2494
Diabetes @	4%	Yes	Yes	Yes	Total	NIDDK	Yes	0.4576
Digestive Diseases #	4%	Yes	Yes	No	Total	NIDDK	Yes	0.6485
Digest--(Gallbladder Disease)	4%	Yes	No	No	Total	NIDDK	Yes	0.0127
Digest--(Peptic Ulcer)	4%	Yes	No	No	Total	NIDDK	Yes	0.0104
Disability (Rehabilitation Research)		No	No	No	Total	NICHD	Yes	0.1992
Drug Abuse (Including AIDS due to IV Drug Use)	6%	Yes	Yes	Yes	Total	NIDA	Yes	0.6262
Epilepsy		No	No	No	Total	NINDS	Yes	0.0817
Eye Diseases and Disorders of Vision #	NA	NA	NA	NA	Total	NEI	Yes	0.4257
Eye Diseases--Diabetic Retinopathy	6%	NA	NA	NA	Total	NEI	Yes	0.0224
Heart Diseases #	6%	No	No	No	Total	NHLBI	Yes	1.2560
Heart Diseases--Coronary Heart Disease	6%	No	No	No	Total	NHLBI	Yes	0.3136
HIV/AIDS Infections ~	3%	No	No	Yes	Total	OAR, OD	Yes	1.7927
Homicide and Legal Interventions	3%	No	No	No	Age 12+	NIMH		0.0109
Infertility		No	No	No	Total	NIEHS		0.0251

Table 1: Costs of Illness and NIH Support For Selected Diseases and Conditions--Part 2A

February 11, 2000

	Death		Cost Estimate				Estimate Includes					
	Rank			$ Billions			Direct Costs	Indirect Costs				
Diseases/Conditions	Rank by 1998 Death Rates	1998 (1,000s)	Ref. Year of Cost Data	Total Costs	Direct Costs	Indirect Costs	Due to Other Related Non-Health Costs	Due to Mortality of Patient (premature death)	Due to Morbidity Of Patient (lost workdays)	Due to Morbidity of Patient (reduced productivity)	Due to Services of Unpaid Caregivers	Due to Other Related Non-Health Costs
1	2	3	4	5	6	7	8	9	10	11	12	13
Injury (Total), including Accidents and Adverse Effects #	6	93.2	1995	338.0	89.0	248.0	Yes	Yes	Yes	Yes	No	No
Injury--Childhood injuries			1995	69.6	19.2	50.3	Yes	Yes	Yes	Yes	No	No
Injury--Lead Poisoning			1994	17.2	11.5	5.7	Yes	Yes	Yes	Yes	No	No
Injury--Trauma, Central Nervous System (Head and Spine)			1992	35.0	10.0	25.0	No	No	No	No	No	No
Kidney & Urology Diseases, including nephritis,												
nephritic syndromes, and nephrosis #	9	26.3	1985	40.3	26.2	14.1	No	Yes	Yes	Yes	No	No
Kid & Urology--End Stage Renal Diseases			1997	NA	15.6	NA	No	NA	NA	NA	NA	NA
Kid & Urology--Incontinence			1995	26.3	12.5	13.8	No	No	No	No	No	Yes
Kid & Urology--Kidney Stones			1985	NA	1.4	NA	No	No	No	No	No	No
Kid & Urology-- Prostate Diseases			1985	NA	3.1	NA	No	NA	NA	NA	NA	NA
Kid & Urology--Urinary Infect.(Kid, cystitis, urethritis)			1985	NA	4.4	NA	No	NA	NA	NA	NA	NA
Mental Disorders			1992	160.8	66.8	94.0	Yes	Yes	Yes	Yes	Yes	Yes
Multiple Sclerosis			1991	5.0	2.5	2.5	No	No	Yes	Yes	No	No
Obesity			1995	99.2	51.6	47.6	No	Yes	Yes	No	No	No
Osteoporosis			1995	NA	13.8	NA	No	No	No	No	No	No
Otitis Media			1993	5.0	2.9	2.1	No	No	No	No	Yes	Yes
Pain Conditions, Chronic			1986	79.0	45.0	34.0	No	No	Yes	No	No	Yes
Parkinson's Disease			1992	6.0	2.0	4.0	No	No	No	No	No	No
Pelvic inflammatory Disease			1996	6.8	NA	NA	No	Yes	Yes	No	No	Yes
Perinatal Period, Conditions Originating in the # ^	15	13.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Perinatal Period-- Births, Preterm and Low Weight			1994	NA	2.0	NA	No	No	No	No	No	No
Perinatal Period-- Neonatal Resp. Distress Syndrome			1997	1.1	0.7	0.4	No	Yes	No	No	No	No
Perinatal Period-- Sudden Infant Death Syndrome (SIDS)			1995	NA	NA	1.0	No	Yes	No	No	No	No
Pneumonia and influenza	5	94.8	1999	25.6	18.6	7.0	No	Yes	No	No	No	No
Psoriasis			1994	NA	3.0	NA	No	No	No	No	No	No
Respiratory Distress Syndrome, Acute			1999	4.1	3.2	0.9	No	Yes	No	No	No	No
Septicemia	11	23.6	1998	7.2	4.9	2.3	No	Yes	No	No	No	No
Sickle Cell Anemia			1995	0.9	0.6	0.3	No	Yes	No	No	No	No
Smoking		422.1*	1995	138.0	80.0	58.0	No	Yes	Yes	No	No	No
Suicide	8	29.3	1985	NA	NA	10.2	No	Yes	NA	NA	NA	NA
Tuberculosis			1991	NA	0.7	NA	Yes	No	No	No	No	No

