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A Framework for Estimating the National Economic Benefits of ATP Funding of Medical Technologies

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Preliminary Applications to Tissue Engineering Projects Funded from 1990 to 1996

Final Report

Prepared for

U.S. Department of Commerce
National Institute of Standards and Technology
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Administration Building, Room A303
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Preface

The Economic Assessment Office (EAO) of the Advanced Technology Program (ATP) seeks to measure the economic impacts of ATP's funding of high-risk, enabling technologies and also to increase understanding of underlying relationships between technological change and economic phenomena, to further the program's ability to achieve its mission. To this end, the EAO compiles data, conducts economic studies, and commissions studies by outside research organizations and economists. The study described by this report was carried out by the Center for Economics Research at Research Triangle Institute (RTI), under contract to the ATP.

The RTI study was intended to achieve four goals:

- to estimate potential benefits of an inclusive portfolio group of ATP projects;
- to perform seven case studies within the portfolio group using a consistent methodology;
- to develop an evaluation framework that ATP could consider for possible adoption—for evaluating a wide variety of technologies with medical applications; and
- to inform the emergent ATP focused program in tissue engineering of the potential for economic benefit in this technology field.

The four goals were largely achieved by the study.

A case study approach was taken, one of a multiple of evaluation techniques used by the ATP. Case study entails detailed investigation of projects to evaluate technical accomplishments, commercialization progress, the role played by the ATP, and

economic outcomes. Since ATP-funded projects are in relatively early-stage research and development, assessment of potential economic outcomes depends necessarily on numerous projections and estimates for future conditions; understandably, this part of the analysis entails considerable uncertainty.

Results of the RTI study relating to each of the four goals, together with ATP's perspective on the results, are as follows.

GOAL 1—ANALYSIS OF PORTFOLIO BENEFITS

RTI's study estimated many billions of dollars of social returns from the group of tissue engineering technologies in ATP's portfolio, large spillover benefits, and an impressive contribution to benefits attributable to the ATP. By considering *all* of the tissue engineering projects underway at the time of the study, the study was able to avoid selection bias and presented the first analysis of ATP-funded projects at the portfolio level. While the ATP is obviously gratified that RTI's findings lend further evidence that the program is on the way to meeting its mission, it recognizes the substantial uncertainties entailed in the analysis and realizes that the eventual economic outcome from this portfolio of projects may be considerably different from today's projections. A principal limitation of the study is that it does not sufficiently treat the uncertainties entailed in the estimates.

RTI developed quantitative estimates for the key analytical concepts that ATP requested: social and private returns, and social return on public investment. The measures were given in terms of net present value and internal rate of return. Sensitivity analysis was performed for four variables in the estimation of social returns and five variables for the estimation of private returns. With the exception of one of the projects, the projected benefits remained large as input values were varied in the sensitivity analysis. Nevertheless, the results as presented do not adequately convey the uncertainties that are inherent in such analyses of prospective returns.

None of the technologies examined are yet actually in use by doctors. The analyses are *ex ante,* not *ex post.* Companies—

particularly small companies, which are prominent in this group—go out of business with great frequency. Short-run cash-flow crunches, unforeseen technical obstacles that arise at the last moment, patient complications that derail clinical trials, unanticipated alternative technologies that suddenly make obsolete what had previously been envisioned as a great new technology, and countless other surprise developments can overturn even the most promising of ideas. If any of these unexpected developments were to occur for any of the seven projects, the private and social benefits would decrease and the economic return would be lower than estimated.

The risk that the technology will not successfully move forward into actual use, even if it has been successful from a research standpoint, is likely relatively low for several of the technologies, and somewhat higher for others. In future studies, the ATP will require more extensive sensitivity analysis and more careful modeling of probabilities; the ATP will request reporting of results in terms of ranges or confidence intervals, rather than point estimates, to better reflect and emphasize the uncertainty of results in prospective analysis of returns.

GOAL 2—CONSISTENT APPROACH ACROSS CASE STUDIES

The goal of consistently applying the same framework to all seven case studies for comparability was generally successful. The one important difficulty with respect to consistency that was encountered proved to be not with the model itself, but with obtaining all of the necessary data needed to apply all elements of the model to each of the cases. In particular, the model included utility weights known as quality-adjusted life-years (QALYs) as measures of the value of patient pain and suffering, but this information was not available for all of the specific medical conditions relevant to each of the technologies.

GOAL 3—A GENERAL MODEL FOR EVALUATING MEDICAL TECHNOLOGIES

The study provided a useful first step in developing an evaluation framework for medical technologies that had the capability of accounting for improvements in patient outcomes. Development of this early model has helped us identify issues for further discussion and has highlighted potentially productive approaches to consider in completing an evaluation framework for medical technologies.

The model correctly identified three ways that ATP funding can make a difference:

- ATP funding can accelerate a project by causing it to have an earlier start or by speeding the rate of performance.
- ATP funding can increase the probability of project success.
- ATP funding can widen a project's scope.

The study identified the economic burden of a disease as including the following three cost categories:

- direct medical costs (i.e., costs of medical treatment);
- indirect costs (i.e., loss in productivity and unpaid care giver time); and
- intangible costs (i.e., pain and suffering of patients with acute and chronic diseases and illnesses).

As acknowledged in the study, indirect costs were omitted from both the model and the case-study applications.

The outcomes of the model were expressed in terms requested by the ATP: measures for the social return on public investment, the social return on total investment, and the private return to the innovating firms. The social return on *public* investment is based in the model on a comparison between a "world with ATP" and a hypothetical "world without ATP," and focuses on those social benefits that are attributable to the ATP award. The *social* benefits concept includes benefits that extend beyond the private benefits captured by the innovating companies, what economists call "spillover" effects. As modeled by RTI, the spillover effects include an estimated value for patient pain and suffering avoided, to the extent that such patient benefits are not captured by the firms in their pricing of their new medical treatments. To assign a value to

the impacts on patients, the model incorporates the concept of QALYs, where utility weights are used to account for different health states associated with different chronic and acute medical conditions.

Limitations of the model or its application include the following. Not included in the modeling of spillovers is an assessment of the value of knowledge gained by other firms from the research carried out by the ATP awardees, so-called "knowledge spillovers." The model also makes no allowances for evaluating projects that are interrelated, to avoid double counting in the case of overlapping technologies, or to take into account complementary effects of synergistic technologies. The model is presented and applied for a single application, whereas all the technologies evaluated are in fact multiple-application technologies. In addition, indirect medical costs are not included in the model. From the standpoint of empirical implementation of the model, information needed to support the QALY approach may not be available for all medical technologies and may require additional research to derive. A critical parameter for estimating the distribution of benefits, between private benefits captured by the innovators and spillover benefits to the patients, is the pricing of the medical treatments, and this is an issue deserving of more investigation since it bears heavily on the results. Finally, as pointed out previously, additional attention to the estimation of probabilities is desirable.

GOAL 4—INFORMATION FOR ATP'S EMERGENT FOCUSED PROGRAM

The study's estimated benefits for the portfolio of seven tissue engineering projects, though likely more uncertain than indicated in the study, nevertheless suggests a very strong potential for national benefits from new approaches to the treatment of diseases and illnesses that offer lower treatment costs in combination with better patient outcomes. The opportunities for an ATP Focused Program in the emerging field of tissue engineering seem promising.

We plan to extend our efforts to improve the evaluation of medical technology investments in two major directions. First, we expect to refine and improve both the theoretical modeling and the empirical

estimation of the impact of public investments. Second, with the passage of time we intend to revisit projects that have been the subject of *ex ante* analysis to provide an *ex post* analysis of economic returns; this will enable us to compare prospective and retrospective analyses and hence to identify shortcomings in the early analysis.

In summary, it is important to note that the RTI study is an early effort at modeling and measuring economic returns for new technologies. This type of modeling, too, is an emerging field, and the existing methods and tools of evaluation are as yet inadequate to the task. Yet, it is important—and, in fact, required by law—that federal agencies be accountable for and report on the inputs, outputs, and outcomes of the programs they operate for the benefit of the nation. Assessing the social impact of government cost sharing of high-risk research to develop breakthrough, infrastructural, and multiapplication technologies lies at the frontier of program evaluation and offers both theoretical and practical challenges. RTI did a good job with a very tough task. Our criticisms of the study do not reflect poor performance on the part of RTI; rather, our comments are indicative of the challenges in developing and applying such a model. We welcome comments and advice from the evaluation community on ways to improve modeling and analysis of economic benefits.

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Executive Summary

The National Institute of Standards and Technology's (NIST's) Advanced Technology Program (ATP) began in 1990 as a cost-sharing program to assist U.S. industry in pursuing high-risk, enabling technologies with potential for significant national economic benefit.

ATP conducts economic analyses of these technologies to assess the short- and long-run impact of ATP-funded projects on project participants and on others in the economy. As part of this effort, Research Triangle Institute (RTI), under contract to NIST, addressed the specific challenges of developing and employing a framework for estimating social and private returns on ATP-funded innovations used in medicine.

This executive summary provides an outline of the study's methodology and summarizes key findings. Chapter 1 of the report gives a complete overview of the study, describing objectives and methodology, the specific tissue engineering projects, and findings and conclusions. Chapter 2 explains the methodology in greater detail. Chapter 3 provides case by case analysis of each of the seven ATP-funded tissue engineering projects.

Our approach to modeling the social and private returns on ATP-funded projects in medical technologies is based on the methodology recommended by Mansfield (1996). We modify Mansfield's methodology for the specific case of medical innovations. In particular, we use nonmarket methods to value the benefits of new medical treatments. Nonmarket valuation methods are useful for valuing benefits of new technologies that are not

priced in markets—cleaner water or air, reductions in crime, or, as in this case, improvements in health.

ATP-funded medical technologies may improve the long-run health outcomes of thousands of patients each year with acute and chronic diseases. They may also reduce the cost of health care. Valuing these effects requires extending conventional benefit-cost models and applying methodologies commonly used in health economics.

The economic burden of a disease is usually divided into three components: direct medical costs, indirect costs, and intangible costs. Direct medical costs are costs of medical treatment. Indirect costs are the societal costs associated with the loss in productivity due to illness and unpaid caregiver time. Intangible costs measure the patient's pain and suffering. Our methodology measures how ATP-funded technologies change both the direct medical costs and the intangible costs of a disease. Changes in indirect costs are generally not included in our estimates.

Social return on public investment quantifies the incremental improvement in social outcomes attributable to ATP investment.

The primary emphasis of the methodology developed and used in this study is to evaluate the *social return on public investment* for ATP projects. From a public policy perspective, this evaluation factor is central, because it quantifies the incremental improvement in social outcomes attributable to ATP's investment.

Our methodology allows ATP funding to affect the development of medical technology in three ways:

- **Accelerate the technology's benefits:** ATP funding can catalyze and accelerate the R&D phase, bringing benefits to the private sector, patients, and society sooner and for a greater number of years than without ATP funding. In some cases, ATP funding may persuade a company to conduct research in a technology that it otherwise would not pursue.
- **Increase the likelihood of success:** By reducing the cost of R&D to the companies developing the technology, ATP funding can increase the amount of R&D conducted and increase the likelihood that a project will be technically successful.
- **Widen the technology's applications:** ATP funding can also widen the scope of the project, enabling the company to apply its technology to additional diseases or patient populations.

To determine the social return on public investment, we constructed two scenarios for each project: one with ATP funding and one without ATP funding. The with-ATP scenario can differ from the without-ATP scenario through any of the three impact channels described above. We first calculated the social benefits and costs for each scenario and then calculated the difference in the stream of benefits and costs between the with-ATP and the without-ATP scenarios.

Social return on investment quantifies the net benefits to society resulting from public *and* private investment in ATP-funded technologies.

Private return on investment considers only the investment costs and revenues to the companies participating in the technology's development.

Social return on investment quantifies the extent to which the nation is better off as a result of public and private investment in the development of these technologies. The concept of social return considers the costs of public investment and the value of medical benefits to individuals in addition to private investment costs and private company profits.

Private return on investment is a component of social return on investment. The concept of private return considers only investment costs and revenues of companies carrying out the research, commercialization, and manufacturing of the new technologies and does not consider either costs of public investment or value of medical benefits to individuals.

Social return on public investment is based on a comparison between social return with ATP and social return without ATP; that is, between cell A and cell C in Figure E-1.

Figure E-1. Social and Private Returns With and Without ATP

	Social Returns	Private Returns
With ATP	A	B
Without ATP	C	D

To demonstrate the feasibility of the methodology, we examined one specific application for each of seven multiple-application tissue engineering projects funded from 1990 to 1996. Assuming that these technologies are developed and used for the specific applications we studied, our analysis shows the following expected benefits:

- The expected *social return on ATP public investment* in these technologies, or the increment to social returns attributable to ATP funding, is estimated at $34 billion in net present value.
- The expected *social rate of return on ATP public investment* in these technologies is estimated at an annual rate of 116 percent.
- The expected total *social return* on public and private investment in these technologies is estimated at $112 billion in net present value, or an annual rate of 115 percent.
- The expected total *private return* on investment in these technologies to ATP-award companies and their partners in commercialization and production is estimated at $1.6 billion in net present value, or an annual rate of 12 percent. Of the $1.6 billion in net present value of private returns, $914 million is estimated to be attributable to ATP funding.

These results illustrate two important points about ATP's role in funding these technologies:

- ATP plays a significant role in increasing the expected social and private returns on these projects.
- The social returns are far greater than the private returns. Private companies will therefore tend to underinvest in these technologies. The wide disparity between social and private returns indicates the importance of public incentives to the private sector to pursue these technologies.

This study analyzed only the preliminary applications of these technologies; their long-term impact may be much greater than suggested here.

The study analyzed only the preliminary applications of these technologies. Because these technologies provide the scientific basis for a wide range of applications, their long-term impact may be much greater than suggested here, as companies apply their discoveries to a variety of medical applications. In addition, the knowledge generated by these initial applications may lead to advances in additional, unrelated areas by other companies.

Because none of these technologies has yet reached the commercial market—though several are in clinical trials—the results of this analysis are based on the expectations of the innovators and other informed individuals. Whether these expectations will be realized is uncertain. However, the methodology will allow us to update these results as data on the actual costs and benefits of the projects become available.

1 Overview

The National Institute of Standards and Technology's (NIST's) Advanced Technology Program (ATP) began in 1990 as a cost-sharing program to assist U.S. industry in pursuing high-risk, enabling technologies with significant potential for commercial and national economic impact.

ATP conducts economic analyses of these technologies to measure the short- and long-run impacts of the specific development projects it funds on the project participants and on others in the economy. ATP's evaluation strategy includes, among other activities, the development of evaluation methodologies and case studies of ATP projects (Ruegg, 1996) and continuous improvement of the methods and data used to estimate the economic impact of ATP innovations.

As part of ATP's methodology development effort, Research Triangle Institute (RTI), under contract to NIST, addressed the special challenges of developing and employing a framework for estimating social and private returns to ATP-funded innovations used in medicine. We developed a methodology for measuring the benefits resulting from improving patient health, reducing the cost of medical care, and creating new business opportunities for the innovators and their partners. We also demonstrated the feasibility of this approach by applying the methodology to seven ATP-funded technologies in tissue engineering.

This report describes RTI's general approach to assessing the impact of ATP funding on the social benefits of these technologies. It also describes our procedures for applying the methodology to

seven tissue engineering case studies and reports the results of these analyses.

This chapter provides an overview of the entire study. It describes the project's objectives and scope, reviews the methodology, and explains why this approach is valid for evaluating ATP projects with medical applications. This chapter also summarizes our findings from the seven ATP-funded projects in tissue engineering that serve as case studies for applying the methodology and offers conclusions about the validity of the methodology and the meaning of the results. The other chapters of this report provide a more thorough discussion of these topics.

1.1 PROJECT OBJECTIVES AND SCOPE

The primary objective of this project was to develop a methodology for estimating the expected social economic return on public investment in ATP-funded projects with medical applications. Medical technologies present specific methodological challenges that have not been addressed in ATP's previous methodological development efforts.

The primary objective of this project was to develop a methodology for estimating the expected social economic return on public investment in ATP-funded projects with medical applications.

The second objective was to illustrate this methodology by applying it to seven ATP-funded projects in tissue engineering. Tissue engineering integrates discoveries from biochemistry, cell and molecular biology, genetics, material science, and biomedical engineering. It produces materials that can be used either to replace or correct poorly functioning components in humans or animals (NIST, 1997). These seven projects, which comprise all of the tissue engineering projects funded from 1990 to 1996, constitute a "virtual program" in tissue engineering.[1]

The third objective was to estimate the social return on public investment in seven ATP projects chosen for the case studies. Estimating the return on public investment in these ATP-funded projects was difficult not only because of the methodological challenges, but also because of the shortage of *ex post* empirical data. None of the tissue engineering technologies chosen for this study have been commercialized (although some are in clinical trials), and many of the ATP-funded projects are still underway.

[1]The ATP has since announced a "formal" focused program competition in tissue engineering; the first proposals were awarded in October 1997.

Thus, the analysis of these projects is very preliminary and focuses only on the first applications of these multiple-application technologies.

Our final objective was to provide insight regarding the factors that affect the social return on public investment in ATP-funded projects with medical applications. By examining how the results of the case studies differ across projects, we can draw some conclusions about the characteristics of ATP projects that tend to improve their expected social benefits.

In developing and implementing a methodology for measuring the social and private returns on ATP projects in tissue engineering, we limited the scope of the analysis in several ways. First, ATP asked that we examine seven projects in tissue engineering, with specific emphasis on four of the seven. Thus, for those four projects, the methodology and data collection were more detailed and complete than for the other three projects.

Second, we examined only one application of each of the seven projects. The technologies being developed through these projects will probably lead to a number of other applications, both by the innovating companies and by other companies that may receive knowledge "spillover" benefits through dissemination of research results. However, because time, resources, and data were limited, we focused on the single application for each project that our industry informants told us would be the most likely to be commercialized in the near term.

Third, we limited the time horizon for evaluating each project. The time horizon includes an R&D phase, a commercialization phase, and a production phase. We assume that the production phase would last only 10 years before the technology would be replaced by a newer technology. Thus, the time horizon of costs and benefits for specific projects varies from 14 to 18 years, and the time horizon for the costs and benefits of all the projects combined is 20 years.

Our assumption that technologies will only be produced and used for 10 years is based on the fact that medical technologies are replaced over time with improved techniques. However, there is little research quantifying this process; better information about

how quickly the value of a medical innovation depreciates over time could lead in the future to a more realistic assumption regarding the relevant time horizon.

In addition, our methodology and assumptions reflect two important conditions that affect the economic analysis of all ATP projects:

- **The limitations of available data**. ATP needs a method that can provide early forecasts of economic returns and be updated as needed. ATP needs early assessments of the potential returns of a project before *ex post* data are available. We can update these early estimates once the actual benefits and costs of these technologies become more apparent, as recommended by Mansfield (1996).
- **The need for flexibility**. ATP funds a variety of projects that affect medical costs and outcomes. To maximize the flexibility of the method, ATP needs a model that we can adapt to analyze other medical technologies.

1.2 METHODOLOGY

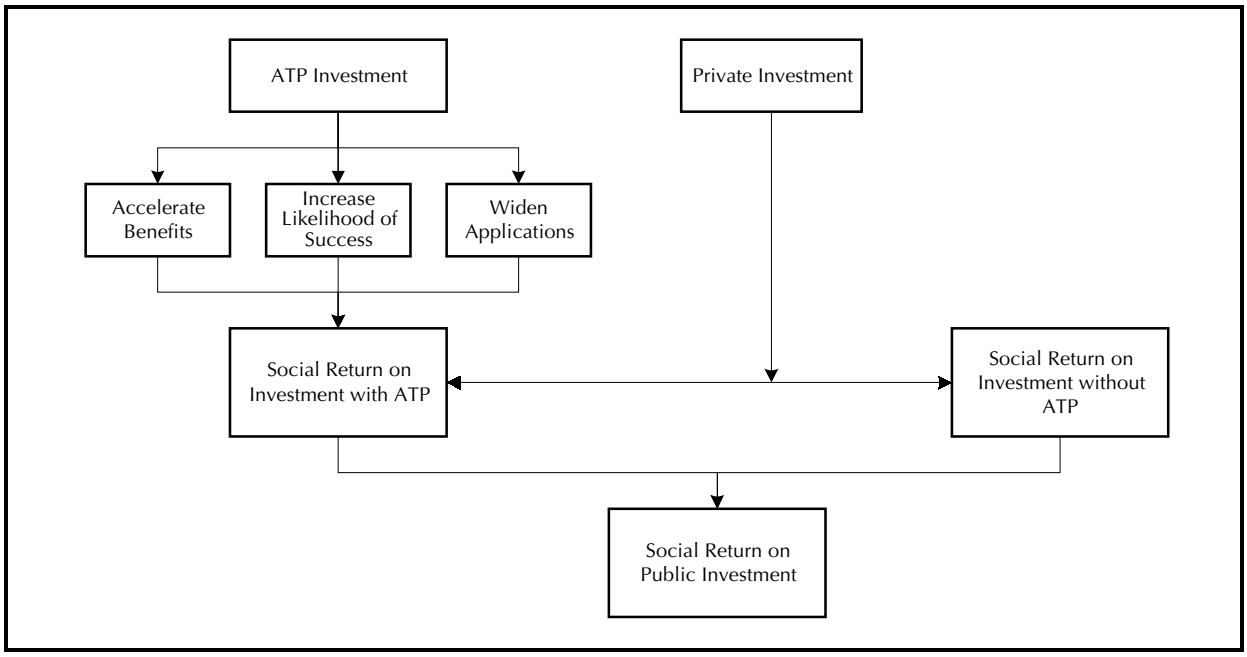
The primary emphasis of this study is the development of a methodology for evaluating the *social return on public investment* in ATP projects. From a public policy perspective, this evaluation factor is central, because it quantifies the improvement in social outcomes attributable to ATP's investment.

From a public policy perspective, the social return on public investment is the central factor for determining the impact of ATP, because it quantifies the increment in expected social outcomes that is attributable to ATP's investment.