Table 1: Costs of Illness and NIH Support For Selected Diseases and Conditions--Part 2B

February 11, 2000

		Estimate Includes Costs			Scope of Estimate	ICD		NIH Support $ Billions
Diseases/Conditions	Discount Rate	Of Related Conditions Beyond Primary ICD-9-CM Codes**	Attributable As A Secondary Diagnosis	Of Underlying Causes of Other Conditions	Total U.S. Population or Subset	Identifying Cost Data	Quoted By ICD	FY 1999 Spending***
1	14	15	16	17	18	19	20	21
Injury (Total), including Accidents and Adverse Effects #	2.5%	No	No	No	Total	NICHD		0.2385
Injury--Childhood injuries	2.5%	No	No	No	Age<20	NICHD	Yes	0.0131
Injury--Lead Poisoning		No	No	No	Total	NIEHS		0.0167
Injury--Trauma, Central Nervous System (Head and Spine)		No	No	No	Total	NINDS	Yes	0.1588
Kidney & Urology Diseases, including nephritis,								-
nephritic syndromes, and nephrosis #	4%	Yes	Yes	Yes	Total	NIDDK	Yes	0.3100
Kid & Urology--End Stage Renal Diseases		No	No	No	Total	NIDDK	Yes	0.0230
Kid & Urology--Incontinence		No	Yes	Yes	Age65+	NIA	Yes	0.0069
Kid & Urology--Kidney Stones		No	Yes	Yes	Total	NIDDK	Yes	0.0056
Kid & Urology-- Prostate Diseases	4%	No	Yes	Yes	Total	NIDDK	Yes	0.1791
Kid & Urology--Urinary Infect.(Kid, cystitis, urethritis)	4%	No	Yes	Yes	Total	NIDDK	Yes	0.0120
Mental Disorders #	6%	Yes	Yes	No	Total	NIMH	Yes	0.7487
Multiple Sclerosis		No	No	No	Total	NINDS	Yes	0.0965
Obesity	4%	Yes	No	Yes	Total	NIDDK		0.1616
Osteoporosis		No	No	No	Total	NIAMS	Yes	0.1367
Otitis Media		No	No	No	Total	NIDCD		0.0081
Pain Conditions, Chronic		NA	NA	NA	Total	NIDCR,NINDS	Yes	0.1044
Parkinson's Disease		No	No	No	Total	NINDS	Yes	0.1323
Pelvic inflammatory Disease	4%	Yes	No	Yes	ge15-44,wome	NIAID	Yes	0.0045
Perinatal Period, Conditions Originating in the # ^	NA	NA	NA	NA	NA			0.3170
Perinatal Period-- Births, Preterm and Low Weight		No	No	No	Total	NICHD	Yes	0.2924
Perinatal Period-- Neonatal Resp. Distress Syndrome	6%	No	No	No	Total	NHLBI		0.0073
Perinatal Period-- Sudden Infant Death Syndrome (SIDS)	6%	No	No	No	Total	NHLBI		0.0493
Pneumonia and influenza	6%	No	No	No	Total	NHLBI		0.0744
Psoriasis		No	No	No	Total	NIAMS		0.0052
Respiratory Distress Syndrome, Acute	6%	No	No	No	Total	NHLBI		0.0308
Septicemia	6%	No	No	No	Total	NHLBI		0.0165
Sickle Cell Anemia	6%	No	No	No	Total	NHLBI		0.0505
Smoking	4%	No	No	Yes	Total	NIDA	Yes	0.3539
Suicide	6%	No	No	No	Total	NIMH		0.0251
Tuberculosis		No	No	No	Total	NIAID	Yes	0.0729