As shown in Figure 1-1, our methodology allows for ATP funding to fundamentally affect the development of medical technology in three ways:

- **Accelerate the technology's benefits:** ATP funding can catalyze and accelerate the R&D phase, bringing benefits to the private sector, patients, and society sooner and for a greater number of years than without ATP funding. In some cases, ATP funding may persuade a company to conduct research in a technology that it otherwise would not pursue.
- **Increase the likelihood of success:** By reducing the cost of R&D to the companies developing the technology, ATP funding can increase the amount of R&D conducted and increase the likelihood that a project will be technically successful.
- **Widen the technology's applications:** ATP funding can also widen the scope of the project, enabling the company to apply its technology to additional diseases or patient populations.

Figure 1-1. Elements Determining Social Return on Public Investment and Social Return on Investment



Determining the social return on public investment requires comparing the social return on investment with ATP funding to the social return on investment without ATP funding.

To determine the social return on public investment in ATP projects, we constructed two scenarios: one with ATP funding, and one without ATP funding. The with-ATP scenario can differ from the without-ATP scenario through any of the three ATP impact mechanisms described above. Figure 1-1 shows that to determine the expected social return on public investment we first calculated the social return on investment for each scenario and then calculated the return attributable to ATP from the difference in the stream of expected net social benefits in the with-ATP and without-ATP scenarios.

The social return on investment quantifies the extent to which the nation is better off as a result of public *and* private investment in the development of these technologies. The social return on investment includes the value of medical benefits to patients receiving new treatments, the value of changes in the cost of health care to all stakeholders in the medical care system, revenues to private companies, and ATP and private-sector investment costs.

The private return on investment is a component of social return on investment. The private return on investment considers the costs and revenues to the companies carrying out the research,

commercialization, and manufacturing of the new technologies, but does not consider public investment, the full value of medical benefits to patients, and changes in health care cost.

1.2.1 Constructing the Timeline of R&D Costs and Benefits

Investments in new technology often do not result in benefits to society or to private companies for a number of years. This is especially true in the biotechnology industry, where regulatory hurdles, such as multiphase clinical trials, may lengthen the R&D process. A simplified stylized characterization of the time path of investments and revenues includes three phases:

- **R&D phase:** R&D is the primary focus of the firm's activities and investment during this phase. Public investment in ATP funding occurs at this time.
- **Commercialization phase:** Private investment in marketing and manufacturing occurs during this phase, but only if the R&D phase has been technically successful.
- **Production phase:** During this phase, manufacturers produce a product that embodies the technology providing revenues to companies and benefits to patients. Costs and benefits in the production phase occur only if R&D has been technically successful.

Some activities of these three phases may overlap. For example, the company may develop a commercialization strategy early in the R&D phase and may continue to conduct commercialization activities during the production phase. However, this simplified version provides a useful framework for developing scenarios of social and private returns. In the sections that follow, we describe when costs and benefits occur relative to this timeline.

1.2.2 Measuring the Impact of ATP on Social Returns

As explained above, we assume that ATP funding affects the innovation process by accelerating the development of the medical technology, increasing the likelihood of technical success, and widening the technology's applications. Without ATP funding we expect a lower probability of technical success, a delay of the benefits of the innovation, or a narrower scope of the technology's applications. The magnitude and importance of these effects vary by project.

R&D acceleration lengthens the window of market opportunity in our model. We assume that a newer treatment or technology will replace the ATP-funded technology 10 years after its expected commercialization date in the with-ATP scenario. Thus, if we expect a technology to reach the market in 2000, we assume that a new technology will take its place in 2010. If the without-ATP scenario includes a 2-year project delay, market introduction does not occur until 2002, but the end of the market opportunity window is still 2010. Thus, when ATP funding accelerates R&D by 2 years, the with-ATP scenario allows for 2 additional years of benefits.

Accelerating Benefits. Because ATP funding accelerates R&D, the R&D phase in the with-ATP scenario is shorter than the R&D phase in the without-ATP scenario. Commercialization, production, and the associated benefits to private companies and patients all occur sooner. Social benefits are greater for two reasons:

- the time horizon for these technologies is fixed, so the total number of years during which benefits accrue to companies and patients increases when the R&D phase is shorter (see sidebar); and
- discounting implies that benefits that occur earlier are valued more than benefits that occur later.

Increasing Probability of Technical Success. The probability of technical success affects the expected value of net benefits to society. To arrive at the expected value of net benefits, we multiplied all costs and benefits that occur after the R&D phase by the probability of technical success.

To assess ATP's influence on the likelihood of success, we assume a simple relationship between the price of R&D to the company, total R&D effort by the company, and the probability of technical success. ATP funding reduces the price of R&D to the company, which leads to an increase in R&D effort applied to the project. We assume that an increase in R&D effort leads to an increase in the probability of technical success. Therefore, the with-ATP scenario includes the possibility of an increased probability of technical success and consequently a higher expected value for the stream of benefits.

Widening Technology Scope. ATP funding may also enable a company to research a wider range of applications of the technology. The with-ATP scenario may include, for example, benefits to a larger class of patients, treatments for a greater number of diseases or injuries, or changes in a greater number of health outcomes.

1.2.3 Determining Medical Benefits to Patients

ATP-funded medical technologies may improve the long-run health outcomes of thousands of patients per year with acute and chronic diseases. The magnitude of these health benefits of new technology depends on both the magnitude of the health

improvement of an individual patient and the number of patients that will be treated.

The medical benefits of ATP-funded medical technologies depend on both the per-patient benefits and the number of patients that will be treated.

Valuing Per-Patient Changes in Health Outcomes

Determining the value of changes in health outcomes is difficult because market prices that accurately reflect the values of these health outcomes are not available. We use nonmarket methods to assess the value of medical goods and services to patients. These methods use data other than market prices to determine the value that patients place on improvements in health outcomes.

We employed a three-step methodology to determine the value of the health benefits of a new technology. As illustrated in Figure 1-2, the first step is to model the impact of the new technology on health outcomes. Our methodology for modeling health outcomes involves developing either a chronic disease model or an acute illness and injury model for each affected disease or condition. These models use medical statistics and the results of clinical trials to show how the number of patients experiencing different health states or health outcomes changes when doctors adopt the new treatment developed with ATP funding.

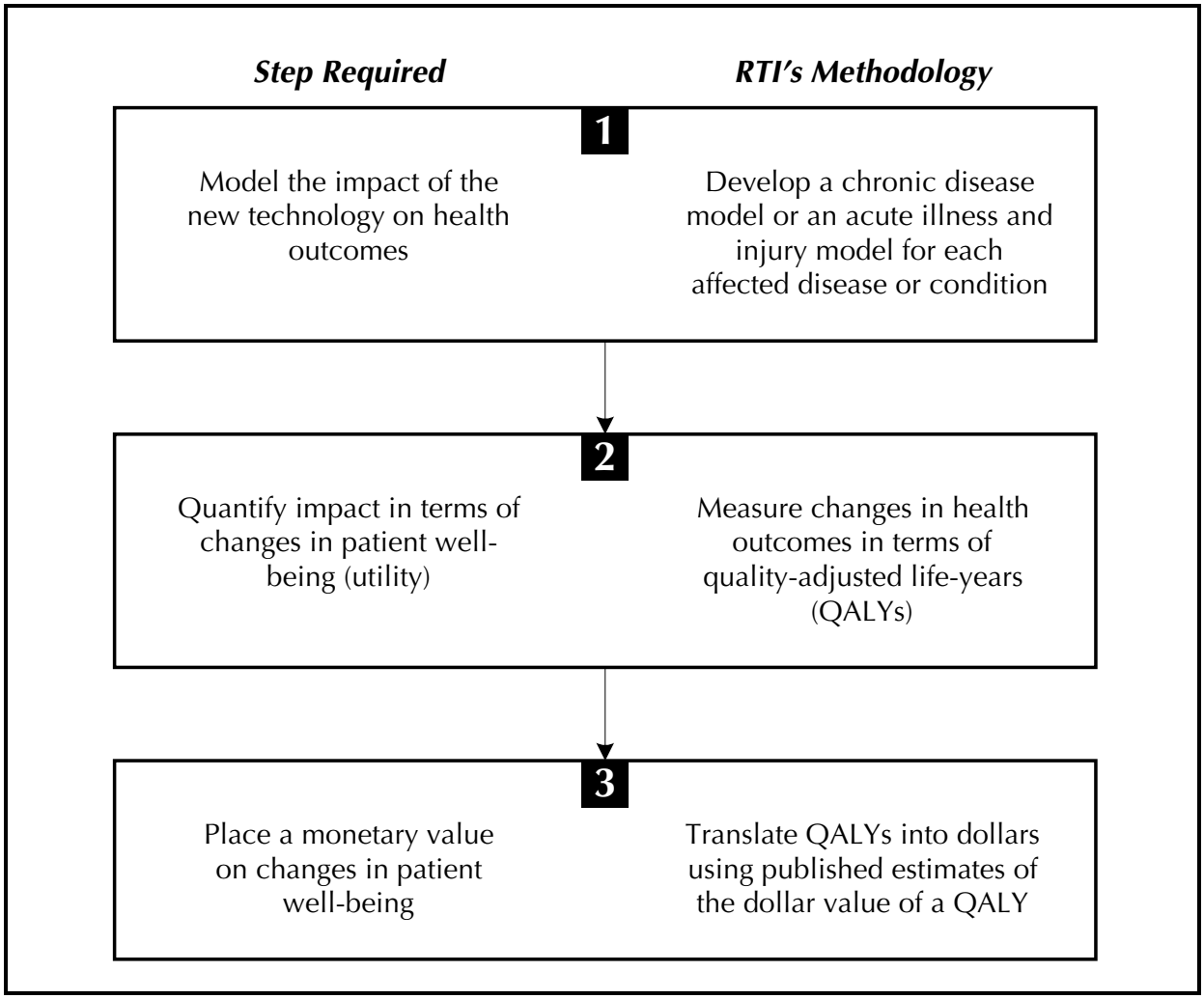
The second step is to assess how those changes in health outcomes affect the well-being of the patient (i.e., how the quality and length of life is affected). We use the *quality-adjusted life-year* (QALY) to measure the utility associated with different health states. The QALY combines morbidity and mortality into a single measure that ranges from zero (death) to one (a year in perfect health). Through extensive surveys of patients, health researchers have established QALY values for a variety of different health states.

The third step is to determine a dollar value for the change in the patient's well-being. We used recent empirical estimates of the economic value of a QALY based on willingness-to-pay (WTP) values for avoiding illness and accidents (Mauskopf and French, 1991; Moore and Viscusi, 1988b).

Determining the Number of Beneficiaries

The social benefits of a new technology depend not only on the value of health improvements to each patient, but also on the

Figure 1-2. Valuing Per-Patient Changes in Health Outcomes



To estimate the number of patients to be treated with the new technology in each year, we collected the predictions of early market penetration from experts and fit these estimates to a widely accepted market penetration model.

number of patients that will receive the new treatment in each year. In the first few years after a new treatment becomes available, a relatively small proportion of the medical profession will use the new technology. Hence, only a small percentage of the total patient population will receive the benefits from the innovation in the early years of its use. How rapidly a technology spreads depends on the degree of the improvement in health it provides over existing treatments, how easy it is to use, and how costly it is compared to the defender technology.

We projected the market penetration of each technology over time by estimating a commonly accepted diffusion model, called the Bass model. To estimate the Bass model, we needed to collect

information about the early penetration of the technology and its maximum market penetration after 10 years. Because these technologies have not yet been commercialized, we asked experts in the treatment of each disease to provide their estimates of these parameters. We asked them to predict market penetration in the first several years after introduction and the ultimate market penetration after 10 years. We used these predictions to estimate a Bass diffusion model, which provided 10-year forecasts of market penetration.

1.2.4 Estimating Changes in Health Care Costs

Our model includes estimates of changes in the cost of health care due to the use of ATP-funded technologies. We compared the expected cost of treating patients with the new technology to the cost of using the existing technology. Where appropriate, we also incorporated the costs of treating the side effects and complications associated with the new and defender technologies.

1.2.5 Estimating Private Return on Investment

Expected private returns to the companies engaging in R&D, commericalization, and production of these technologies depend on the following factors:

- ➤ projected costs for the R&D, commercialization, and production phases;
- ➤ projected revenues for the production phase; and
- ➤ probability of technical success.

In our framework, private return on investment includes the returns to the innovator as well as other companies that may play a role in commercializing and producing the technology.

ATP-funded companies may specialize in the R&D phase of the innovation process, while other companies might carry out commercialization and production. Companies that specialize in R&D earn revenues by licensing their technology to other firms that commercialize and produce new products. However, our definition of private returns includes the costs and benefits from all three phases regardless of whether the ATP-funded firm or another firm carries out marketing and production. Thus, our definition of private returns includes returns not only to the ATP-funded company but also to other companies that may play a role in commercializing and producing the technology.

Analysis of private company costs and benefits requires information about the company's R&D, commercialization costs, fixed and variable costs of production, revenue, and the probability of technical success. Data on these items are difficult to obtain. We followed a series of procedures, briefly described below, to develop estimates and assumptions for the case studies:

- **R&D investment:** For the with-ATP scenario, we assume private R&D investment is equal to the total size of the ATP-funded project, minus the funds provided by ATP. For the without-ATP scenario, we developed a simple model of the impact of ATP funding on company R&D spending to derive estimates of R&D spending in the absence of ATP.
- **Costs of commercialization and production:** We used industrywide cost information from the biotechnology and pharmaceutical industries to estimate commercialization and production costs as a percentage of expected revenues.
- **Revenues:** In each year of the production phase, revenue is equal to the per-unit price, as estimated by the companies, multiplied by the quantity sold, which is estimated from the diffusion model described above.
- **Probability of technical success:** For the with-ATP scenario, we used the companies' own assessment of their technical progress. For the without-ATP scenario, we reduced the probability of technical success as a function of the estimated decrease in total R&D effort.

1.2.6 Calculating Measures of Economic Return

We calculated measures of economic return from three perspectives: the social return on public investment, the social return on (public and private) investment, and the private return on (private) investment.

For each of the three perspectives, we calculated two summary measures of economic return: the net present value (NPV) and the internal rate of return (IRR). NPV is the most accurate method for evaluating the economic impact of a project. NPV is defined by

$$NPV = \sum_{t=1}^{n} \frac{NB_t}{(1+r)^t} \qquad (1.1)$$

where t indexes the year in which either benefits or cost occur, NB_t is the expected net benefit (benefit minus cost) in year t, n is the number of years over which benefits or costs accrue, and r is a

We use two summary measures of economic return: the net present value (NPV), and the internal rate of return (IRR).

prespecified discount rate. An NPV greater than zero indicates that the discounted value of the benefits is greater than the discounted value of the costs, so the project has positive net benefits.

The IRR is another commonly used measure of the economic benefits from an investment. It is the discount rate that sets the NPV to zero. Thus, to calculate the IRR, we set Eq. (1.1) to zero and solve for r. We can interpret the IRR as the rate of return associated with the investment project over the life of the project.

To calculate the social return on public investment, the annual expected net benefit, NB_t, in Eq. (1.1) is defined as the difference between the annual social expected net benefit with ATP and without ATP. For the social return on investment, NB_t includes all social benefits and costs, including medical benefits to patients, changes in the cost of health care, benefits and costs to private companies, and the cost of ATP public investment. For the private return on investment, NB_t includes only benefits and costs to private companies.

The composite measure of return for the seven projects as a group is based on a sum of expected benefits and costs in each year across all projects.

For social return on public investment, social return on investment, and private return on investment, we also calculated composite measures of NPV and IRR for the seven case study projects as a group. We calculated the composites by summing the total expected benefits and costs for each year for all the projects and calculating NPV and IRR for all the projects as a group over the time period covering the life of all projects.

Many of the variables in this model are measured with considerable uncertainty. The estimates of expected return depend, in part, on the opinions of representatives of ATP-funded companies and other industry experts. These estimates of social and private returns should be updated as new data become available.

1.3 CASE STUDIES OF SEVEN ATP PROJECTS IN TISSUE ENGINEERING

ATP asked RTI to apply the methodology described above to a single application for each of seven multiple-application tissue engineering projects funded from 1990 to 1996. These seven projects are described in Table 1-1.

Table 1-1. Overview of ATP Projects Included in this Study

ATP Project Title[a]	Project Sponsor	ATP Award		
		Competition No.	Duration	Funding Level
In-Depth Case Studies				
Human Stem Cell and Hematopoietic Expansion Systems *"Stem Cell Expansion"*	Aastrom Biosciences, Inc.	91-01	2 years	$1,220,000
Structurally New Biopolymers Derived from Alpha-L Amino Acids *"Biopolymers for Tissue Repair"*	Integra LifeSciences Corporation	93-01	3 Years	$1,999,000
Disease Treatment Using Living Implantable Microreactors *"Living Implantable Microreactors"*	BioHybrid Technologies Inc. (lead company in joint venture)[b]	93-01	3 years	$4,263,000
Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules *"Proliferated Human Islets"*	VivoRx, Inc.	94-01	3 years	$2,000,000
Brief Case Studies				
Fabrication Using Clinical Prosthesis from Biomaterials *"Biomaterials for Clinical Prostheses"*	Tissue Engineering, Inc.	92-01	3 years	$1,999,000
Application of Gene Therapy to Treatment of Cardiovascular Diseases *"Gene Therapy Applications"*	Progenitor, Inc.	94-01	3 years	$1,996,000
Universal Donor Organs for Transplantations *"Universal Donor Organs"*	Alexion Pharmaceuticals	95-01	3 years	$1,999,000

[a]Throughout this report, we refer to each project by the abbreviated title listed below the full title.

[b]BioHybrid has recently been approved for a 2-year no cost project extension.

At the request of the ATP staff, we spent a greater share of our effort and resources modeling and collecting data for the first four projects listed in Table 1-1. ATP expected that for these projects better information about the potential impact of the technology and the costs of its development would be available. For these in-depth case studies, we spent more time searching for secondary data in

the medical literature, collected a greater quantity of data for the diffusion forecasts, and used a more detailed medical benefits modeling strategy.

We consulted a number of sources for information. The most important sources of information about each technology were representatives of the companies receiving ATP funding. We interviewed representatives of each lead company and, in some cases, also interviewed representatives of partner companies. We also talked with a number of physicians and consulted a variety of secondary data sources, including medical literature and statistical databases, to develop estimates of costs and benefits.

Below, we provide brief descriptions of each of the technologies. We describe the in-depth case study projects first, in chronological order according to date of funding; then we move on to the brief case study projects, also in chronological order.

1.3.1 Human Stem Cell and Hematopoietic Expansion Systems

Aastrom Biosciences' ATP project addresses improvement of bone marrow and stem cell transplant, an increasingly popular therapy in the U.S. A particular growth area is autologous bone marrow transplant (ABMT), in which the patient's own bone marrow or stem cells are first harvested for safe-keeping and then replaced after high-dose cancer chemotherapy. Physicians are rapidly increasing the use of ABMT in treating a variety of cancers because it allows patients to tolerate very high doses of chemotherapy with less risk of infection and bleeding, improving the patients' health outcomes. Although ABMT has clear therapeutic advantages, it remains a difficult, fairly risky, and expensive procedure.

The Aastrom CPS will greatly reduce the invasiveness, inconvenience, cost, and risks associated with ABMT.

The objective of this project was to develop a laboratory-scale prototype bioreactor called a Cell Production System (CPS). The Aastrom CPS will be able to culture and grow bone marrow cells, reducing the need for invasive procedures to obtain sufficient bone marrow or stem cells for ABMT. Instead, only a small quantity of cells must be harvested, because they can be expanded within the CPS to provide the quantity required for ABMT. This will greatly reduce the invasiveness, inconvenience, costs, and risks of this increasingly popular procedure.

The proposed procedure offers the potential of removing tumor cells and other undesirables in the bone marrow as well. The current form of the bioreactor is suitable for growing bone marrow cells; further advances may make growing blood cells themselves possible, supplementing the blood donor system.

1.3.2 Structurally New Biopolymers Derived from Alpha-L Amino Acids

Integra LifeSciences Corporation received ATP funding to develop a novel synthetic polymer technology to create a cache of new bioabsorbable polymers for use in biomedical implants. The resulting new polymers will be designed and developed into prototype orthopedic devices in collaboration with the Hospital for Joint Diseases.

The concept of biodegradable medical implants has gained acceptance over the years as researchers and practitioners have realized that an implanted material does not have to be inert but can be degraded and/or metabolized in vivo once its function has been accomplished. This approach can alleviate some of the problems associated with nondegradable implants, such as long-term safety and/or implant removal.

Integra's polymer technology will have broad applications in orthopedics, wound care, cardiovascular repair, and drug delivery. The initial application is orthopedic fracture fixation.

This platform technology has broad applications in orthopedics (fracture fixation, cartilage and ligament repair), wound care, cardiovascular repair, and drug delivery. However, in the near term, Integra is focusing on the orthopedic fracture fixation market to demonstrate success and generate revenue. The fracture fixation applications, in order of expected market penetration, are

1. nonweight-bearing pins and screws;
2. dental and maxillofacial fixation devices; and
3. weight-bearing plates, screws, and rods.

Because the first of these three orthopedic applications is closest to market, RTI focused on it.

Bioabsorbable fixation devices have two primary advantages over the metal devices they will replace. Their use will minimize or eliminate the need for a second surgery to remove the implant, which eliminates the attendant costs and risks of such a surgery. In addition, if the device works as anticipated (i.e., eventually being

completely replaced by bone), it should reduce the likelihood of secondary fractures resulting from the stress-shielding effect or the presence of screw holes that serve as stress concentrators.