Table: Costs of Illness and NIH Support for Selected Diseases and Conditions

GENERAL CONSIDERATIONS IN REVIEWING COST OF ILLNESS DATA

Cost of illness (COI) estimates provide order of magnitude indicators for the economic burden of disease and should be interpreted with caution. They neglect other equally important but difficult to measure dimensions -- such as the prevalence of disease, and the effect on the quality of life and daily functioning -- in considering and understanding the true cost of illness to society. Although only a single point estimate is provided for each disease and condition listed in the table, a range of uncertainty should be attached to each estimate. The cost estimates are based on a series of parameters, each of which is, at best, estimated from survey data with implicit sampling error. Judgments regarding selection and interpretation of proxies for missing or incomplete data influence the derivation of the final value and add further uncertainty. Finally, the published literature on cost of illness studies documents significant variations in methods and data (see report text and related references) which result in the incomparability of results from different studies.

Any attempt to compare cost data across disease categories must consider in depth the many conceptual and methodological issues that may lead to variations in cost estimates. Major considerations for interpreting and comparing the cost estimates in the table with each other and with estimates from other sources include the following: definition of disease; cost components; discount rate; reference year; and method, approach, and scope and perspective of the estimation. Some of these variations are summarized by the columns in the table. More detailed information, including related measures of disease burden and references to the underlying cost reports for each disease, are included in the attached *Table Notes*, the *Presentation of the Data* section of the report, and the documentation summaries in the *Appendix*.

Table Legend

#	The cost estimates and the NIH support for disease subcategories do not add up to the values displayed for the corresponding major categories. Not all subcategories are included, and the cost estimates for the subcategories are frequently obtained from several different studies that use different methods and data sources.
^	No cost estimate could be located by the NIH Institutes and Centers for Conditions Originating in the Perinatal Period. Please refer to the *Appendix* for further relevant information and comments.
*	Deaths for these 3 major external factors that contribute to death refer to 1996 and are based on a methodology explained in the McGinnis and Foege paper. Please refer to the attached table Notes and to the text of this report for additional explanation. See appendix pages for sources.
**	ICD-9-CM code = *International Classification of Diseases, 9th Revision, Clinical Modifications*
***	Figures for NIH support reflect NIH-wide spending on the listed diseases. In most cases, these support figures include spending from several Institutes and Centers.
NA	Not available

Notes for Table: Costs of Illness and NIH Support for Selected Diseases and Conditions

Top 15 causes of mortality. The annual deaths for each of the top 15 causes of mortality in 1998 as identified by the Centers for Disease Control and Prevention National Vital Statistics Reports, Vol 47, No. 25, october 5, 1999. Estimates for the deaths dues to Alcohol Abuse and Dependence, due to Drug Abuse, and due to Smoking (for tobacco use) in 1996 are identified with an asterisk (*) in column 3. These three conditions were listed among the top 9 major external (non-genetic) factors that contribute to death in the United States in 1990 (J. Michael McGinnis and William H. Foege, "Actual Causes of Death in the United States," JAMA, Nov. 10, 1993, Vol. 270, No. 18, pp. 2207-2212). Four sources see the appendix pages for Alcohol Abuse and Dependence, for Drug Abuse, and for Smoking.