1.3.3 Disease Treatment Using Living Implantable Microreactors

BioHybrid Technologies, Inc., is working on an ATP project to develop the capability to implant specific cells into the human body that produce hormones or other bioactive agents that the patient cannot produce or is not producing in sufficient quantity. BioHybrid's approach is to encase the transplanted cells in microspheres to isolate them from the immune system. These "microreactors" have pores large enough to permit glucose; nutrients; electrolytes; oxygen; and relatively small bioactive species, like insulin, to pass but are small enough to block the larger immunocytes and other relatively large molecules involved in transplant rejection. Isolating the implanted cells from the immune system opens up the possibility of using cells from sources other than the recipient, for treatment of diseases such as diabetes.

The most immediate application of BioHybrid's microreactor technology is the treatment of insulin-dependent diabetes.

This "microreactor" technology has the potential to be applied to a number of other therapeutic applications, including hemophilia, Parkinson's disease, Alzheimer's disease, and hepatic failure. However, the most immediate application—that considered for this study—is for diabetic patients who are unable to produce insulin to control blood glucose. This technology would be used in place of multiple daily insulin injections.

The application will involve an outpatient procedure and a local anesthetic. Encapsulated islet cells will be injected into the peritoneal cavity under ultrasound control. Because the transplanted islet cells have a finite life, the patient will receive an injection once or twice a year. The dose and frequency of treatment have not yet been finalized but will be determined during the planned clinical trials.

If successful, the transplants will allow patients to achieve close to normal glycemic control, virtually eliminating many of the risks of long-term complications of diabetes, including retinopathy, nephropathy, and renal disease.

1.3.4 Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules

VivoRx, Inc., is developing a new treatment for diabetes that will consist of transplanting human islets that have been encapsulated in immunoprotective membrane consisting of a novel material. This material protects the cells from the host's immune response. This technology has potential applications for liver disease, thyroid disease, Parkinson's disease, and Alzheimer's disease. However, the most immediate application—that examined for this study—is for the treatment of diabetes. It will eliminate the need for daily insulin injections and will enable patients to achieve tight glycemic control, reducing the risk of the common complications of diabetes.

VivoRx has tested the effectiveness of its diabetes treatment using islet cells from human cadaver pancreata. The success of these tests has encouraged VivoRx to take the next step in making this treatment widely available: providing proliferated human islets for transplant.

The objective of VivoRx's ATP project is to make this therapy widely available by producing a source of human islet cells. VivoRx is developing the culture conditions and methods for proliferating human islets. They are simultaneously perfecting the polymers and biomaterials that are required to achieve immunoprotection and biocompatibility for the encapsulation technology.

The application will involve an outpatient procedure and a local anesthetic. Proliferated, encapsulated human islet cells are injected into the peritoneal cavity. The procedure will be repeated once per year or perhaps once every 2 years to replenish the cells. The dose and frequency of treatment have not yet been finalized but will be determined during the current Phase I/Phase II trials.

If successful, the procedure will allow patients to achieve close to normal glycemic control, virtually eliminating many of the risks of long-term complications of diabetes, including retinopathy, nephropathy, and renal disease.

1.3.5 Fabrication of Clinical Prosthesis from Biomaterials

Tissue Engineering, Inc., developed materials and methods for replacing damaged or dysfunctional tissues and organs in the body. The replacement "prostheses" are designed to provide templates that mobilize the body's own cells and induce them to rebuild the lost tissue, gradually replacing the prosthesis itself. Regeneration of body parts requires a biomaterial with the specific structure, or

"microarchitecture," and the proper chemical signals and components that the body's tissue cells can recognize, respond to, and remodel.

The objective of Tissue Engineering's ATP project was to further the development of its new class of biomaterials that provides the needed structure. ADMAT, or animal-derived extracellular matrix, provides an ordered, three-dimensional structure that can be used to support tissue regeneration. The material can be spun and woven into fibers, or formed into films, foams, and sheets using techniques borrowed from the fabric industry. With ATP funding, Tissue Engineering developed its basic ADMAT materials technology to be able to produce a variety of ADMAT forms, characterized the necessary properties of the ADMAT substrate to promote cell growth and differentiation, characterized ADMAT for immunogenicity, and developed cell banks to support five types of proposed cell-incorporating prostheses.

ADMAT can be used for vascular grafts, ligament and tendon repair, and peridontal and similar reconstruction.

ADMAT can be used to enhance collagen scaffolds for vascular grafts, ligaments, tendons, periodontal tissue, and similar reconstructions. ADMAT alone can be used as a matrix on which "glandular" cells such as insulin-producing cells, nerve cell precursors, thyroid cells, and others can grow and function. At the time of our survey, a likely early commercial application was thought to be reconstruction of ligaments, tendons, and articular cartilage. A specific sub-class of those therapies is the application of ADMAT to repair the anterior cruciate ligament (ACL), which is the application modeled for this project.

Banked tissue for repairing ACLs is in short supply, and the lack of uniformity and predictability of this banked tissue leads to a high failure rate. If the repair is accomplished by removing a portion of the patient's own patella tendon, the patient's patella is weakened. Thus, the new technology will improve the quality of life for patients who suffer from ACL injuries.

1.3.6 Application of Gene Therapy to Treatment of Cardiovascular Diseases

Progenitor, Inc.'s, original premise for its ATP project was to exploit the versatility of primitive stem cells as the basis for treating a range of ailments anchored in endothelial cells, which form blood vessels

that make up the circulatory system. Endothelial cells are thought to be common culprits in the emergence and development of vascular-based diseases and medical crises, among them hypertension, hardening of the arteries (atherosclerosis), heart attacks (ischemia), and strokes. The present set of medical treatments for these conditions is limited.

Progenitor's first application of its discovery will be the diagnosis, location, and staging of soft tissue cancer metastases. The resulting improvement in diagnosis of these metastases will allow more effective cancer therapy.

Thus, one of the original goals of the project was to develop a supply of transplantable endothelial cells from precursor stem cells that can be genetically engineered or otherwise modified for specific medical purposes. Progenitor originally envisioned that this particular project goal would result in using these cells to repair damaged vascular tissue, with the most immediate application being the treatment of damage associated with coronary angioplasty.

Other potential medical application areas originally identified by Progenitor and included in the R&D were cancer treatments and bone development. In the course of its research, Progenitor discovered a molecule that provided an opportunity to strengthen the goals and activities related to cancer treatments. However, research continues in evaluating the utility of the molecule in vascular biology, oncology, and bone development.

This molecule plays an important role in the growth, differentiation, and proliferation of endothelial cells. Progenitor believes that eventually this discovery will lead to a new treatment for solid tumor cancers. However, its most immediate application is the diagnosis, location, and staging of soft tissue metastases. The resulting improvement in diagnostic techniques will allow for more aggressive, effective cancer therapy at an earlier stage of metastasis, improving patients' prognosis.

Currently no technologies image soft tissue adequately to diagnose metastasis at a very early stage. Thus, Progenitor's product will not replace any current technologies but will supplement the current diagnostic techniques.

1.3.7 Universal Donor Organs for Transplantations

Alexion Pharmaceuticals' ATP project offers an approach to solving the shortage of donor organs for transplantation. Wider use of organ transplants could offer many patients significant

improvement in the quality and duration of their lives while improving the cost-effectiveness of treatment. Patients with prolonged waiting times are at risk for end-organ deterioration, have an increased risk of transplant failure, or may die before a donor organ becomes available (Mehta et al., 1995).

The single biggest roadblock to broader, more effective use of organ transplants is a severe shortage of donor organs. As long as we are restricted to allogeneic (human-to-human) transplants, the shortage is likely to continue. Xenogeneic transplants—transplants from other animals—are one possible solution. In most cases, xenogeneic transplants fail because of hyperacute rejection (HAR), which causes graft failures within minutes to hours.

The objective of Alexion's ATP project is to develop transgeneic animals that express key human genes to eliminate the HAR response. They plan to develop organs, called UniGraft organs, from transgeneic pigs.

The immediate availability of UniGraft organs would change the use of organ transplantation by

- eliminating long waiting times for donor organs and the associated negative medical effects,
- allowing surgeries to be scheduled optimally,
- eliminating the cost of maintaining a recipient in the hospital while awaiting a donor organ, and
- eliminating the need to keep a donor alive on life support.

Although the transplant procedure for a UniGraft organ would be identical to that used to transplant a human organ, immediate availability of needed organs would dramatically change the process of transplantation. Surgeries could be scheduled at the time that is optimal for the patient, eliminating the costs of maintaining a recipient in the hospital while awaiting an organ. If UniGraft transplants replaced human transplants, they would also eliminate the need to keep a donor alive on life support until the removal surgery can take place. The costs to transport organs to the patient would also decrease.

Although Alexion's technology may enable the xenographic transplant of hearts, kidneys, lungs, and islets, we modeled the medical and economic benefits of transplanted xenogeneic hearts only. This analysis illustrates the potential benefits of xenogeneic transplants for other organs.

1.4 SUMMARY OF SPECIFIC FINDINGS

In this section, we summarize the results of our analysis of the social return on public investment, the social return on investment, and the private return on investment for the seven ATP projects described in Section 1.3. We also provide an analysis of the

observed variations in the estimates of project returns, assessing why some projects provide higher expected returns than others, given the methodology and assumptions used in this project. In addition, we discuss some of the limitations of the model and the analysis.

1.4.1 Summary of Results

The composite social return on public investment represents the returns on all of the projects taken together.

Table 1-2 shows the expected social return on public investment for each of the ATP projects examined in this study and for all of the projects taken together (the composite). These projects demonstrate a wide range in net present value and internal rate of return; as a group, they generate over $34 billion in social return on public investment and an IRR of 116 percent annually over 20 years. These results mean that the ATP funding invested in these projects provides a net benefit of over $34 billion dollars in expected net benefits to the nation.

Table 1-2. Expected Social Return on Public Investment: ATP Projects in Tissue Engineering for a Single Preliminary Application

ATP Project	Project Time Horizon	NPV (1996$ millions)	IRR (%)
Stem Cell Expansion	1992 to 2009	$47	21%
Biopolymers for Tissue Repair	1994 to 2009	$98	51%
Living Implantable Microreactors	1994 to 2009	$17,750	148%
Proliferated Human Islets	1995 to 2008	$1,297	34%
Biomaterials for Clinical Prosthesis	1993 to 2010	$15,058	128%
Gene Therapy Applications	1995 to 2011	$945	111%
Universal Donor Organs	1995 to 2011	$783	92%
Composite[a,b,c,d]	1992 to 2011	$34,258	116%

[a]The composite measure of return is based on a sum of expected benefits and costs in each year across all projects.

[b]The time period for the composite measure includes all years from all the individual project periods.

[c]The composite NPV is not a simple sum of individual NPV because the time periods are different.

[d]The composite IRR is not an average of the individual project IRRs because IRR is not additive.

Table 1-3 compares expected social return on public investment to expected social return on investment for each project. This comparison provides perspective on the importance of ATP funding

Table 1-3. Social Return on Investment and Social Return on Public Investment: ATP Projects in Tissue Engineering for a Single Preliminary Application

	Expected Social Return on Investment		Expected Social Return on Public Investment	
ATP Project	NPV (1996$ millions)	IRR (%)	NPV (1996$ millions)	IRR (%)
Stem Cell Expansion	$134	20%	$47	21%
Biopolymers for Tissue Repair[a]	$98	51%	$98	51%
Living Implantable Microreactors	$74,518	149%	$17,750	148%
Proliferated Human Islets	$2,252	36%	$1,297	34%
Biomaterials for Clinical Prosthesis	$32,855	118%	$15,058	128%
Gene Therapy Applications	$2,411	106%	$945	111%
Universal Donor Organs	$2,838	91%	$783	92%
Composite[b]	$109,229	115%	$34,258	116%

[a]For Biopolymers, the two sets of figures are identical because all of the social return can be attributed to ATP investment.

[b]See notes to Table 1-2 for an explanation of the derivation of the composite measure of return.

in catalyzing the social return on investment. As demonstrated by the composite return, ATP funding is responsible for inducing about 31 percent of the total social returns from all of these projects over 20 years. For the individual projects, the effect of ATP on social returns ranges from about 25 percent to 100 percent of the social returns.

Social returns to these projects can vary with respect to the number of patients treated, the value of the health benefits of the new technology, their impact on health care costs, and the probability of technical success. For example, our models of the applications for "Stem Cell Expansion" and "Biopolymers for Tissue Repair" include health care cost savings but no health benefits.[2] The projects "Living Implantable Microreactors" and "Proliferated Human Islets" provide similar health benefits but differ with respect to their impact on health care costs and their probability of technical success.

[2]As explained in Chapter 3, these technologies both provide potential health benefits; however, we were not able to obtain data to quantify these benefits.

To demonstrate the pathways by which ATP funding induces this increase in social returns, Table 1-4 shows how ATP funding affects the three channels of social returns identified earlier. Recall that ATP might affect the development of medical technologies by accelerating the technology's benefits, increasing the probability of success, or widening the technology's applications. Table 1-4 shows the magnitude of these impacts for each project. As explained in Chapter 3, the acceleration effect contributes about 81 percent of ATP's impact on social returns.

Table 1-4. Impact of ATP Funding on the Development of Medical Technologies for Seven Tissue Engineering Projects

ATP Project	Project Acceleration[a] (years)	Increase in the Probability of Success (percent)	Widening of Technology Applications[b]
Stem Cell Expansion	1 to 2	9%	None reported
Biopolymers for Tissue Repair	At least 10	171%	Significant but not quantified
Living Implantable Microreactors	2	11%	None reported
Proliferated Human Islets	3 to 5	2%	None reported
Biomaterials for Clinical Prosthesis	2	1%	None reported
Gene Therapy Applications	2	20%	Some effects reported but not quantified
Universal Donor Organs	1 to 2	16%	None reported

[a]This is the number of years of acceleration reported by the ATP-funded companies. For the 2-year ranges, we used the lower number for our analysis. For the 3-year range, we used the midpoint of the range.

[b]Our model allows conceptually for ATP funding to widen the scope of a project. In practice, for the applications examined in this study, there was little or no impact in all but two cases, which we did not quantify.

Clearly, ATP has the greatest impact on social returns for the second project, "Biopolymers for Tissue Repair." ATP accelerates the benefits from this project by at least 10 years, has a significant impact on the probability of success, and affects the scope of the project. According to company officials, in the absence of ATP funding, the company might not have developed this technology at all or might have developed it so slowly that the market opportunity for this technology would have passed before it was ready for commercialization. Although the impact of ATP is less dramatic for the remaining projects, it is clear that two of the three

possible mechanisms by which ATP affects the R&D process are important in increasing social returns.

Table 1-5 shows the composite private return on investment for all of the ATP projects in tissue engineering.[3] The composite NPV is about $1.5 billion, and the impact of ATP funding on private returns is equal to about $914 million.

Table 1-5. Composite Private Returns: ATP Projects in Tissue Engineering for a Single Preliminary Application[a]

	NPV (1996$ millions)	IRR (%)
Project returns	$1,564	12%
Increment attributable to ATP	$914	13%

[a]See notes to Table 1-2 for an explanation of the derivation of the composite measure of return.

The wide disparity between social and private returns indicates the importance of ATP incentives to the private sector to pursue these technologies. Because the social returns far outweigh the returns to the companies developing, commercializing, and producing these technologies, the private sector may underinvest in these kinds of high-risk projects. Hence, ATP funding serves to provide the incentives needed to stimulate the private sector's investments in these activities.

1.4.2 Sources of Project Variations

Tables 1-2 through 1-4 demonstrate a wide variation in the social return on public investment and in the social return on investment, in terms of both the NPV and the IRR. Some reasons for this variation include the following:

- **Breadth of applications:** Technologies that apply to more patients and diffuse more quickly throughout the patient population have a greater expected social return on investment.
- **Significant health benefits:** Technologies that lead to more significant improvements in the health of patients over and above the defender technology have a greater expected social return on investment.

[3]Although we calculated the private returns for each project, we do not disclose them to preserve the confidentiality of proprietary information.

- **Cost-effectiveness:** Technologies that offer health care improvements at relatively lower costs provide greater expected social return on investment.
- **Technical success:** Technologies with a greater expected probability of technical success have a higher expected social return on investment.

The impact of ATP funding on the magnitude of social returns also varies from one project to the next. The primary factors affecting these differences, as demonstrated above, include

- **ATP impact on project timing:** The number of years by which ATP funding accelerates the R&D phase of the project has an important impact on social returns. Conditions that lead to high estimates of the acceleration effect from ATP funding include the absence of alternative capital sources and the risk of the project, as perceived by the company and its potential sources of capital.
- **ATP impact on R&D funding and the probability of technical success:** The impact of ATP funding on the total R&D investment has an important effect on the social return on public investment because it affects the project's expected probability of technical success. The impact of ATP funding depends on the company's motivation and ability to pursue the project in the absence of ATP funds. For all but two projects, ATP stimulated increases in R&D investment enough to make a significant difference in the probability of technical success.
- **ATP impact on project scope:** If ATP funding encourages the company to pursue additional applications and patient populations, the social return on the public investment will increase. We did not explicitly model any scope effects for the projects we examined. However, our study investigated only one application of each of the technologies studied. The scope effects may be evident in the number of applications in which the technology is eventually used.

1.4.3 Methodological Limitations

The results of this study are subject to a number of methodological limitations and assumptions that may affect the results. Some of the limitations of our analysis include

- analyzing only a single application of each technology,
- omitting the value of some medical benefits that could not be quantified, and
- basing assumptions about costs and benefits on the expectations of informed individuals.

Single-Application Analysis

The study analyzed only one application for each project. Because these technologies provide basic scientific platforms for many applications, their long-term impact may be much greater than suggested here, as companies apply their discoveries to a wide variety of medical applications. In addition, the knowledge generated by these initial applications may lead to advances in additional, unrelated areas by other companies.

Limitations of the Health Benefits Models

The models we used to quantify the health benefits of these technologies have limitations that may affect the results of the study. In some cases, the medical benefits per patient did not consider some effects that we could not quantify, usually because the required data were not available. For example, although Integra LifeSciences believes that its fracture fixation devices will improve healing, clinical data to support an assessment of that improvement are not available. Similarly, some of the cost savings may be underestimated because of our inability to quantify them. For example, we could not quantify the cost impact of changes in intermediate health states resulting from the two new diabetes treatments.

The economic burden of a disease is usually divided into three components: direct medical costs, indirect costs, and intangible costs. Direct medical costs are the total cost of medical treatment. Indirect costs are the societal costs associated with the loss in productivity due to illness and unpaid caregiver time. Intangible costs measure the patient's pain and suffering. Because we measured the health benefits of these technologies in terms of QALYs, our estimates capture how ATP-funded technologies change both the direct medical costs and the intangible costs of a disease. However, they may not capture changes in the indirect costs. Improvements in the health of a patient population with a particular illness or injury may reduce the indirect costs of the disease, allowing those receiving an improved treatment to lead more productive lives. These benefits to society may not be captured by QALYs.

Data Limitations

Because none of these technologies have yet reached the commercial market—though several are in clinical trials—the results of this analysis are based in part on the expectations of the innovators and other informed individuals. We do not know at this time whether these expectations will be realized. However, the methodology we employed can be used to update our estimates as better data on the actual costs and benefits of the projects become available.

1.5 CONCLUSIONS

The primary objective of this project was to develop a methodology for estimating the expected social economic returns on public investment in ATP-funded projects with medical applications. To address the specific methodological challenges presented by new medical technologies, we used a currently accepted framework for calculating private and social returns, incorporating nonmarket methods for valuing the benefits of these technologies to patients.

The second objective was to illustrate this methodology by applying it to seven ATP-funded projects in tissue engineering. We have demonstrated that this methodology is useful for analyzing ATP-funded medical technologies, particularly under the following conditions:

- ➤ One or several primary applications are apparent.
- ➤ The health outcome and resource cost differences between the new and defender technologies can be quantified (e.g., because some clinical trials or other studies have produced the required data).
- ➤ The impact of changes in health outcomes on patients' well-being has been quantified by other studies (e.g., QALYs for health outcomes or health states are available).
- ➤ The market potential for the new technology is apparent.
- ➤ The technology is sufficiently close to commercialization to enable company representatives to project the costs of commercialization and production.

Aside from medical technologies, this methodology is also applicable to other situations in which the technology affects goods and services whose values are not adequately reflected in market prices. For example, technologies that improve environmental quality or reduce the crime rate provide benefits that are not traded in traditional markets.

Aside from medical technologies, this methodology is also applicable to other situations in which the technology affects goods and services whose values are not adequately reflected in market prices. For example, technologies that improve environmental quality or reduce the crime rate provide benefits that are not traded in traditional markets. Nonmarket valuation methods are required to quantify these kinds of social benefits. As in this study, valuation of these social benefits requires the methodology used in determining the beneficiaries' willingness to pay for these improvements.

The third objective of this project was to estimate the social return on public investment in seven ATP projects chosen for the case studies and to estimate the impact of ATP funding on these returns. This analysis yielded the following findings:

- The expected *social return on ATP public investment* in these technologies, or the increment to social returns attributable to ATP funding, is estimated at $34 billion in net present value.
- The expected *social rate of return on ATP public investment* in these technologies is estimated at an annual rate of 116 percent.
- The expected total *social return* on public and private investment in these technologies is estimated at $112 billion in net present value, or an annual rate of 115 percent.
- The expected total *private return* on investment in these technologies to ATP-award companies and their partners in commercialization and production is estimated at $1.6 billion in net present value, or an annual rate of 12 percent. Of the $1.6 billion in net present value of private returns, $914 million is estimated to be attributable to ATP funding.
- To the extent that the technologies will yield applications in addition to those we investigated, it is likely that public and private returns on these projects will be higher.

These results illustrate two important points about the role of ATP in funding these technologies:

- ATP plays a significant role in increasing the expected social and private returns on these projects.
- The social returns are far greater than the private returns. Private companies will therefore tend to underinvest in these technologies relative to what would be optimal from society's perspective. The wide disparity between social

and private returns indicates the importance of ATP's incentives to the private sector to pursue these technologies.

Our final objective was to provide insight regarding the factors that affect the social return on public investment in projects with medical applications. We found that three primary factors affect the extent to which ATP funding influences social returns:

- the number of years by which ATP funding accelerates the R&D phase of the project;
- the impact of ATP funding on the probability of technical success; and
- the impact of ATP funding on the scope of the project.

2 Methodology

Our approach to modeling the social and private returns to ATP funding in medical technologies is based on the methodology recommended by Mansfield (1996). We modify Mansfield's methodology for the specific case of medical innovations. In particular, we use nonmarket methods to value the benefits of new medical treatments.

Our methodology focuses on evaluating the social return on public investment for ATP-funded projects. Determining the social return on public investment requires that we estimate social return on investment under two scenarios: one with ATP funding and one without ATP funding. As described in Chapter 1 and illustrated in Figure 1-1, we developed the two scenarios by constructing timelines of costs and benefits, including

- medical benefits to patients,
- changes in the cost of health care,
- revenues to companies,
- private investment and costs, and
- public investment in ATP funding.

The with-ATP scenario and the without-ATP scenario can differ with respect to three mechanisms of ATP impact:

- project acceleration,
- probability of technical success, and
- project scope.

This chapter provides additional detail regarding our methodology for constructing the two scenarios and calculating measures of

economic return. Section 2.1 describes how we constructed the timelines of investments and benefits from ATP-funded technologies. Section 2.2 describes how we modeled the impact of ATP on the benefits of ATP-funded technologies. Sections 2.3, 2.4, and 2.5 discuss estimation of the three main components of social returns:

- ➤ medical benefits to patients,
- ➤ changes in the cost of health care, and
- ➤ costs and revenues to private companies.

In Section 2.6, we discuss how we calculated measures of social and private returns once the two scenarios of benefits and costs had been constructed. Section 2.7 discusses the limitations of the methodology and suggests improvements.

This chapter does not discuss the details of applying this methodology to each of the seven tissue engineering projects analyzed for this study. That discussion, together with the results of the analysis, is provided in Chapter 3.

2.1 THE TIMELINE OF R&D INVESTMENT COSTS AND BENEFITS

One of the first challenges to modeling the social return on public investment for ATP projects with medical applications was to develop assumptions about the timing of the benefits and costs of the new technology. The timing of these benefits and costs is important because benefits and costs that occur earlier are more valuable than those that are delayed. This is the basic principle of discounting.

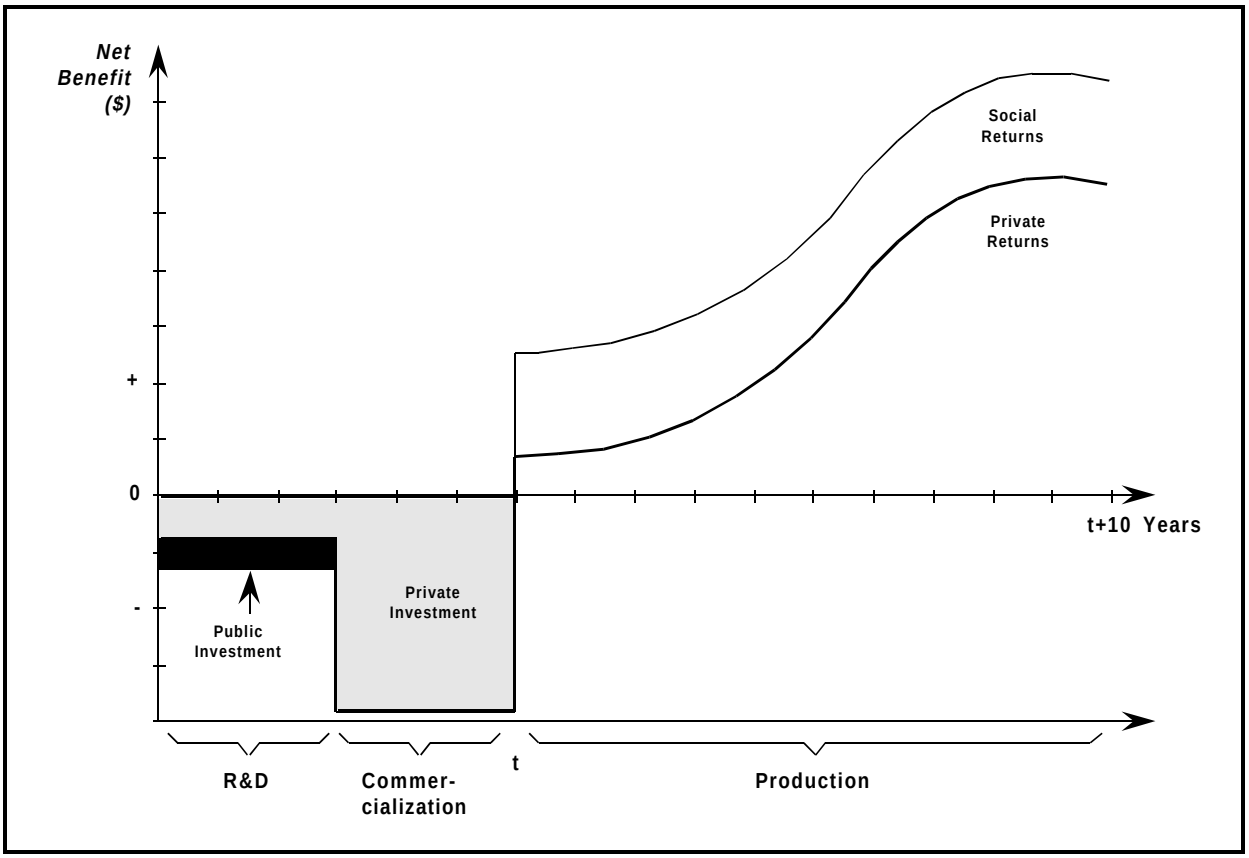
Discounting involves adjusting the values of future benefits and costs to render them comparable to the values placed on current benefits and costs. With discounting, the timing of benefits and costs becomes an important determinant of economic returns.

Investments in new technology often do not result in benefits to society or private companies for a number of years. The cycle of investment and benefits for a product or service based on a new medical technology typically consists of three phases:

- ➤ R&D phase,
- ➤ commercialization phase, and
- ➤ production phase.

These three phases of the innovation process, which are illustrated in Figure 2-1, are not always sequential. However, this stylized classification mirrors the typical evolution of a biotechnology company. Early in the company's evolution, R&D activities—applying resources and scientific principles toward solving a technical problem—are the primary focus. In the commercialization phase that follows, the company invests in sales, marketing, and manufacturing infrastructure. These activities bring the results of R&D in the form of specific technology applications to the market. Product sales revenues become significant in the production phase as the company produces the product or service that embodies the innovation (Burill and Lee, 1992).[1] Companies and society realize the benefits of investments in R&D in this final phase.

Figure 2-1. The Timing of Costs and Benefits from Investments in New Technologies



[1]We are speaking of the company narrowly as the business unit developing the new technology, under the assumption that it produces no other products.

2.1.1 The R&D Phase

During the R&D phase, firms invest in R&D to increase the probability of success on the project. Strategic R&D investment models, such as those presented in Beath, Katsoulacos, and Ulph (1989); Loury (1979); and Lee and Wilde (1980), commonly assume that the probability of success in any year is a function of the R&D that is spent in that year.

$$Pr = f(R) \tag{2.1}$$

Empirical studies conducted by Griliches, Pakes, and Hall (1987) verified the plausibility of this assumption. They found a strong contemporaneous relationship between aggregate R&D expenditures and patenting and an estimated elasticity of about 0.3. This aggregate relationship may not hold for specific projects, but it does provide guidance for our assumptions in this model. Similarly, while patenting activity may not be a perfect indicator of the success of a project relative to specific technical objectives, it is an indicator of technical success. Therefore, we assume that the relationship between R&D spending and technical success is similar to that found in the empirical literature on the impact of R&D on patenting.

As R&D effort increases, the probability of discovering a technically viable solution also increases. However, the research is eventually subject to diminishing returns; each unit of effort or successive draw from the distribution is less likely to yield a solution that is superior to the best of the previous draws (Binswanger, 1978).[2] Thus, as shown in Figure 2-2, the marginal probability of technical success declines with increases in R&D effort.

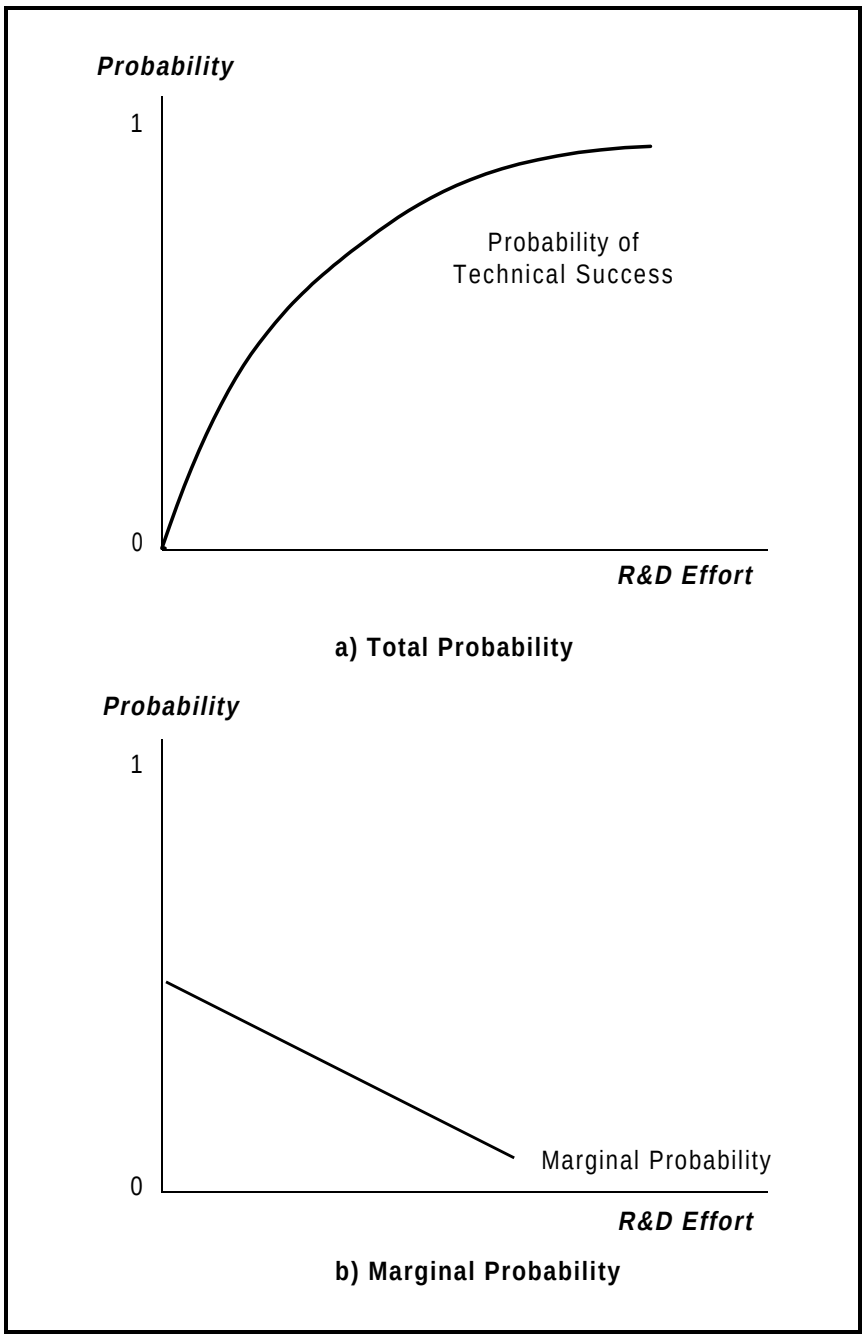
2.1.2 The Commercialization Phase

An innovative application proceeds to the commercialization phase if the R&D phase has been technically successful. In the commercialization phase there is still no revenue from product sales. In many cases, identifying where R&D ends and commercialization begins is difficult. The commercialization phase

[2]This result holds under the assumption that each draw is randomly selected. The rate of decline of return on investment in research is greater if researchers investigate potential solutions in order of their potential benefits.

Figure 2-2. The Total and Marginal Probability of Technical Success

The probability of technical success increases with R&D effort but at a decreasing rate.



includes substantial investments in product development research—for example, the research required for regulatory review or design of a production process. The key distinction between the R&D phase and the commercialization phase in our model is that uncertainty relates to *technical* success in the R&D phase.

Uncertainty relates to *market* success in the commercialization phase.

In our model, the private return on investment includes spillover benefits between the innovator and its partners in commercialization and production.

A company that conducts R&D may retain exclusive rights to marketing, manufacturing, and distribution; license the technology to other companies that will retain these rights; or arrange some other type of agreement with a partner or licensee.[3] Regardless of the method the company uses to capture the benefits of its R&D, our definition of private returns includes the benefits and costs of all three stages of the process. Thus, in our model, the private return on investment includes spillover benefits between the innovator and its partners in commercialization and production. The rationale for this assumption is explained more fully in Section 2.5.

2.1.3 The Production Phase

The production phase includes all activities involved in producing the product or service that embodies the technology in sufficient quantities and consistency to meet quality standards at a price customers are willing to pay. The company incurs costs for production and marketing and earns revenue from the sale of products. Patients benefit from the new technology as doctors adopt the new technology. As shown in Figure 2-1, both private and social returns may become positive during this phase.

This phase continues until the company ceases production of the product or service. Determining the length of the production phase of a new technology is very difficult because it requires forecasting the emergence of new products that may supersede the product or service in question. We assume for this study that the company will manufacture the good or service for 10 years following its expected introduction to the market in the with-ATP scenario. This is an issue of considerable empirical uncertainty. The actual length of the production phase depends on the emergence of new technologies that replace the technology in question. The Committee for Evaluating Medical Technologies in Clinical Use (1985) notes that researchers have observed a variety of patterns regarding the abandonment of medical technologies. Ten years seems to be a reasonable assumption in the absence of empirical

[3]Many choices lie between selling all rights and retaining exclusive rights.

evidence. Empirical research about the rate of depreciation of new technologies and the longevity of their marketability could contribute to the accuracy of forecasts of social and private returns.

2.2 MEASURING THE IMPACT OF ATP ON TECHNOLOGY DEVELOPMENT

In our model, differences between the with-ATP and without-ATP scenarios include (1) the duration of the R&D phase, (2) private-sector R&D investment and its consequences for the likelihood of technical success, and (3) breadth of the technology's applications. The with-ATP scenario also incorporates the cost of ATP funding. This section explains how we modeled these three channels of ATP impact.

2.2.1 ATP's Acceleration of R&D

Previous studies of the impact of ATP indicate that ATP funding accelerates R&D and product introduction (Powell, 1996; Silber, 1996). Acceleration influences net benefits in our model for two reasons. First, future benefits are discounted, so benefits that occur sooner are valued more than benefits that occur later. Second, a company may have a limited window of opportunity for introducing the new technology. Late introduction of a new product may reduce the time period during which the product is successful in the market because newer, competing technologies will eventually come to market.

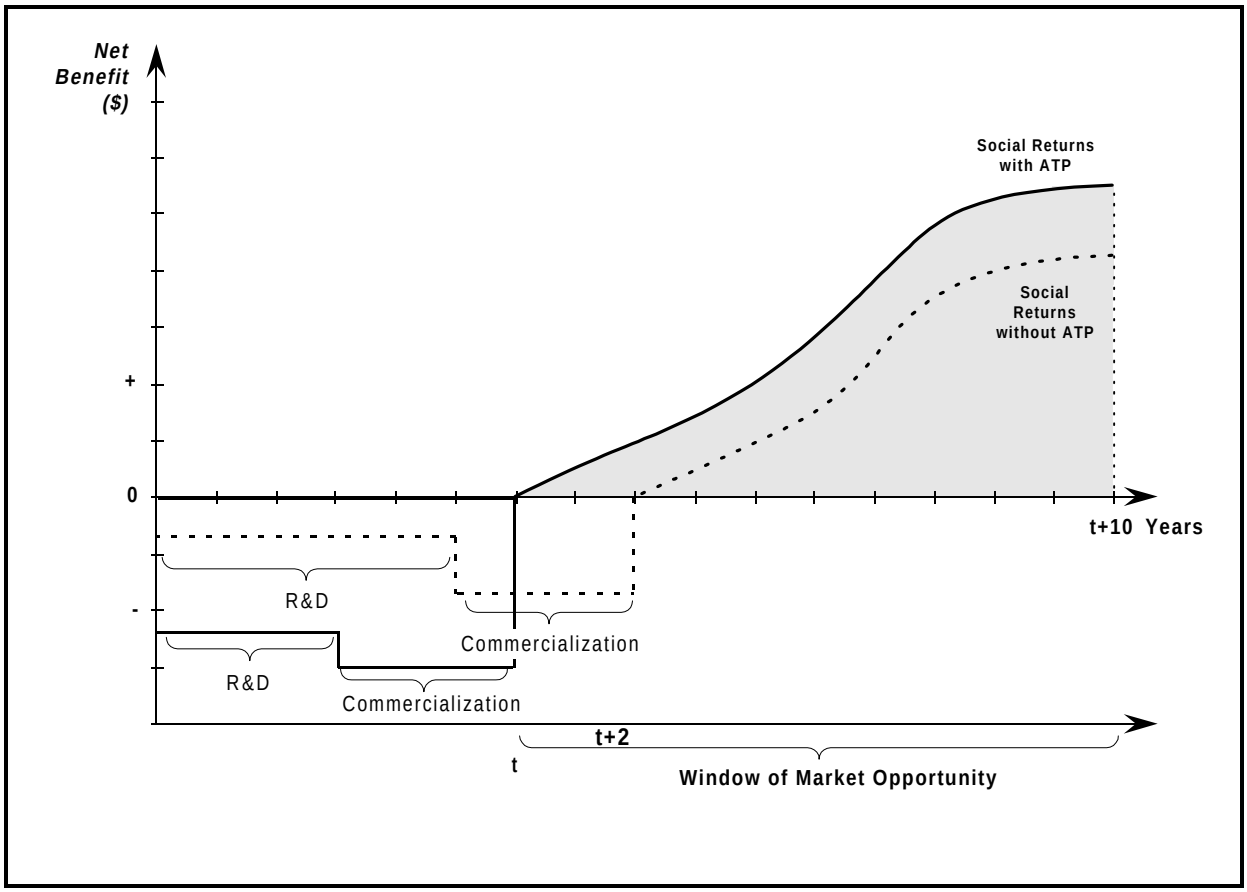
If ATP funding accelerates R&D and new product introduction, the social and private benefits accrue for a greater number of years.

In our model, R&D acceleration caused by ATP funding lengthens the period of market opportunity. We assume that a newer treatment or technology will replace the ATP-funded technology 10 years after the expected commercialization date in the with-ATP scenario. Thus, if we expect a technology to reach the market in 2000, we assume that a new technology will take its place in 2010. If the without-ATP scenario includes a 2-year project delay, market introduction does not occur until 2002, but the end of the market opportunity window is still 2010. Thus, when ATP funding accelerates R&D by 2 years, the with-ATP scenario allows for 2 additional years of benefits.

When ATP funding accelerates the R&D process, the production phase, during which net social benefits are positive, begins sooner

and lasts for a longer time, so social returns are greater. In Figure 2-3, the solid line represents the with-ATP scenario, while the dotted line represents the without-ATP scenario. In this example, the with-ATP R&D phase lasts 3 years, as does the commercialization phase. In the with-ATP scenario, production begins and benefits begin to accrue to the companies and to society in year t. In the without-ATP scenario, the R&D spending is spread over 5 years (total R&D may also be lower in the absence of ATP funding). Thus, the commercialization and production phases are delayed for 2 years, and benefits begin to accrue in year t+2. Because we assume the window of market opportunity closes at year t+10, the without-ATP scenario includes 2 fewer years of benefits.

Figure 2-3. Impact of Acceleration on Social Returns



2.2.2 ATP's Impact on the Probability of Success

As the probability of technical success increases, so does the expected value of net benefits to society. We calculated the *expected* value of net benefits by multiplying all costs and benefits that occur after the R&D phase by the probability of technical success.

In our model, ATP funding affects the probability of technical success by increasing the level of R&D effort. ATP funding decreases the price of R&D to the firm, thus encouraging additional R&D effort. As R&D effort increases, so does the probability of technical success.

The degree to which ATP funding increases the probability of technical success depends on

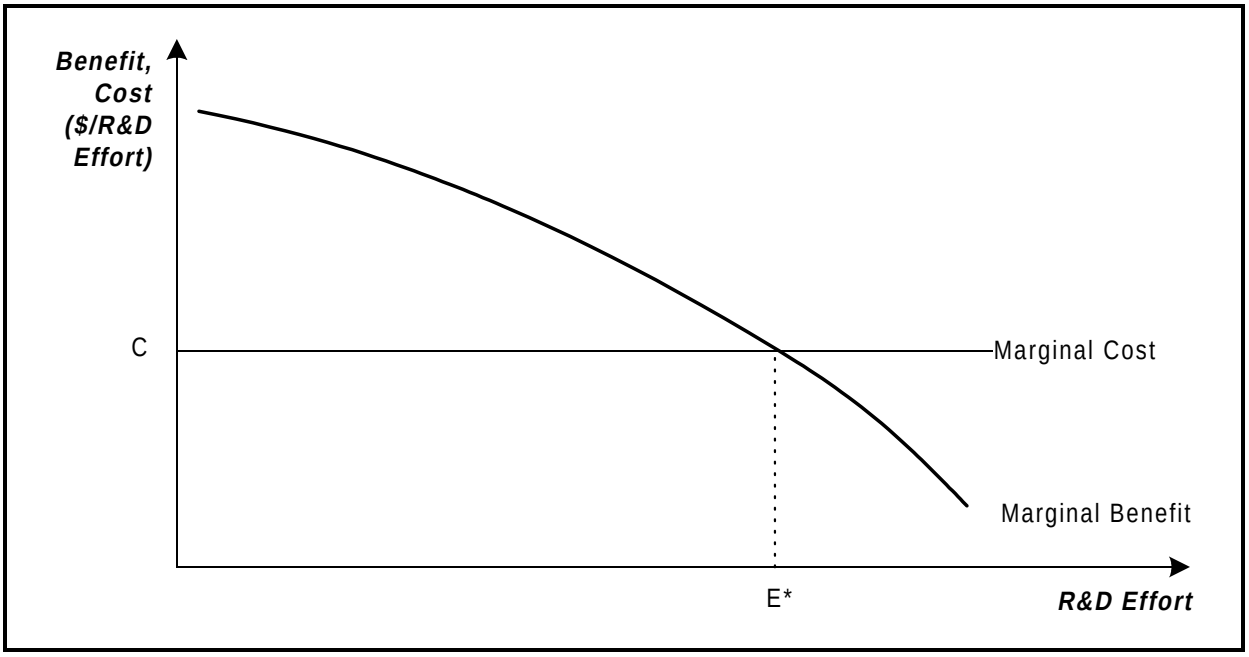
- ATP's impact on the cost of R&D to the firm,
- the expected marginal benefit of R&D effort, and
- the relationship between R&D effort and the probability of technical success.