Unavailability of estimates. No agreed upon cost estimates were located by the NIH Institutes and Centers for two of the top causes of mortality -- Conditions Originating in the Perinatla Period; and, Nephritis, Nephrotic Syndromes and nephrosis. A cost estimate for Kidney and Urologic Diseases (which include nephritis, nephrotic syndromes, and nephrosis) was substituted for the more specific Nephritis, Nephrotic Syndromes and Nephrosis category. The time and effort required to generate an estimate for perinatal conditions was beyond the scope of the Senate's request for this report (see *Appendix*).

Major considerations for interpreting and comparing the cost estimates in the table with each other and with estimates form other sources include the following:

Reference Year (Column 4). The estimates are each expressed in dollars for a particular reference year. To express all estimates in a common reference year, it would be necessary to adjust for changes in the disease burden over time, patterns of treatment and care, and the purchasing power of the dollar for health care services.

Cost components (Columns 5-13). COI studies include direct and indirect cost components. The comprehensiveness of the estimates of direct and indirect costs differs across diseases because of the difficulty and cost required to estimate the non-health related costs, and the indirect costs related to reduced productivity after returning to the job and the value of services of unpaid care givers.

Discount Rate (Column 14). The stream of lost earnings over future years are converted to base or reference year values using a discount rate intended to reflect the tradeoff between the values of a dollar received today versus one received next year. Valid comparison of estimates requires adjustment of discount rates to a common value.

Definition of disease (Columns 15-17). Because the interrelationships between disease categories or causal agents are complex and patients often present with more than one disease or condition, it is not always feasible or appropriate to construct mutually exclusive disease categories and associated cost estimates. Cost estimates depend on how narrowly or broadly the disease is defined, whether it includes related conditions beyond its narrowly defined or primary ICD-9-CM code (col.15); whether the estimates includes identifiable extra costs attributable when the disease is listed as a secondary diagnosis or comorbidity (col.16); and whether the estimate includes costs attributable to the disease or condition as an underlying cause or risk factors of other diseases (col.17).

Method and Approach of Estimation. All of the COI estimates in this table are based on the conventional human capital method rather than the less common willingness-to-pay approach. Because the human capital approach values the indirect costs of illness in terms of market earnings, it yields very low values for the retired elderly and for children. It also ignores certain dimensions of illness and death, such as pain and suffering. Two approaches can be used to determine COI estimates: 1) prevalence-based (annual) cost provides an estimate of the direct and indirect burden incurred by all cases that existed during a specified period of time (year); and 2) incidence-based (lifetime) cost represents the lifetime cost resulting from the illness of all cases that began during a specified year. All of the COI estimates in this table used the prevalence-base approach, except for accidents and adverse effects; homicide and legal intervention; several injury subcategories; and an eye subcategory - diabetic retinopathy.

Scope and Perspective of Estimation (Column 18). Most estimates address the total U.S. resident population; they are not specific to particular geographic area or ethnic groups. However, a few are limited by the age of the patients. Similarly, most of the studies estimate costs to the total society, regardless of who bear the costs. In this table, the only exceptions are end stage renal disease, which is limited to federal payments for Medicare claims, and infertility, which includes only payments by insurance companies.

NIH Support (Column 21). This column contains the NIH spending for each disease from all Institutes and Centers. The support figures contain overlaps. Since overlaps in cost estimates could not be removed, no attempt was made to eliminate overlaps in the corresponding support figures.