The Firm's R&D Investment Decision

Companies invest in R&D to produce potential future profits. Following Binswanger (1978), we consider the R&D process a search or sampling process in which scientists sample from a distribution of possible solutions to the problem they are trying to solve. This sampling process requires the firm to expend real resources (e.g., labor services, capital services, materials). "R&D effort" is a composite input combining these resources. Increasing R&D effort increases the probability of finding a successful technology, which, in turn, increases the expected value of future profits. Firms determine the optimal level of R&D by equating the expected marginal benefits and costs of R&D at the margin.

The function representing marginal expected benefit of R&D effort is the firm's input demand function for R&D. As shown in Figure 2-4, the function is decreasing in R&D effort because of diminishing returns to R&D effort. The firm's optimal level of R&D is the level at which the marginal cost of R&D effort equals the marginal benefit of R&D, or E* in Figure 2-4.

Figure 2-4. The Firm's Optimal Level of R&D Effort



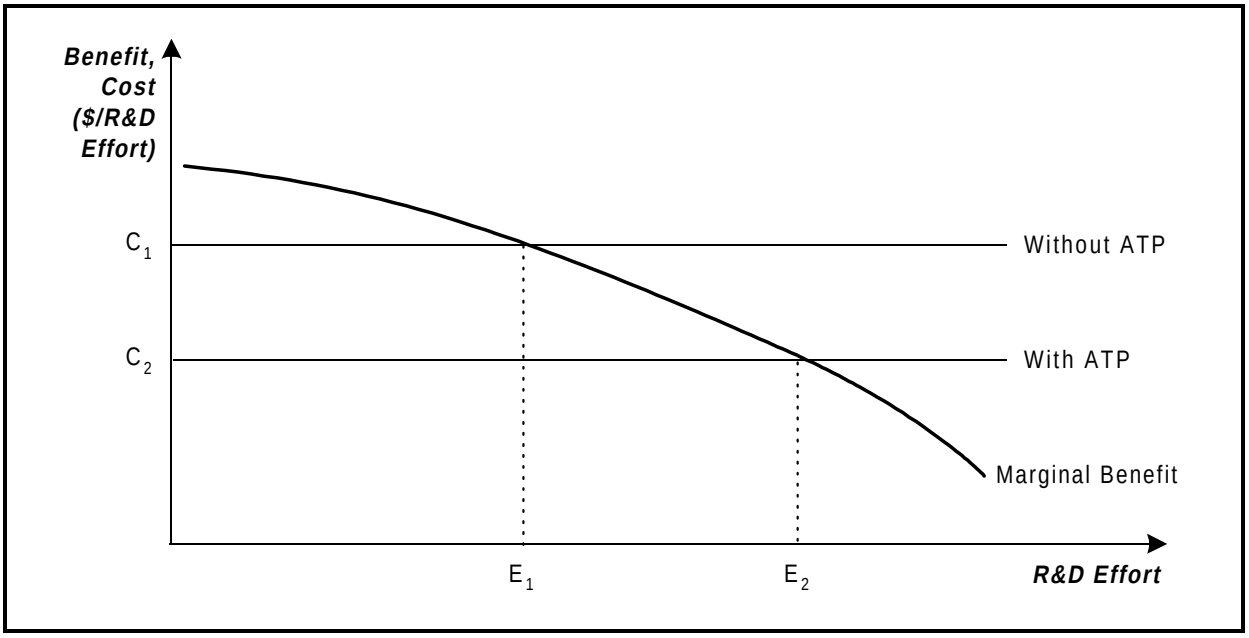
A firm's optimal level of R&D effort equates the marginal expected benefit of R&D with its marginal cost.

ATP's Impact on R&D Price and Investment

The marginal cost of R&D effort is the cost of one additional unit of the composite input "R&D effort." Assuming the components of R&D effort are purchased in competitive markets, their unit costs are constant to the firm, and therefore the marginal cost of R&D effort is constant (see Figure 2-4). The profit-maximizing firm will choose the level of R&D effort at which the expected marginal benefit equals the marginal cost.

ATP funding reduces the marginal cost of R&D effort to the firm. Suppose that a dollar of R&D spending represents a composite unit of R&D effort, and that in the without-ATP scenario, the marginal cost of each unit of R&D effort is $1. If, in the with-ATP scenario, a company receives $1 in ATP matching funds for every dollar it invests in the project, then the marginal cost of R&D is reduced by 50 percent to 50 cents. As shown in Figure 2-5, the reduction in the price of R&D increases the firm's optimal level of R&D effort from E_1 to E_2.

Figure 2-5. Impact of ATP Funding on R&D Effort



The impact of a change in the marginal cost of R&D effort on the quantity of R&D effort depends on the elasticity of the marginal benefits function:

$$\frac{\partial \ln E}{\partial \ln C} = \varepsilon, \qquad (2.2)$$

where ε is the elasticity of the marginal benefits curve, E is R&D effort, and C is the marginal cost of a unit of R&D effort. Thus, if we know the elasticity of the marginal benefit function and the change in the marginal cost of R&D effort due to ATP funding, we can determine the change in R&D effort. Because $1 of R&D spending represents a composite unit of R&D effort, the resulting change in R&D effort is equal to a change in R&D spending on the project.

Unless the expected marginal benefits curve is completely inelastic (vertical), ATP funding must increase the total quantity of R&D effort.

The marginal benefit function is *elastic* if $\varepsilon < -1$; it is *inelastic* if $-1 < \varepsilon < 0$, and *completely inelastic* if $\varepsilon = 0$. As long as ε is not equal to zero, a decrease in the price of R&D will lead to an increase in R&D effort. That is, unless the expected marginal benefit curve is completely inelastic (vertical, with an elasticity of 0), ATP funding must increase the total quantity of R&D effort.

The elasticity of a project's marginal benefit function is difficult to estimate. Because no empirical estimates of the marginal benefit function or its elasticity were available for the tissue engineering projects we analyzed, we made the following assumptions about the elasticity of the marginal benefits curve based on our interviews with the companies:

- For companies that indicated a significant reduction in the funding for the project in the absence of ATP, we assume that their marginal benefit function is elastic with a value of -2.
- For companies that indicated that in the absence of ATP they would have proceeded with the project but under some possible funding constraints, we assume that their marginal benefit function is relatively inelastic with a value of -0.5.
- For companies that told us that the absence of ATP funding would have made little or no difference in the project's funding level, we assume that the cost of R&D was immaterial to their decision to proceed with the project and that the elasticity of the marginal benefit function is -0.01.

Chapter 3 explains our assumptions for each company.

R&D Effort and the Probability of Technical Success

In our model, increases in R&D effort induced by ATP funding lead to increases in the probability of technical success. In keeping with the empirical literature discussed in Section 2.1, we assume that the elasticity of the probability of technical success, P_r, with respect to R&D effort, E, is equal to 0.3. Thus,

$$\frac{\partial \ln P_r}{\partial \ln E} = 0.3. \qquad (2.3)$$

This assumption allows us to estimate the difference between the with-ATP and without-ATP probability of technical success.

2.2.3 Widening the Scope of an ATP Project

ATP funding can also widen the scope of a project. Additional resources from ATP funding may make it possible for a company to consider additional applications of a technology or, for a given application, expand the scope of research to include a wider patient population. For example, additional research may adapt a treatment for special populations such as children or the elderly.

If ATP funding encourages a company to consider additional applications or patient populations, the with-ATP scenario should include the additional health benefits and costs. These increases in scope may increase both private and social returns.

2.3 EVALUATING MEDICAL BENEFITS TO PATIENTS

ATP-funded medical technologies may improve the long-run health outcomes of thousands of patients per year with acute and chronic diseases. They may also reduce the cost of health care. The magnitude of the total health benefits of a new technology depends on the benefit per patient and the number of patients that will be treated.

2.3.1 Valuing Per-Patient Changes in Health Outcomes

To derive an estimate of the per-patient value of changes in health outcomes attributable to new medical technologies, we followed three steps:

- Step 1: Model the technology's impact on health outcomes
- Step 2: Quantify changes in health outcomes in terms of patient well-being
- Step 3: Determine the monetary value of patient changes in well-being

Modeling Differences in Health Outcomes

ATP supports technologies that are likely to have many applications. Each technology usually has an immediate application that is most likely to develop in the short term, as well as applications that will probably develop later. The earlier applications may be easier to analyze because the data regarding their impacts on health outcomes, resource use, the timing of their diffusion, and costs are more readily available and more reliable than data regarding later and more uncertain applications.

For this study, we analyzed one application for each technology—the application that the companies believe has the greatest chance of near-term commercialization. However, later applications may also have a significant welfare impact; our inability to model these later applications probably results in an

underestimation of the social and private returns on investments in ATP-funded technologies.

The defender technology is the most widely used current treatment technology for the specific application of interest.

Mansfield (1996) emphasized the importance of clearly identifying the alternative technology when estimating the returns on investments in new technologies. For this study, the alternative to the new medical technology—the defender technology—is the current treatment technology for the specific application of interest.

Identifying a single defender technology for each application may lead to either understatement or overstatement of the benefits of the new technology. For some diseases or injuries, the appropriate defender technology may depend on the patient's age or medical condition. The less uniform the current treatment for each application, the more serious the implications of assuming that a single defender technology applies to all patients. In some cases, dividing the patient population into different groups according to the most appropriate defender technology may improve the accuracy of the results.

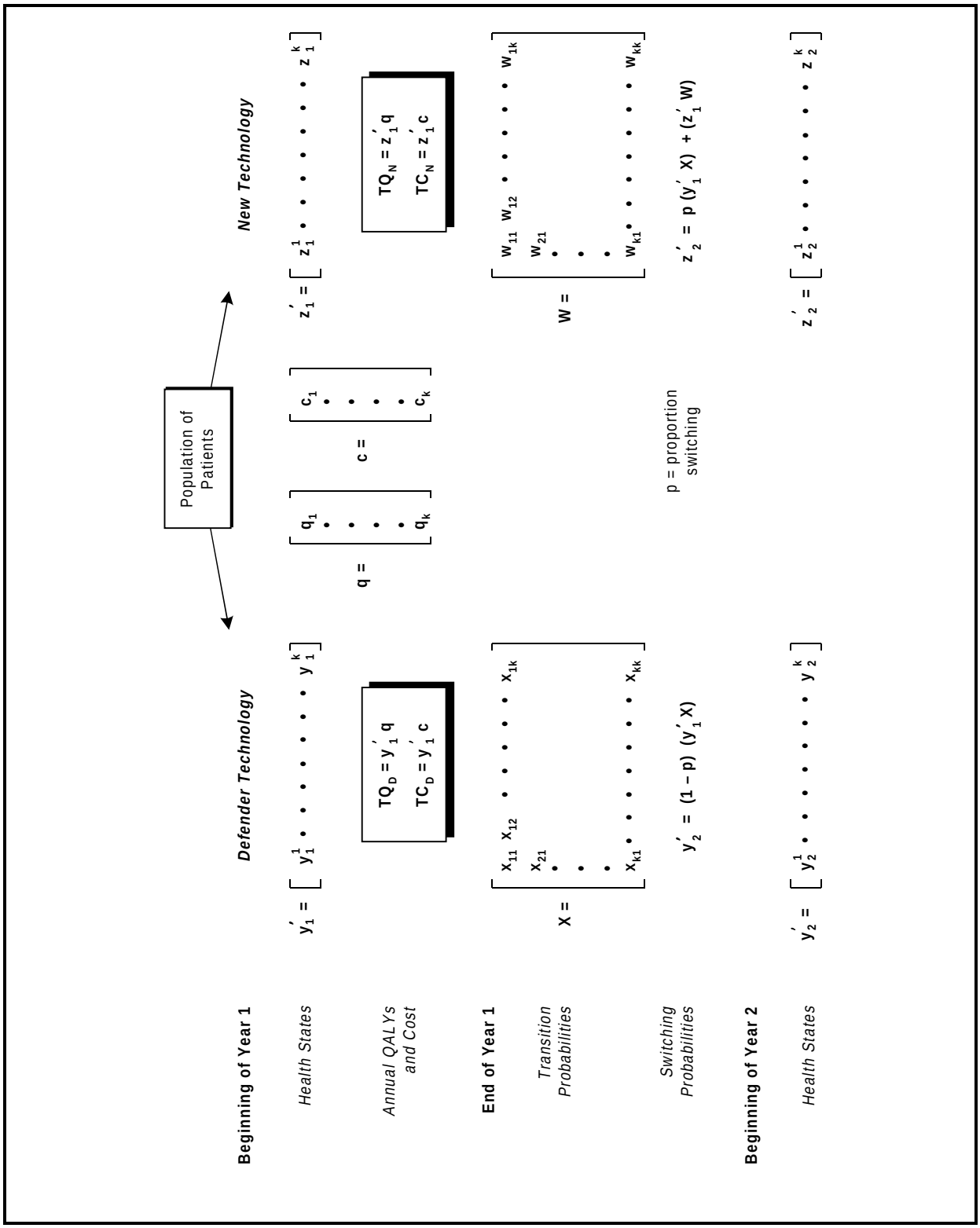
After identifying the technology's application and its defender technology, we modeled the health benefits of each application. Some ATP-funded medical technologies affect the long-run health outcomes of patients with chronic diseases that progress over time. Other medical technologies affect acute illnesses and injuries whose outcomes occur in a single period.

The chronic disease model quantifies the impact of a new technology on the progression of a chronic disease over time. The acute illness and injury model quantifies the impact of a new technology on the health outcome of an acute illness or injury.

We developed two basic models to capture these possibilities: the *chronic disease* model and the *acute illness and injury* model. The chronic disease model incorporates a Markov probability matrix that contains the probabilities that patients transition from one health state to the next over time. The acute illness and injury model, which is actually a single-period case of the chronic disease model, is similar to the traditional decision-tree framework commonly used to assess the impact of health interventions.

Chronic Disease Model. The chronic disease model, illustrated in Figure 2-6, employs a multiple-step process that is repeated in each year beginning with the first year in which the technology is available. The model calculates benefits of the new treatment technology for patients receiving the new treatment over the remainder of patients' lives.

Figure 2-6. Chronic Disease Model of Health and Cost Impacts of New Technologies



In the first step, the patients are allocated between the defender technology and the new technology. The market forecasting model, described in Section 2.3.2, determines this allocation.

In the second step, the patients are allocated among the health states associated with the disease. If there are k health states, then the number of patients in each health state in the first year defines a vector $\mathbf{y_1}$ for the defender technology and $\mathbf{z_1}$ for the new technology where the subscript 1 refers to the first year.

Each health state is associated with a quality-adjusted life-year (QALY) value and a treatment cost. We discuss QALYs below and treatment costs in Section 2.4. The vector of QALYs associated with each health state is **q**, and the vector of costs associated with each health state is **c**. The total annual QALYs for all patients treated with the defender technology in the first year is $\mathbf{y_1'q}$; the total cost is $\mathbf{y_1'c}$. For patients treated with the new technology, the annual QALY and cost totals are $\mathbf{z_1'q}$ and $\mathbf{z_1'c}$, respectively.

The chronic disease model quantifies differences between the new and defender technologies with respect to

- the proportion of patients in each health state and
- the patient's probability of moving from one health state to the next.

It also incorporates the expected penetration of the new technology.

The transition probability matrix, **X**, for the defender technology and **W**, for the new technology, specify the probabilities of transitioning from one health state to another. For example, x_{12} is the probability of moving from health state 1 to health state 2 while being treated with the defender technology. **X** and **W** are two separate matrices because the transition probabilities can differ between the new and defender technologies.

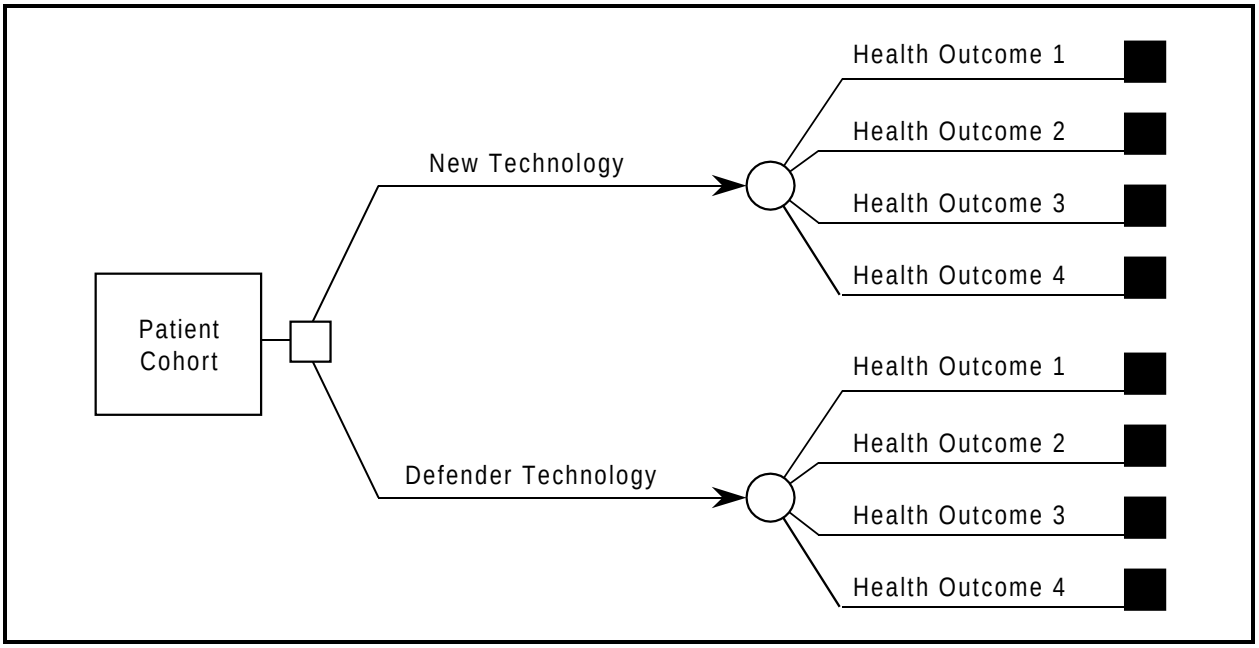
At the end of each year, the vector of health states is multiplied by the transition probability matrix to determine the distribution of patients among health states at the beginning of the next year. Differences between **X** and **W** cause differences between the future health states of patients who are treated with the new technology and patients who are treated with the defender technology. These differences between future health states cause differences between the total QALYs and treatment costs for the new technology and those of the defender technology.

At the end of each year, some proportion of patients in the defender technology cohort is switched to the new technology. This proportion, together with the transition matrices, determines the allocation of patients among health states the next year for both the new and defender technology.

Acute Illness and Injury Model. Acute illnesses and injuries do not progress over time. The acute illness and injury model has many of the same elements as the chronic disease model, but it is much simpler: it is essentially a one-period chronic disease model.

Figure 2-7 illustrates how a decision between the new and defender technologies leads to differences in the probability of health outcomes and also associated costs and benefits. The open square node represents the point at which a decision must be made between the new and defender technologies. Each branch following the decision node is associated with a choice of treatment technology and a treatment cost. For each technology, an open circle represents a chance node. Each branch following the chance node represents the outcomes associated with the illness or injury; each outcome is characterized by a probability, a QALY, and a cost.

Figure 2-7. Acute Illness and Injury Model of Health and Cost Impacts of New Technologies



The acute illness and injury model describes how the new and defender technologies leads to different health outcomes and their associated QALYs costs.

The model calculates expected benefits and costs for each technology by multiplying the probability of each health outcome by the associated QALYs and costs. We compared the expected benefits and costs of the two technology choices to determine the net benefit of the new technology.

Model Data. Below, we describe the data required to implement the health benefits models.

Patient Cohorts. The chronic disease model examines a single cohort of patients and analyzes how this cohort transitions through time from one health state to the next. The patient cohort is defined as the number of people diagnosed with the relevant disease.

For most chronic diseases, the number of newly diagnosed patients is small compared to the pool of patients in any given year. For example, in 1996, the number of patients who could benefit from a new treatment for diabetes was 1.6 million. The number of new patients that enter this cohort each year is approximately 90,000. Thus, by following only the patients included in the first cohort, we underestimated the benefits, but by a small amount compared to the total benefits.

Some patient populations change each year as some patients die or experience other changes in health status that remove them from the relevant population, while other patients are newly diagnosed. To simplify the model, we analyzed a constant patient cohort and did not add newly diagnosed patients in later years. The number of new patients is probably small relative to the total pool of patients at any one time. Thus, although the model ignores the benefits to the newly diagnosed patients, the effect is probably relatively small. This methodology parallels common practice in clinical trials of new drugs and treatments (DCCTRG, 1996).

In the acute illness and injury model, the relevant patient population is defined somewhat differently. Because acute illnesses and injuries do not progress over time, it is not necessary to track a cohort's changes in health states. Therefore, the patient population is the number of patients diagnosed with the particular injury or illness in that year.

Information about the size of various patient populations is available from medical databases provided by medical research organizations, such as the American Diabetes Association, the American Heart Association, the United Network for Organ Sharing, and the National Institutes of Health.

Health States. The chronic disease model allocates patients among the health states associated with the disease. For example, the health states associated with the nephropathy resulting from diabetes include no nephropathy, microalbuminceria,

albuminceria, and end-stage renal disease. The initial allocation is based on information from medical databases about the share of patients in each health state at a given time. The transition matrix and the switching probabilities from the model determine allocations of patients across health states in subsequent years.

The acute illness and injury model requires specification of final health outcomes rather than transitional health states, as in the chronic disease model. The acute illness and injury model assumes that a health outcome is permanent. For example, if an injury and subsequent treatment leave a patient with impaired function of a hand, the patient experiences this health outcome throughout life.

The differences between the new technology transition matrix and the defender technology transition matrix reflect the impact of the new technology on the progression of the disease.

Transition Probabilities. The transition matrices **X** and **W** in Figure 2-6 specify probabilities for transitions from one health state to another. When a new technology affects the probability of progressing from one health state to another, the transition probability matrices differ between the new and defender technologies.

The acute illness and injury model is a special case of the chronic disease model in which there is only one period. In the acute illness and injury model, a vector of health outcome probabilities specifies a probability for each health outcome. This vector may differ between new and defender technologies.

Transition and health outcome probabilities may be difficult to obtain. For the defender technology, transition and outcome probabilities may be available from medical studies of the effectiveness of the treatment. For the new technology, if no clinical trials have been completed, the only source of transition and health outcome probabilities may be the expectations of representatives of the companies conducting the research.

Switching Probability. For the chronic disease model, the switching probability specifies the proportion of patients switched from the defender technology in each year. The switching probability is derived from a technology diffusion model that we estimate. The diffusion model is described in Section 2.3.2.

Quantifying Changes in Patient Well-Being

The changes in health states or health outcomes identified by the acute and chronic disease models affect patient welfare. The economic concept of individual welfare is "utility," which is the individual's subjective sense of well-being associated with a particular action or condition. Our health benefits models incorporate QALYs as a measure of patient utility. This section describes QALYs and why they are appropriate measures of welfare. Then it discusses how health researchers determine QALY values for different health states or health outcomes.

Quantifying Utility. Although utility is generally regarded as the proper conceptual measure of individual welfare, it is unobservable. An empirical surrogate is needed to provide a cardinal measure of the value of the health benefits identified by our models. The observable utility surrogate that is typically used in benefit-cost analyses is the maximum dollar amount the individual would be willing to pay for the expected welfare improvement or the minimum amount he/she is willing to accept to forego the improvement.

Although willingness to pay (WTP) and willingness to accept (WTA) are not perfect surrogates for utility changes, the consensus among economists is that WTP and WTA do provide the best available utility surrogate (Tolley, Kenkel, and Fabian, 1994; Sloan, 1995; Haddix et al., 1996). An obvious problem with these measures is that they are conditional on an individual's wealth or income. Different people with similar preferences for the benefits provided by new medical technologies could experience the same utility change but have different WTP or WTA values if their incomes were different.

In some cases WTP and WTA are revealed in markets. For example, when an individual purchases a commodity in a market, the monetary sacrifice is the price of the commodity. In such cases, price is the appropriate WTP/WTA value of the welfare change of a one-unit change in the individual's consumption rate of the commodity.[4]

[4]The price actually indicates the WTP for the marginal consumer. Inframarginal consumers earn consumer surplus on their purchases; their actual WTP is higher than the price.

Because the health care market is distorted by the intervention of third parties, market prices may not reflect the value of their resulting health outcomes; nonmarket valuation methods are required to quantify their value.

However, the prices of goods such as health care do not reflect the values of their benefits to patients. In this case, nonmarket methods must be used to value the benefits of health care. These methods include

- expressed preference, in which individuals are surveyed directly to elicit their WTP/WTA for the desirable change or to prevent an undesirable change, and
- revealed preference, which uses market data and transactions for goods and services that include the nonmarket commodity as one of their attributes to estimate the value of the commodity. For example, if, all else being equal, people are willing to accept lower wages for work with less risk of injury or illness, the wage difference is a proper WTP/WTA value of some of the health benefits of the less risky occupation.

Although WTP provides the most comprehensive and theoretically consistent measure of the value of health outcomes, it is also difficult and expensive to implement. If neither expressed nor revealed preference estimates are available from empirical studies for the health outcome of interest, primary data must be collected from individuals to assess their WTP/WTA values. This approach is often not an option given the time and resource constraints of an analysis.

A QALY is a measure of the utility associated with health outcomes that combines morbidity and mortality into a single measure.

QALYs as a Measure of Utility. An alternative method for measuring utility for health benefits is to measure and value the change in a patient's quality-adjusted life-years (QALYs). A QALY is a measure of the utility associated with health outcomes that combines morbidity and mortality into a single measure of annual well-being. QALYs assign each health state a value between zero and one, where zero corresponds to death and one to a year in perfect health. The scale is based on the idea that the value of a year of life varies depending on a person's state of health. A year of life in perfect health is worth more to a person than a year experiencing a chronic and painful disease. QALYs quantify this difference in well-being and therefore capture the effects of pain and suffering. QALYs have been used extensively for cost-utility analyses of new medical treatments and are well accepted among the medical community. The Panel on Cost-Effectiveness in Health and Medicine recommends using QALYs to measure morbidity and mortality consequences of an intervention (Gold et al., 1996).

The economic burden of a disease is usually divided into three components: direct medical costs, indirect costs, and intangible costs. Direct medical costs equal the total cost of medical treatment. Indirect costs are the societal costs associated with loss in productivity due to illness and unpaid caregiver time. Intangible costs measure the costs due to the pain and suffering of the patient. QALYs are generally assume to measure the change in both the direct medical costs and the intangible costs of a disease. Changes in indirect costs are generally not included in our estimates. However, there is some debate about whether QALYs actually include indirect costs; some researchers believe that when providing their QALY estimates, patients include indirect costs in their estimates.

Determining QALYs for Specific Health States. Health researchers collect QALYs from patients using sophisticated survey methods. The QALY values developed through these surveys are then used to quantify the impact of health states and health outcomes on the utility of a wider population. The extent to which the QALYs developed from a sample are accurate predictors for the patients in the study population depends on the extent to which the sample is representative of the study population. Obviously, the best way to ensure that QALYs are accurate for the study population is to interview each patient in the study population to develop individual-specific QALY values. Because this is not usually possible, researchers aim to ensure that the sample is representative of the population with respect to variables that they suspect will affect QALY values.

Because the time and resources did not permit it, we were not able to conduct direct surveys of the patient populations affected by each of our case study technologies. Instead, we used average QALY values available from other empirical studies. Table 2-1 lists available QALYs for a number of health states. When assigning QALYs for this study, we used the closest health state for which QALYs were available. If possible, we used QALYs that were developed especially for the patient population of interest.

Table 2-1. Comparison of QALY Utility-Weights for Different Health States

Health State	Utility Weight	Study
Full Health	1.00	
Life with menopausal symptoms	0.99	Torrance and Feeny, 1989
Side effects of hypertension treatment	0.95 - 0.99	Torrance and Feeny, 1989
Mild angina	0.90	Torrance and Feeny, 1989
Kidney transplant	0.84	Torrance and Feeny, 1989
Chronic lung disease	0.83	O'Brien and Viramontes, 1994
Lower extremity amputation	0.80	DCCTRG, 1993, 1995, 1996
Mechanical equipment to walk	0.79	Torrance and Feeny, 1989
Mild shingles pain	0.73	Wood et al., 1997
Permanent ostomies	0.70	Burckhardt et al., 1993
Moderate angina	0.70	Torrance and Feeny, 1989
Blindness	0.69	DCCTRG, 1993, 1995, 1996
Some physical and role limitation with occasional pain	0.67	Torrance and Feeny, 1989
Severe menopausal symptoms	0.64	Daly et al., 1993
Home dialysis	0.64	Torrance and Feeny, 1989
Chronic lung disease	0.63	O'Brien and Viramontes, 1994
End-stage renal disease	0.61	DCCTRG, 1993, 1995, 1996
Insulin-dependent diabetes	0.58	Burckhardt et al., 1993
Osteoarthritis	0.52	Burckhardt et al., 1993
Rheumatoid arthritis	0.52	Burckhardt et al., 1993
Fibromyalgia syndrome	0.51	Burckhardt et al., 1993
Severe angina	0.50	Torrance and Feeny, 1989
Severe shingles pain	0.47	Wood et al., 1997
Anxious/depressed and lonely much of the time	0.45	Torrance and Feeny, 1989
Blind or deaf or dumb	0.39	Torrance and Feeny, 1989
Chronic obstructive pulmonary disease	0.38	Burckhardt et al., 1993
Mechanical aids to walk, needs help of another person to get out, and learning disabled	0.31	Torrance and Feeny, 1989

(continued)

Table 2-1. Comparison of Utility-Weights for Different Health States (continued)

Health State	Utility Weight	Study
Dead	0.00	
No use of arms and legs, blind, unable to attend school or work, needing help with self care and getting around, and depressed	<0.00	Torrance and Feeny, 1989
Confined to bed with severe pain	<0.00	Torrance and Feeny, 1989
Unconscious	<0.00	Torrance and Feeny, 1989

Determining the Monetary Value of Changes in Well-Being

The final step in determining the monetary value of the per-patient change in health outcomes is to assign a monetary value to a QALY.

Recently, economists have developed empirical methods to estimate the dollar value of reducing fatal and nonfatal health risks. We took advantage of previous work in this area, particularly that of Mauskopf and French (1991) and Moore and Viscusi (1988b). They developed estimates of the value of a QALY for the average person based on WTP values for avoiding illness and accidents.[5]

First, they determined the loss in QALYs associated with published WTP estimates. For example, a study by Moore and Viscusi (1988a) estimated the dollar value of avoiding immediate premature death based on data on working men with an average age of 40 years. The expected loss in life-years is 36 years, assuming a life expectancy of 76 years. If we assume perfect health until death, then the QALYs lost are also 36 years. Thus, if the marginal dollar value of a life-year is constant, the dollar value of one QALY can be estimated by dividing the dollar value of avoiding premature death by 36. Alternatively, we can apply a

[5]The values developed by these studies represent average WTP values for a QALY among the U.S. population. The value that people place on a year of good health is likely to vary by a number of factors, including income. WTP surveys can be conducted for the specific population of interest to determine that population's value for a QALY. The averages used for this study are widely used when population-specific values are not available.

discount rate to the remaining life-years, assuming that life-years in the near future are more highly valued. Then the WTP estimate is divided by the total discounted life-years to determine the value of a QALY.

For this study, we used Moore and Viscusi's (1988a) estimate of $5 million for the value of avoiding premature death at age 40. This is also the mid-point of estimates reviewed by Fisher, Violette, and Chestnut (1989). Table 2-2 provides alternative values of a QALY under alternative assumptions regarding the QALY discount rate. These values are obtained by finding the 36-year annuity value of a $5 million principal at each discount rate. Thus,

$$V = \frac{5{,}000{,}000}{\sum_{t=1}^{36}\left(\frac{1}{1+d}\right)^t} \qquad (2.4)$$

where V is the annual QALY value, d is the QALY discount rate, and t indexes the year.

Table 2-2. Alternative QALY Values

Discount Rate	QALY Value[a]
0%	$138,889
3%	$229,019
5%	$302,173
7%	$383,577

[a]Assumes that payments are made at the end of the year.

Health economists disagree about the appropriateness of discounting QALYs. The issue in question is a patient's time preference for quality of life and life-years. That is, should a life-year gained 10 years from now have the same value as one gained next year? If not, what is the appropriate discount rate?

We followed the recommendations of Lipscomb, Weinstein, and Torrance (1996) who advise using a 3 percent discount rate and conducting sensitivity analysis on a range of discount rates. The choice of a discount rate is discussed in greater detail in Section 2.6.3.

2.3.2 Determining the Number of Beneficiaries

The total medical benefits of a new technology and the revenues to private companies depend on the speed of the new technology's market penetration.

The total medical benefits of a new technology and the revenues to private companies depend on the speed of the new technology's market penetration. The adoption of a new technology is typically a function of the benefits of adoption to firms or consumers using the technology. Typically, firms and consumers do not adopt new technologies simultaneously; instead, innovations "diffuse" into use over time (Reinganum, 1989).

Gradual diffusion is a result of the heterogeneity of firms or consumers. The expected benefits of adopting a new technology depend on factors such as firm size, access to information, risk aversion, and others that differ among decisionmakers. In the case of medical innovations, the decisionmakers include hospitals, physicians, and patients who are provided choices between the defender technology and the new technology. We expect the heterogeneity of these decisionmakers to result in a gradual diffusion process rather than simultaneous technology adoption.

Diffusion models are appropriate for forecasting the temporal pattern of new technology adoption.

Diffusion models provide a summary statistical description of the adoption process. Empirical studies support an S-shaped diffusion curve for the diffusion of new technologies (Mahajan and Peterson, 1985). As shown in Figure 2-8, technological innovations typically diffuse slowly at first, with few adoptions occurring initially. The rate of adoption increases as early adopters and other factors, such as information dissemination and advertising, influence others to adopt. The rate of adoption declines as the market potential is approached.

The classic diffusion model is the Bass model, or mixed influence model (Bass, 1969; Mahajan and Peterson, 1985), which contains two parameters that characterize the diffusion curve. Figure 2-9 illustrates the model and describes the coefficients and their theoretical interpretation. The coefficient of innovation, p, represents "external influence," or adoptions due to the influence of some external activity, such as professional publications. The coefficient of imitation, q, represents the influence of word-of-mouth effects, or "internal influence." Thus, the number of new adoptions (rate of change in cumulative adoptions) is proportional to the difference between market potential, M(t), and the number of

Figure 2-8. The Classic Diffusion Curve

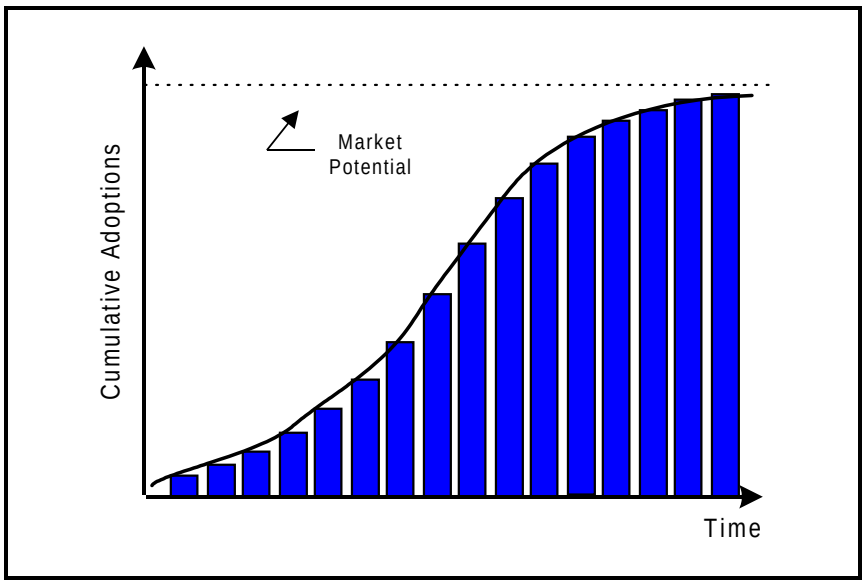
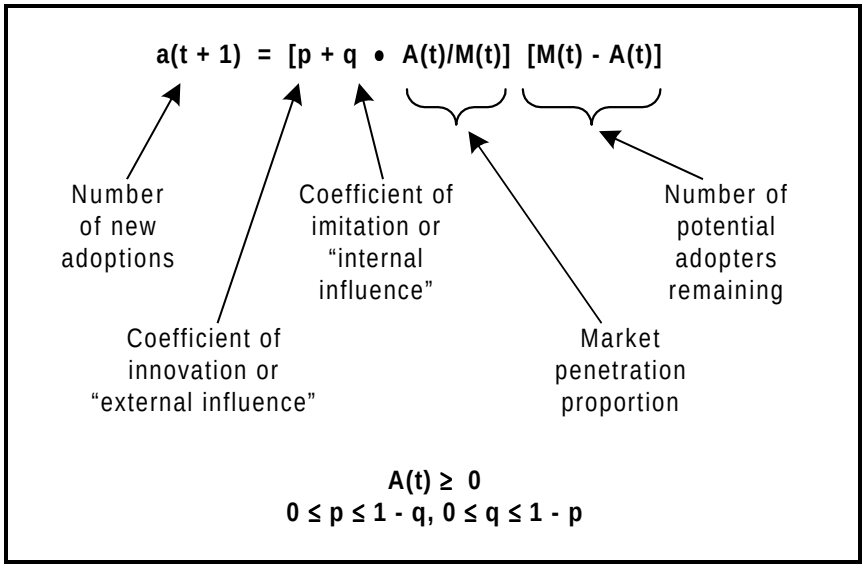


Figure 2-9. Bass (Mixed-Influence) Diffusion Model



previous adopters, A(t). The proportionality factor [p + q • A(t)/M(t)] is sometimes interpreted as the probability of adoption at time t. The Bass model synthesizes the approaches of Mansfield (1961) and Fourt and Woodlock (1960). Their models are special cases of the Bass model.

The Bass model is theoretically consistent with our expectations of the diffusion of biomedical innovations. Upon introduction to the

market (and after Food and Drug Administration [FDA] approval), only a few physicians will use new medical innovations because experience and knowledge about the procedures are limited. However, as information about the new techniques becomes available through professional papers, conferences, and word of mouth, the diffusion rate will increase as more physicians adopt the innovation. Finally, the rate of adoption will slow down as the total market potential is approached.[6]

One important limitation of this model is that the cumulative number of adopters, A(t), always increases over time. Actually most technologies begin to lose market share as new technologies emerge and consumer needs and tastes change. For example, data from the Drug Mentions files produced by the National Center for Health Statistics (NCHS) indicate that the rate at which doctors prescribe new drugs for specific diagnoses has an inverted U-shape; the peak occurs about 10 to 15 years following FDA approval.[7] Ideally, we would forecast not only the rate of penetration of ATP-funded technologies, but also the rate of penetration of technologies that supersede them. For this study, we assume that the new technology will be completely superseded by a newer technology after 10 years.

Implementing the Bass diffusion model requires gathering data on M(t) and A(t), estimating the model, and using the model estimates to forecast the number of patients who will be treated with the technology.

Collecting Model Data

The following data are required to estimate the Bass model:

- M(t) = potential market size in year t and
- A(t) = the cumulative number of early adopters in year t.

In our study, M(t) is the total relevant patient population in a given year.

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[6]Trajtenberg (1990) notes that the government regulatory process has had a profound impact on the diffusion of CT scanners and that it is difficult to fit it to a specific functional form. The true diffusion process for these ATP innovations will become apparent only in retrospect, when actual diffusion data can be examined.

[7]Based on an unpublished analysis of the Drug Mentions files data by Frank Lichtenberg, Columbia University.

Data for the Bass model can include observations of the actual early market penetration of a technology or forecasts of market penetration by technology experts.

Ideally, *ex post* data would be available for A(t). For example, if the technology was introduced in 1992, data from 1992, 1993, 1994, 1995, and 1996 would provide five observations for A(t). In the absence of *ex post* data, some forecast of A(t) must be developed. We obtained these forecasts from company representatives or from physician interviews. Expert interviews are commonly used to forecast the penetration of new technologies; in the case of medical technologies, physicians with clinical and research experience in the applications of interest are the best experts. Alternatively, forecasts of A(t) can be constructed by examining the diffusion pattern of analogous technologies.

Company representatives or professional associations and institutions (e.g., the American Diabetes Association and the National Cancer Institute) helped us to identify physician experts who specialize in the applications of interest, either in clinical practice, in research, or both.

To familiarize the physicians with the technologies and to ensure that they were considering all aspects of the technologies in their forecasts of A(t), we constructed clinical profiles of each technology. Each profile contained a description of the technology and information such as expected costs and outcomes compared to the defender technology. We obtained permission from the developing companies to provide this profile to physicians and did not disclose the identity of the developing company. Appendix A provides examples of profiles we used to apply this methodology to several tissue engineering projects.

Estimating the Diffusion Model

Ordinary least squares (OLS) regression can be used to estimate a Bass model:

$$a(t+1) = [p+q\ A(t)/M(t)]\ [M(t) - A(t)] \qquad (2.5)$$

where

- a(t+1) is the number of new adopters in the next year,
- A(t) is the cumulative number of adopters in year t,
- M(t) is the total market potential in year t, and
- A(t+1) = A(t) + a(t+1).

Rewriting Eq. (2.5) provides the estimated equation:

$$a(t+1) = p \bullet [M(t) - A(t)] + q \bullet \left[A(t) - \frac{1}{M(t)} \bullet A(t)^2\right]. \quad (2.6)$$

Using data collected from physician interviews and company representatives, we estimated p and q using OLS. In keeping with the structure of the Bass model, we suppressed the intercept.

The forecast equation is

$$\hat{a}(t+1) = \hat{p} \bullet [M(t) - A(t)] + \hat{q} \bullet \left[A(t) - \frac{1}{M(t)} \bullet A(t)^2\right]. \quad (2.7)$$

Forecasts of A(t) for Years 2 through 10 were constructed by inserting estimates of p and q into the equation above. Confidence intervals of 95 percent can be constructed around forecasts of A(t) to provide a measure of the uncertainty of the results. However, note that we used expert forecasts to estimate the model. These forecasts are subject to unmeasurable error; thus, traditional measures of forecast error do not fully capture the error associated with these estimates.

2.4 ESTIMATING CHANGES IN HEALTH CARE COSTS

Our analysis of the impact of new technologies on the cost of health care uses the structure of the chronic disease model and the acute illness and injury model presented in Section 2.3. Recall that, in each year, the distribution of patients among the health states differs between the new and defender technologies. Each health state imposes a treatment cost; the vector **c** in Figure 2-1 specifies these costs. Thus, the total cost of treating all patients in a given year is the product of the cost vector and the patient allocation vector. For year 1,

$$TC_D^1 = \mathbf{y_1'c} \text{ and } TC_N^1 = \mathbf{z_1'c} \quad (2.8)$$

where TC_D^1 is the cost of health care under the defender technology in year 1 and TC_N^1 is the cost of health care using the new technology in year 1.

The cost of treating someone in a given health state can differ between the new and the defender technologies if the new technology affects the method of treatment for a given health state.

Eq. (2.8) includes the costs associated with treating the health states or health outcomes resulting from each technology, but it does not include the cost of the treatment itself. Thus, if the cost of using the new technology is different from the cost of using the defender technology, we added this cost difference to the model. Where appropriate, we also incorporated the costs of treating the side effects and complications of each treatment. Chapter 3 discusses the specific costs associated with the diseases and illnesses considered in this study.

2.5 CALCULATING RETURNS TO PRIVATE COMPANIES

Companies invest in R&D to pursue new technologies because, if successful, the technology will provide a stream of future profits. Expected private returns depend on the following factors:

- ➤ probability of technical success;
- ➤ expected investments and costs for
  - ✓ R&D,
  - ✓ commercialization, and
  - ✓ production; and
- ➤ expected revenues.

In this model, the private return on investment includes the expected investments and revenues of the innovator as well as other companies that may play a role in commercializing and producing the technology.

In this model, private return on investment includes the investments and revenues of the innovator as well as other companies that may play a role in commercializing and producing the technology. This definition of private returns is somewhat different from the one commonly used in the literature. Normally, private returns to R&D refer to the returns to the innovator, while returns to downstream companies are "spillovers" and are counted as part of social returns but not private returns.

Companies that receive ATP funding may specialize in one phase of the innovation process while developing contractual relationships with other companies that participate in other phases. Companies that specialize in R&D activities do not incur the costs of commercialization and production. Their benefits are limited to licensing fees, royalties, or the sale of patents to other firms that will commercialize and manufacture the new technology.

Our model includes the costs and benefits from all three phases in our definition of private returns regardless of whether the ATP-sponsored firm is responsible for all of these activities. The early stage of many of these ATP projects makes it difficult to predict the R&D, marketing, and production relationships that will emerge among our case study companies and, therefore, the distribution of benefits among them. Thus, our definition of private returns aggregates the costs and revenues of the initial innovator and other companies that play a role in commercialization. Provided the estimates of private return on investment are interpreted correctly as returns to all private companies participating in R&D, commercialization, and production, this assumption has no impact on the empirical results.

Constructing the schedule of expected benefits and costs for the private sector requires the following information for both the with-ATP scenario and the without-ATP scenario:

- R&D investment for each year of the R&D phase,
- investment in commercialization for each year of the commercialization phase,
- annual expenditures on the fixed and variable costs of production,
- annual revenue, and
- probability of technical success.

2.5.1 Determining R&D Investment

We assume that the company's R&D investment in the ATP project is equal to its contribution to the ATP project's total budget—that is, the total project budget minus the amount funded by ATP.

The private sector's R&D investment in the with-ATP scenario is equal to its matching funds for the ATP project. R&D investment in the without-ATP scenario is determined by the model as described in Section 2.2.1.

This assumptions reflects a narrow view of private-sector R&D investment. An alternative views R&D as a production process whose inputs include the stock of the company's knowledge resulting from previous R&D in related projects. Thus, at least a portion of the R&D invested in previous related projects should be counted as an investment in the current project.

Nevertheless, we applied the more practical, narrower approach to determining R&D investment because of the lack of data for determining the total quantity of R&D invested in a general research area. This may result in an underestimate of the

company's investment in ATP-funded technologies. As a consequence, the resulting estimates of social and private returns may be biased upward for some projects, especially those in which the ATP project builds on accomplishments of previous R&D by the same company. On the other hand, knowledge spillovers from these ATP projects to other projects are also likely. In fact, ATP projects are chosen because of their potential to lead to advances in science and technology that enable advances in other areas. Our estimates do not account for these spillover benefits, which bias the estimates of social and private returns downward.

2.5.2 Determining Costs of Commercialization and Production

Our model includes costs incurred during the commercialization phase due to activities such as preparing for regulatory review, developing marketing networks, building production capacity, and developing supplier networks. In our model, companies do not incur these expenses unless the project is technically successful. The commercialization phase begins at the completion of the ATP project period and ends when the project is brought to market.

ATP funding recipients may not be able to provide an estimate of the cost of conducting these activities, particularly if their projects are still in the R&D phase. In this case, assumptions about the relationships between these costs and available company information must be developed.

We derived our assumptions about these costs from industry profiles. According to a composite balance sheet of the biotechnology industry, selling, general, and administrative expenses represent about 37 percent of total revenue (Lee and Burill, 1996). We used this information to construct a timeline of commercialization costs. We assume that some of these costs are fixed and the company incurs them in the commercialization phase. Another portion is variable and the company incurs them annually in conjunction with production. If γ represents the portion of these costs incurred prior to production, the fixed commercialization costs are

$$CC_F = \gamma * \left[0.37 * \sum_{t=1}^{n} TR_t \right] \qquad (2.9)$$

where CC_F represents the fixed portion of commercialization costs, TR_t is total revenue in year t, and n is the number of years of production. If the commercialization phase is longer than 1 year, we spread the fixed costs over the commercialization phase. For our case studies of ATP-funded tissue engineering technologies, we assume that $\gamma = 0.25$; thus, 25 percent of total commercialization costs are fixed and incurred during the commercialization phase; the remainder occur during the production phase.

Our model also includes the cost of additional research required in the commercialization phase to bring the technology to market, such as the costs of conducting the research required for regulatory review. Several of our case study companies provided estimates of these costs. For those that could not, we developed an estimate based on average R&D spending in the industry. For the pharmaceutical industry, R&D spending accounted for 12.5 percent of revenue in 1993 (NSF, 1996). Thus, we assume that total research spending, including the total ATP project budget, equals 12.5 percent of revenue:

$$CC_R = 0.125 * \left[\sum_{t=1}^{n} TR_t\right] - R_A - R_C \qquad (2.10)$$

where CC_R represents the portion of commercialization costs due to additional research. R_A is public investment of ATP funds to the project, and R_C is the company's contributions to the ATP budget. Again, if the commercialization phase is longer than 1 year, we spread these costs over the entire commercialization phase.

Rather than explicitly including a fixed cost of the plant and equipment, we used a production cost estimate that incorporates the cost of capital depreciation.

We also developed estimates of production costs from industry data. According to a composite balance sheet of the biotechnology industry, the ratio of production costs (including capital depreciation) to the value of shipments is 0.42 (Lee and Burill, 1996). Because the costs included in the numerator of this ratio include capital depreciation, there is no need to account for the fixed costs of plant and equipment elsewhere. Thus, we assume that production costs equal 42 percent of revenue.

Ideally, we can replace these assumptions about the relationship between revenue and the costs of commercialization and production with actual data from the companies as it becomes available. Because these assumptions are based on an aggregate

balance sheet of the biotechnology industry, they do not reflect differences among segments of the industry or the specific situation of the ATP-sponsored companies and their partners. As the biotechnology industry matures, its aggregate balance sheet may show some reduction in R&D and commercialization costs while production costs as a percentage of revenue may increase. How well these assumptions fit the companies in our case study depends on their stage of development relative to the industry.

2.5.3 Calculating Revenues

Revenue is equal to the per-unit price multiplied by the quantity sold. We derived our estimates of the quantity of sales for the goods embodying each technology from the diffusion model described in Section 2.4. ATP-funded companies provided an estimate of the price of the product or service embodying the ATP-funded technology. The companies sometimes based these estimates on the cost of the defender technology. If the companies' goal is to provide the product or service at the same or lower cost than the defender technology, the price of the defender technology guided their estimate of the expected price.

2.5.4 Estimating the Probability of Technical Success

We used the companies' own assessment of their progress toward demonstrating the technical feasibility of the project as a proxy of the probability of technical success. We adjusted this assessment to account for the percentage of project R&D that has been completed.

Assessing the probability of technical success for ATP projects in tissue engineering is very difficult, especially for projects that are relatively young. We derived our estimates of the probability of technical success from the companies' own assessments of their progress toward demonstrating the technical feasibility of their ATP projects, as reported in quarterly and anniversary business reports. We adjusted their estimates to account for the projects' expected completion dates:

$$P_r = TP/PF \qquad (2.11)$$

where TP represents the percentage of progress the companies have made toward demonstrating technical feasibility, and PF is the percentage of the projects' calendar time that had elapsed at the time TP was assessed.[8]

[8]Ideally, we would use the percentage of the project budget spent at the time technical progress was assessed; however, this information was not available.

In their quarterly and anniversary business reports, companies report their progress toward demonstrating the feasibility of their technical goals. The companies report a range (e.g., 0 to 25 percent). We used the midpoint of the range for the value of TP. We calculated PF as the ratio of the elapsed project time to the total project period. For example, suppose one of the ATP-funded companies reported in its business report that it had made 25 to 50 percent progress toward demonstrating technical feasibility. Also suppose that at the time the company filed the report, 50 percent of the ATP project period had elapsed. Then the probability of technical success is

$$\frac{0.375}{0.5} = 0.75.$$

This method of estimating the probability of technical success has important limitations. Even the companies cannot predict whether they will meet all of their technical goals. Furthermore, our method of adjusting the company assessments to account for the status of the projects can result in probabilities greater than one. Clearly, a more robust method for determining this probability is needed. The sensitivity of our results to our estimates of the probability of technical success is reported in Appendix B.

We determined the probability of technical success in the without-ATP scenario by applying the model described in Section 2.2.1. This model determines the change in the probability of technical success as a function of the change in R&D spending.

2.6 CALCULATING MEASURES OF ECONOMIC RETURN

After gathering the data and completing the modeling activities, we calculated measures of economic return from three perspectives: the social return on public investment, the social return on public and private investment, and the private return on private investment.

Measures of economic return on investments in ATP-funded technologies can be calculated from the time profile of benefits and costs to the public and to the private sector in each scenario. We

used four steps to develop the measures of social and private returns:

1. Construct the time profile of benefits and costs for the with-ATP and without-ATP scenarios.
2. Choose measures of economic return.
3. Choose a discount rate.
4. Conduct sensitivity analysis on key parameters.

2.6.1 Constructing the Time Profile of Benefits and Costs for Each Scenario

The relevant time horizon for evaluating the R&D investment depends on our expectations for the emergence of a new technology that will replace the ATP-funded technology.

The with-ATP and without-ATP scenarios specify the expected private and social benefits and costs in each year. The first year of the scenario is the first year in which benefits or costs are incurred (e.g., Year 1 of the ATP project funding). The last year of the scenario is defined as the final year of the production phase. Determining the last year of the scenario requires speculation about the emergence of new technologies that may replace the ATP-funded technology. As explained in Section 2.1, we assume that this occurs 10 years after expected market introduction in the with-ATP scenario.

The annual net benefit to the private sector is the difference between annual revenues and annual costs to the innovator and its partners. The annual net benefit to society is equal to the net benefit to the private sector, minus ATP funds provided by taxpayers, plus net benefit to patients, plus net benefit due to changes in the cost of health care. During the R&D phase, the expected net benefit to both the private sector and society is the same as the net benefit. In the years after the R&D phase, the expected net benefit is the product of the probability of technical success and the net benefit.

To calculate the social return on public investment, we calculated the difference between the expected net benefit to society for the with-ATP scenario and the expected net benefit to society for the without-ATP scenario for each year:

$$IENB_t = ENB^{W}_{t} - ENB^{WO}_{t} \qquad (2.12)$$

where $IENB_t$ is the incremental expected net benefit in year t, ENB^{W}_{t} is the with-ATP expected benefit in year t, and ENB^{WO}_{t} is the

without-ATP expected net benefit in year t. We used the annual values of $IENB_t$ to calculate the social return on public investment.

All the data in our model are expressed in constant (1996) dollars. We adjusted any data that were denominated in pre-1996 dollars by applying either the consumer price index (CPI) or, for medical expenses, the medical care component of the CPI.[9]

2.6.2 Choosing Measures of Economic Return

NPV and IRR are appropriate choices for measuring public- and private-sector research because they have been widely used to evaluate public-sector research and are also commonly used in the private sector.

NPV and IRR are appropriate choices for measuring the net benefits of ATP projects because they have been widely used to evaluate public-sector research and can provide comparable estimates. They are also commonly used in the private sector to estimate the potential benefits of alternative investment projects.

NPV provides the most straightforward method for evaluating the economic impact of a project. NPV is

$$NPV = \sum_{t=1}^{n} \frac{NB_t}{(1+r)^t} \qquad (2.13)$$

where NB_t is the net benefit (benefit minus cost) in year t, n is the number of years over which benefits or costs accrue, and r is a prespecified discount rate. An NPV greater than zero indicates that the discounted value of the benefits of investing the technology is greater than the discounted value of the costs. Although NPV is the most correct measure of the economic value of a project, it does not allow for comparisons across projects of different sizes.

The correct discount rate to apply to the NPV calculation is the subject of a great deal of debate, especially for cases in which some of the benefits are health related. Section 2.6.3 provides a discussion of the issues relevant to choosing a discount rate. As described below, the sensitivity of the empirical results should be tested for their sensitivity to the discount rate assumption.

The IRR is another commonly used measure of the economic benefits from an investment. The IRR is the interest rate that forces

[9]Cutler et al. (1996) assert that the medical care CPI overstates inflation in medical care costs. However, we believe that some of the shortcomings of the medical care CPI (e.g., lack of adjustment for changes in quality) are mitigated by our explicit accounting for changes in the patient's benefits from new treatment technologies.

the NPV of the project's expected net benefits to be 0. Thus, to calculate the IRR, we set Eq. (2.13) to zero and solve for r.

We considered the IRR's bias toward earlier payoff projects by calculating both a rate of return and an NPV for each project.

An IRR that refers to the costs and benefits to the company receiving ATP funding and its partners is called the private rate of return (PRR). An IRR that refers to the benefits and costs to all stakeholders is called the social rate of return (SRR). The IRR can be interpreted as a percentage yield occurring over a defined period of time. One benefit of the IRR over NPV is that it does not require selection of a discount rate. However, we do need to compare the IRR to an appropriate discount rate or to an alternative project to decide whether the project is socially desirable.

The IRR suffers from several potential shortcomings for evaluating investments in technologies. These shortcomings, which have been discussed by Tassey (1996), include its bias toward projects that provide benefits earlier in the study period and its failure to consider explicitly the reinvestment rate of interim receipts. We considered the IRR's bias toward earlier payoff projects by calculating both a rate of return and an NPV for each project.

A potential solution to the IRR's failure to consider the reinvestment rate of interim receipts is to use the "adjusted" IRR, or AIRR. The AIRR was defined by Ruegg and Marshall (1990) as the annual compound percentage yield from a project over the study period, taking into account the rate for reinvestment in interim receipts. Calculating the AIRR requires choosing a reinvestment rate. However, it may be conceptually faulty to assume that the returns from medical innovations can be reinvested. A large portion of these benefits are benefits to patients who enjoy a better quality of life than they would in the absence of these new innovations. It seems inappropriate to assume that these benefits, which are embodied in patients' well-being, can be reinvested. Thus, we chose not to calculate the AIRR.

We calculated social return on public investment and social return on investment using both NPV and PRR for each project. In addition, we calculated composite measures of NPV and IRR. We calculated the composites by summing the total expected net benefits and costs for each year for all the projects:

$$NB_t = \sum_{j=1}^{7} NB_{j,t} \qquad (2.14)$$

Because the expected net benefit is used to calculate NPV, and because all benefits and costs have been converted to constant dollars, a riskless real discount rate should be used to determine the NPV.

where j indexes the project. Then we substituted Eq. (2.14) into Eq. (2.13) to calculate the NPV and IRR for all projects taken together.

The composite NPV and IRR combine the benefits and costs from all projects. The first year of benefits or costs from any project is 1992; the final year is 2011. Thus, the composite benefits and costs occur over a 20-year time period. The composite NPV is not equal to the sum of the individual project NPVs because no single project has benefits and costs over all 20 years.

2.6.3 Choosing a Discount Rate

We consulted several sources to consider the merits of alternative discount rates. As discussed in OMB Circular A-94 and in Gold et al. (1996), OMB recommends discounting all costs and benefits in a cost-benefit analysis at the real rate of 7 percent, which, according to OMB Circular A-94, "approximates the marginal pretax rate of return on an average investment in the private sector in recent years" (p. 9).

However, for discounting costs to government (e.g., in a cost-effectiveness analysis) OMB recommends using "the real treasury borrowing rate on marketable securities of comparable maturity to the period of analysis." The rates most recently published by OMB for this purpose range from 2.1 percent for 3-year projects to 2.8 percent for 30-year projects. Their rationale for using this rate for a cost-effectiveness analysis is that these analyses seek to find the lowest-cost way for government to achieve some predesignated objective.

The basic difference between these two OMB recommendations relates to risk. The 7 percent assumption was developed by OMB as an average rate that theoretically combines the riskless rate, which they recommend for discounting costs to society in cost-effectiveness analysis, with a risk-adjusted rate, which is normally used to discount private investments that have high opportunity costs and high risks. Thus, if we did not adjust private costs for risk

(if we were discounting a stream of uncertain costs and benefits), we might want to use the 7 percent recommended by OMB.

However, the Panel on Cost Effectiveness in Health and Medicine has examined OMB's recommendations, as well as the recommendations of scores of empirical and theoretical researchers in health benefits analysis, and has recommended the following:

- ➤ first convert all uncertain costs and benefits into "certainty equivalents," expressed in real terms, and
- ➤ discount at a selected riskless real discount rate (Gold et al., 1996).

Assuming risk neutrality, the certainty equivalent is equal to the real expected net benefits, which we have calculated by multiplying the real net benefits by the probability of technical success.

Risk neutrality is a common assumption when quantifying medical benefits (Gold et al., 1996). It is convenient operationally because it implies that the certainty equivalent of benefits is equal to the expected value. This implies that patients are indifferent between two events with the same expected value. We do not know the actual risk preferences of the patients affected by these technologies. Because we did not have the resources necessary to explore the risk preferences of the specific populations of interest in this study, we followed the conventional practice and assumed risk neutrality.

The riskless rate recommended by the Panel on Cost Effectiveness in Health and Medicine is 3 percent (Gold et al., 1996). This is based on the recommendations of a number of researchers, including Viscusi (1995).

The Panel also recommends the following:

- ➤ discounting costs and benefits at the same rate and
- ➤ conducting sensitivity analysis at 5 percent because many other studies have used 5 percent as their base case.

In our analysis of ATP projects in tissue engineering, we followed the Panel's recommendations. We

- ➤ assumed risk neutrality and developed the certainty equivalent by multiplying the net returns by the probability of success,

- discounted costs and benefits at the same rate,
- discounted social and private returns at the same rate (since they have been risk-adjusted),
- used the 3 percent discount rate, and
- conducted sensitivity analysis for discount rates of 1 and 5 percent.

2.6.4 Conducting Sensitivity Analysis

Because many of the variables in a model of the returns on investment in ATP-funded medical technologies are measured with considerable uncertainty, it is important to test the sensitivity of our results to specific parameter values. Sensitivity analysis can be conducted in a variety of ways. The results can simply be calculated for a range of values for each of the parameters of interest. Alternatively, Monte Carlo simulation, using a program such as @RISK, allows the analyst to incorporate measures of uncertainty of the parameters to generate the probability distribution functions for the results.

We tested our results with respect to changes in the following parameters:

- discount rate,
- per-patient treatment costs and QALYs,
- probability of technical success,
- commercialization cost parameters,
- R&D cost parameters,
- production cost parameters, and
- product price.

Appendix B contains the results of these sensitivity analyses.

2.7 METHODOLOGICAL CHALLENGES AND LIMITATIONS

Implementing the methodology described in this report is challenging. Analysts face a number of difficulties regarding modeling and data collection in each of the implementation steps.

2.7.1 Characterizing New and Defender Technologies

A significant challenge is choosing the applications to study. Choosing to analyze the most immediate and probable application is the most practical approach and probably provides the most reliable data. However, ignoring the later applications probably underestimates the project's benefits.

Existing or prospective studies of project spillovers may provide a general guideline for forecasting the return on investment from later applications of ATP-funded technologies.

A potential approach to this problem may be to draw from existing or prospective studies of project spillovers. An empirical analysis of trends in the return on investment in the application of an enabling technology as it ages may provide a general guideline for forecasting the return on investment for later applications. For example, a retrospective study of the medical applications resulting from the discovery of imaging technology might show that the return on investment in each application rise at first, then decline as the enabling technology ages and is replaced by a new discovery.

Until this type of information is available, the best approach to capturing return on investment from future applications in the absence of data is to describe the applications qualitatively, as we have for the seven tissue engineering projects. A discussion of their potential returns in relation to the application that is studied can also provide some perspective on the potential unmeasured returns. For example, we studied the tumor imaging application of the discovery of a new molecule. While tumor imaging is the most likely commercial success in the short run, the potential of this molecule to assist in discouraging tumor growth has potential implications that go far beyond its potential as a diagnostic tool.

2.7.2 Modeling Medical Benefits

The most challenging task in modeling medical benefits is quantifying the benefits of new technologies to patients. The methodology described in this report uses QALYs to measure the change in a patient's welfare due to changes in their health status. However, this method is limited by the insensitivity of QALYs to small or short-term changes in a patient's health status. This prevented us from calculating the full health benefits of some technologies.

QALY measures are not sensitive enough to capture small or short-term changes in health states. Although the WTP method provides a comprehensive and theoretically consistent alternative, it is also the most difficult to implement.

The alternative is to collect WTP estimates for each change in health status. Although WTP provides the most comprehensive and theoretically consistent measure of the value of health outcomes, it is also the most difficult and expensive to implement. In the absence of WTP estimates of the value of utility losses associated with each of the outcomes relevant to the applications of our technologies, we would need to collect primary data from individuals to assess their WTP values. This approach is often not an option given the time and resources available for a study. Its use must be dictated by the importance of the most accurate health benefits information, given the other limitations of the analysis.

2.7.3 Forecasting Market Penetration

While the Bass model is a generally accepted model for forecasting the diffusion of new technologies, it has one important drawback for studying ATP-funded enabling technologies. The cumulative number of adopters predicted by the Bass model is strictly increasing over time. Yet the market penetration of technologies may fall after it peaks as new technologies emerge and consumer needs and tastes change. Thus, a diffusion model is needed that accounts for the future emergence of technologies that will replace the ATP-funded technology. One way to think of such a model is that it actually forecasts the diffusion of two technologies: the ATP-funded technology and its replacement. Clearly, knowledge of these potential replacements would be limited. It would be helpful to develop data about the likely pattern of obsolescence of ATP-funded technologies.

2.7.4 Estimating Company Costs and Revenues

Estimating company costs and revenues requires information about the expected costs of R&D, production, and commercialization. This information is extremely difficult to collect. Many of these projects are years from commercialization, and many of the companies will license these technologies rather than produce and market them. Even if companies can provide estimates of these costs, they may not because they are concerned about the confidentiality of data such as product price and production costs. Although industry balance sheets and other secondary data can be used to develop assumptions about these costs, these assumptions may be misleading because they do not account for the specific

circumstances of each company. Furthermore, the biotechnology industry is very young. As the industry matures and becomes more profitable, the ratios between sales and these costs will probably change.

It may be useful to refine our techniques for interviewing company representatives to improve our estimates of these costs. For example, if the company produces other products, we may be able to infer some information about costs for developing the ATP technology from the history of the development of other products. Similarly, we may be able to consider the historical costs of commercialization and production of an existing product that uses a current process technology and serves similar markets.

2.7.5 Calculating Social and Private Returns

Constructing a without-ATP scenario is the most challenging task in calculating social and private returns. Because the without-ATP case is the counterfactual, we must rely on the company's conjectures about what they might have done in the absence of an ATP grant and on a model that predicts the results of that behavior. Better information about how companies respond to such funding could improve our models and our estimates of the without-ATP scenario.

3 Tissue Engineering Case Studies

One of the objectives of this project was to illustrate the methodology described in Chapter 2 by applying it to seven ATP-funded projects in tissue engineering. Another objective was to estimate the social return on public investment in the seven ATP projects chosen for the case studies. This chapter describes in detail how we applied the methodology described in Chapter 2 to each of the seven case studies. It also reports the results of the analysis and discusses the limitations of each case study. Finally, we offer conclusions about the suitability of the methodology, the expected social and private return on investment in tissue engineering technologies, and the role of ATP in improving those returns.

3.1 CASE STUDY APPLICATIONS

ATP asked RTI to apply the methodology described in Chapter 1 to a single application of each of seven multiple-application tissue engineering projects funded from 1990 to 1996. Chapter 1 briefly describes these seven projects, and Table 1-1 provides summary information.

At the request of the ATP staff, we spent a greater share of our effort and resources modeling and collecting data for the first four projects listed in Table 1-1. ATP based their selection of these in-depth case studies on the likelihood that key data would be available either from the companies or from other sources. For these projects, we used a more detailed medical benefits modeling strategy, spent more time searching for secondary data in the

medical literature, and collected more data for the diffusion forecasts.

We consulted a number of sources for data and information, including

- ➤ interviews with company representatives,
- ➤ ATP proposals and progress reports,
- ➤ interviews with physicians,
- ➤ medical databases and journals, and
- ➤ publicly available company and industry information.

Sources of medical outcome and cost data are listed in Table 3-1.

Table 3-1. Sources of Outcome and Cost Data

ATP Project	Source of Outcome Data	Source of Cost Data
Stem Cell Expansion	Boogaerts and Demuynck (1994) Champlin (1996) Faucher et al. (1994) Hillner, Smith, and Desch (1993)	Boogaerts and Demuynck (1994) Champlin (1996) Faucher et al. (1994) Hillner, Smith, and Desch (1993)
Biopolymers for Tissue Repair	Sinisaari et al. (1996) Rokkanen et al. (1996)	AHCPR (1996) Böstman (1994) Levin and Condit (1996) Shaw and Lawton (1995) Tiel-van Buul et al. (1995)
Living Implantable Microreactors	Eastman et al. (1993) DCCTRG (1996) DCCTRG (1995)	AHCPR (1996) Eastman et al. (1993) Ray et al. (1996) DCCTRG (1996) DCCTRG (1995)
Proliferated Human Islets	Eastman et al. (1993) DCCTRG (1996) DCCTRG (1995)	AHCPR (1996) Eastman et al. (1993) Ray et al. (1996) DCCTRG (1996) DCCTRG (1995)
Biomaterials for Clinical Prosthesis	Vangsness et al. (1995) Harner et al. (1996) Jackson, Corsetti, and Simon (1996) Mohtadi (1993) Marks and Mohtadi (1996)	None
Gene Therapy Applications	Kosary et al. (1995) Buccheri and Ferrigno (1995)	Virgo et al. (1996)
Universal Donor Organs	Evans (1993) UNOS (1996) UNOS (1997)	Evans (1993) Votapka et al. (1995) AHCPR (1996)

Some of the information we used in our model was taken from confidential sources such as company interviews and reports. To honor our confidentiality agreement with these companies, we do not discuss this information.

3.1.1 Human Stem Cell and Hematopoietic Expansion Systems

Aastrom Biosciences Inc.'s ATP project is developing a CPS to be used in stem cell therapy to make the collection of stem cells easier and more convenient to the donor or patient. Stem cell therapy is often used to enable cancer patients to endure high-dose or multicycle chemotherapy or radiation therapy. The stem cells are removed from the patient prior to the therapy and replaced afterwards to restore the patient's hematopoietic system. Table 3-2 summarizes the assumptions of our analysis of this project.

Timeline of R&D Costs and Benefits

Our model assumes that the relevant time horizon for this project is 1992 to 2009. The 2-year R&D period begins in 1992. Aastrom Biosciences expects that its CPS will enter the market in 2000. Thus, the commercialization phase begins in 1994 and ends in 1999. The production phase lasts 10 years, beginning in 2000 and ending in 2009.

Aastrom estimates that ATP funding accelerated the project by 1 to 2 years. Using the conservative estimate of 1 year of acceleration, the without-ATP scenario includes an R&D phase that lasts 3, rather than 2, years. The commercialization phase begins in 1995 and the production phase begins in 2001. However, because the window of market opportunity ends in 2009, the production phase in the without-ATP scenario is only 9 years.

Impact of ATP on Social Returns

ATP funding accelerated this project by 1-year and increased the probability of technical success by 9 percent.

ATP awarded Aastrom $1,220,000 in matching funds. Aside from the 1-year acceleration effect discussed above, ATP funding also affected the expected probability of success for this project. Recall that the change in the probability of technical success due to ATP funding depends on how ATP funding affects the total spending in

Table 3-2. Model Assumptions for "Human Stem Cell and Hematopoietic Expansion Systems"

Timeline of Costs and Benefits	With ATP	Without ATP
Year 1 of R&D phase	1992	1992
Year 1 of commercialization phase	1994	1995
Year 1 of production phase[a]	2000	2001
Final year of market window	2009	2009
Impact of ATP		
ATP matching funds	$1,220,000	
Acceleration	1 year	
Probability of success		
Elasticity of marginal benefits curve	-0.5	
Total project R&D	$2,734,000 with ATP; $2,034,520 without ATP	
Probability of success	9 percent higher in the with-ATP scenario	
Scope effects	None reported	
Medical Benefits Per Patient		
Application	Stem cell harvest and transplant, especially as used in high-dose chemotherapy and radiation	
Defender technology	PBPC collection	
Patient population	Patients undergoing stem cell harvest and transplant in the U.S.	
Differences in health outcomes (Not quantified)	➤ Reduces the probability of reintroducing tumor cells in some patients ➤ Reduces donor time and discomfort ➤ Eliminates mobilization drugs and their side effects	
Number of Beneficiaries	665 in 2000; 17,251 by 2009 (See Table 3-3)	
Changes in Health Care Costs	Will reduce the number of care episodes, procedure time, and needle sticks required to harvest a sufficient quantity of stem cells. The cost of CPS equipment and consumables will partially offset these savings	
Private Company Costs and Benefits		
Private spending in R&D phase	$1,514,000 with ATP; $2,034,520 without ATP	
Commercialization cost	37 percent of revenue	
Production cost	42 percent of revenue	

[a]RTI's estimate is based on company projections of time required for clinical trials. This estimate applies only to the U.S. market.

the R&D phase. This depends on the elasticity of the marginal benefits function. Our conversations with Aastrom officials indicated that although ATP funding was important to the project Aastrom would have proceeded with the project even in the absence of ATP funding. Thus, we assume that the marginal benefits function was relatively inelastic, with an elasticity of -0.5. Using this elasticity and Eq. (2.2), we estimate that in the absence of ATP funding total spending in the R&D phase would have totaled $2,034,520, rather than $2,734,000, which was spent in the with-ATP scenario. Applying this change in spending to Eq. (2.3), we estimate a 9 percent increase in the probability of technical success in the with-ATP scenario over the without-ATP scenario.

Aastrom reported no impact on the scope of the project. However, Aastrom did indicate that the ATP funding helped position them to obtain other sources of funding. This "halo effect" of ATP funding may have affected Aastrom's cost of capital, their total R&D spending, and the probability of technical success. We did not explicitly quantify this effect; thus, we have probably underestimated the impact of ATP on the benefits of this technology.

Medical Benefits to Patients

Application. The Aastrom CPS will be used to culture and grow bone marrow cells to be used for transplant. In the future, the CPS may be used to grow other cell types, potentially useful in various therapies, such as human gene therapy and adjuvant therapy for T-cell-related disorders like AIDS. However, its most immediate application—that examined for this study—is to transplant bone marrow cells.

We compared the costs and benefits of using the Aastrom CPS to those of using PBPC.

Defender Technology. Aastrom officials told us that the currently preferred method for harvesting stem cells is peripheral blood progenitor cell collection (PBPC), which has replaced traditional bone marrow harvest because it is less costly and painful.

Under PBPC, the patient is given drug injections to encourage the mobilization of stem cells from the bone marrow into the peripheral blood over a week or more. The mobilized cells are then collected by connecting the patient to an apheresis device via

intravenous needles or a surgically placed catheter. The patient's or donor's blood cells are collected, and the therapeutic volume of stem and progenitor cells is separated from it. Then the blood is returned to the patient. The donor must undergo this procedure for 2 to 3 days, for 4 to 6 hours per day.[1] Researchers are trying to reduce the amount of time required for this procedure to a single protracted session. Specialized laboratory testing is conducted on each day of the procedure to determine whether a sufficient quantity of the desired cells has been collected.

Differences in Health Outcomes. Using the CPS will be considerably simpler for the donor than using PBPC. In a brief outpatient procedure, the donor will receive a local anesthetic, and a small aspirate of bone marrow will be taken from the hip. No drugs or procedures will be required to prepare the patient for this procedure prior to the time of the aspirate.

In addition, the CPS method is considerably simpler for the donor than PBPC. Rather than undergoing a series of apheresis sessions preceded by drug therapy for cell mobilization, the patient will receive a local anesthetic, and a single aspirate of bone marrow will be taken from the hip.

We did not explicitly model differences in long-term health outcomes between the CPS and PBPC. Aastrom officials indicated that if the Aastrom CPS is technically successful (e.g., the cells produced in an Aastrom CPS engraft as quickly as the cells collected by PBPC), patients' long-term health outcomes will be similar. However, they did mention two factors that may affect a small portion of patients using the CPS rather than PBPC:

- ➤ reduced probability that cancerous cells will be extracted with the stem cells and reintroduced to the patient and
- ➤ elimination of the drugs used to mobilize stem cells under the PBPC procedure.

[1] *JNCI News* indicates that the procedure requires two to four sessions of 3 to 5 hours each. Physicians we interviewed indicated that there is a trend toward fewer, longer procedures.

The acute illness and injury model probably underestimates the benefits to patients of the Aastrom CPS compared to the PBPC method.

The acute illness and injury model probably underestimates the benefits to patients of the Aastrom CPS compared to the PBPC method. We were not able to explicitly incorporate the benefits of either CPS' potential health effects or its impact on patient convenience and comfort into our model. Empirical data on the changes in health risk are not available; furthermore, QALYs are not sensitive enough to quantify the impact of differences in pain or discomfort for short periods of time. However, we did explain these factors to physicians who provided diffusion estimates. The physicians confirmed that these factors will probably not have significant consequences on the health outcomes of most patients, although they may influence the popularity of the method with physicians and therefore the diffusion rate.

Number of Beneficiaries

Patients receiving autologous or allogeneic stem cell transplants in the U.S. are eligible to benefit from this technology. In 1996, this population totaled 12,000 according to the International Bone Marrow Transplant (IBMT) registry (1997). According to Aastrom, this number will grow as high-dose chemotherapy and radiation therapy become more popular treatments for the relevant forms of cancer. If we use the current rate of increase as cited by the IBMT (1997) registry, this number will increase to 16,000 by the year 2000 and to 25,000 by the year 2009.

Our market penetration model predicts that Aastrom's CPS will be used for 665 patients in its first year. Its market will grow to 17,251 by 2009.

Table 3-3 shows the expected total number of eligible patients from 2000 to 2009. It also shows the results of our analysis of the expected market penetration of the Aastrom CPS. We need the market penetration estimation methodology described in Section 2.3.2 to calculate the estimates in Table 3-3. We interviewed three physicians to obtain input for the diffusion model. Appendix A provides their names and affiliations, the clinical profile we used to inform them about the technology, the interview guide, and the raw data we collected.

Using the data we collected from the experts, we estimated the Bass diffusion model according to the procedures described in Section 2.3.2. The Bass model provided the parameter estimates for the forecast equation (Eq. [2.7]). We used these parameters to estimate the number of patients who will be treated using the CPS for each year in the production phase.

Table 3-3. Expected Market Penetration of Aastrom's CPS

Year	Eligible Patients	Number Using CPS	
		With ATP	Without ATP
2000	16,000	665	0
2001	17,000	1,060	665
2002	18,000	1,674	1,060
2003	19,000	2,606	1,674
2004	20,000	3,976	2,606
2005	21,000	5,890	3,976
2006	22,000	8,384	5,890
2007	23,000	11,334	8,384
2008	24,000	14,424	11,334
2009	25,000	17,251	14,424

Changes in Health Care Costs

Publicly available information from Aastrom indicates that the CPS will reduce the resources required to harvest stem cells. Aastrom officials and physicians we interviewed verified that the cost of PBPC is between $12,000 and $20,000; we used the midpoint, $16,000, in our comparison of the cost of PBPC and the procedure using CPS. The cost of CPS equipment and consumables will partially but not completely offset these savings. Aastrom's estimate of these costs is confidential information.

Estimating Private Return on Investment

R&D Costs. Aastrom's contribution to the cost of the ATP project was $1,514,000. As explained above, we estimate that in the absence of ATP funding Aastrom would have spent $2,034,520 on this project.

Commercialization and Production Costs. Aastrom could not provide an estimate of the costs of commercialization or production of their CPS instruments and consumables. Thus, we used data from the biotechnology industry described in Chapter 2 to assume

that commercialization costs would be 37 percent of total revenue and that production costs would be 42 percent of revenue.

Summary

Our model assumes that the Aastrom CPS will enter the U.S. market in 2000, following a 6-year commercialization phase and a 2-year R&D phase. In the absence of ATP funding, Aastrom estimates product introduction would be delayed by 1 year. ATP funding also led to an increase in the total R&D spent on the project, increasing the probability of technical success by 9 percent.

If it is technically successful, the Aastrom CPS will replace the PBPC method for patients undergoing stem cell harvest and transplant. This technology will reduce the discomfort associated with the procedure, may reduce the probability of reintroducing tumor cells to some patients, and may reduce the risks of some side effects. This treatment will also be less expensive than the average cost of PBPC. Because we were not able to quantify the medical benefits of this technology, our analysis of the medical benefits focused on the reduction in cost.

Based on physician interviews and model forecast, we expect that the Aastrom CPS will be used to treat over 600 patients in its first year of production and over 17,000 patients in 2009.

Aastrom and its partners in commercialization and production will incur commercialization and production costs, which we assume will be 37 percent and 42 percent of total revenue, respectively.

Our analysis probably underestimates the benefits of this application of Aastrom's technology. We were not able quantify the benefits of the following factors:

- ➤ possible decreases in the probability of reintroducing cancer into some patients,
- ➤ the benefit to the patient of reducing the inconvenience and discomfort of the procedure, and
- ➤ the potential benefits of eliminating mobilization drugs.

In addition, we only considered the U.S. population in estimating the number of patients who will benefit from this technology. The European market will probably lead to greater revenues for Aastrom and its partners.

3.1.2 Structurally New Biopolymers Derived from Alpha-L Amino Acids

Integra LifeSciences Corporation received ATP funding to develop a novel synthetic polymer technology to create a cache of new bioabsorbable polymers for use in biomedical implants. Integra will develop the resulting new polymers into prototype orthopedic devices in collaboration with the Hospital for Joint Diseases. Table 3-4 summarizes the assumptions of our analysis of this project.

Timeline of R&D Costs and Benefits

Our model assumes the relevant time horizon for this project is 1994 to 2009. Integra LifeSciences begins its 3-year ATP project in 1994; the R&D phase is 1994 through 1996. Integra expects that its bioabsorbable fracture fixation materials will enter the market in 2000. Thus, the commercialization phase begins in 1997 and ends in 1999. The production phase lasts 10 years, beginning in 2000 and ending in 2009.

Integra estimates that ATP funding accelerated the project by at least 10 years. In our model, the R&D phase in the without-ATP scenario lasts 13, rather than 3, years. The commercialization phase begins in 2007. In the absence of ATP funding, the production phase would not have begun until after the market window had closed. Thus, we assume that without ATP this product would never enter the production phase.

Impact of ATP on Social Returns

ATP funding accelerated this project by 10 years, increased the probability of technical success by 171 percent, and expanded the scope of the project.

ATP awarded Integra $1,999,000 in matching funds. Aside from the 10-year acceleration effect discussed above, ATP funding also affected the expected probability of technical success for this project. Our conversations with Integra officials indicated that ATP funding was crucial to the success of this project. Although Integra would have pursued the technology even in the absence of ATP funds, they would have funded the project at a much lower annual rate. Other projects would have taken prominence. Thus, we assume that their marginal benefits function was relatively elastic, with an elasticity of -2. Using this elasticity and Eq. (2.2), we estimate that in the absence of ATP funding total spending in the R&D phase would have totaled $89,124 rather than $2,468,000,

Table 3-4. Model Assumptions for "Structurally New Biopolymers Derived from Alpha-L Amino Acids"

Timeline of Costs and Benefits	With ATP	Without ATP
Year 1 of R&D phase	1994	1994
Year 1 of commercialization phase	1997	2007
Year 1 of production phase	2000	N/A
Final year of market window	2009	N/A
Impact of ATP		
ATP matching funds	$1,999,000	
Acceleration	At least 10 years	
Probability of success		
Elasticity of marginal benefits curve	-2	
Total project R&D	$2,468,000 with ATP; $89,124 without ATP	
Probability of success	171 percent higher in the with-ATP scenario	
Scope effects	Significant but not quantified	
Medical Benefits Per Patient		
Application	Bioabsorbable fracture fixation devices (pins, screws, rods, plates)	
Defender technology	Metal fixation devices	
Patient population	Patients with nonweight-bearing fractures of the shoulder, elbow, wrist, hand, knee, and ankle	
Differences in health outcomes (Not quantified)	➤ Reduces stress shielding and secondary fractures due to screw holes ➤ Eliminates removal surgery ➤ Reduces potential for tissue abrasion or device loosening and migration	
Number of Beneficiaries	8,173 in 2000; 34,889 by 2009 (See Table 3-6)	
Changes in Health Care Costs	Eliminates need for second surgery in some patients, but material costs are higher.	
Private Company Costs and Benefits		
Private spending in R&D phase	$469,000 with ATP; $89,124 without ATP	
Commercialization cost	37 percent of revenue	
Production cost	42 percent of revenue	

which was spent in the with-ATP scenario. Applying this change in spending to Eq. (2.3), we estimate a 171 percent increase in the probability of technical success in the with-ATP scenario over the without-ATP scenario.

Integra reported that ATP funding also affected the scope of the project. The funding allowed Integra to attract talented scientists who will explore the technology's applications in a number of areas other than fracture fixation, including additional orthopedic applications such as dental and maxillofacial fixation devices and weight-bearing plates, screws, and rods. These applications would open the technology to a greater number of orthopedic patients.

Although we did not quantify the impact of ATP on the project's scope, this had no impact on our results. In the without-ATP scenario, production is delayed by 10 years; thus, the model attributes 100 percent of the net benefits of this project to ATP funding. The scope effects do not create any additional differences between the with-ATP and the without-ATP scenarios.

Medical Benefits to Patients

Integra representatives stress that the early applications of this technology are only a small fraction of the potential uses of this product.

Application. This platform technology has broad applications in orthopedics (fracture fixation, cartilage and ligament repair); wound care; cardiovascular repair; and drug delivery. However, in the near term, Integra is focusing on the orthopedic fracture fixation market to demonstrate the material's properties and generate revenue. The first fracture fixation applications—those examined for this study—will be nonweight-bearing pins and screws to repair fractures of the shoulder, elbow, wrist, hand, knee, and ankle.

Defender Technology. Because current bioabsorbable fixation devices have not achieved widespread acceptance to date, the defender technology remains metal fixation devices such as pins, rods, plates, and screws. These devices are surgically placed after reduction of the fracture to maintain alignment and provide stability for the fracture segments. A small proportion of these devices (10 percent at Integra's estimate) are later removed at a second surgery after complete healing.[2] Removal is most common in the ankle area where the threat of abrasion is highest because of the

[2]Our interviews with physicians indicate that the removal rate is much higher in children. Our model analyzes the adult and pediatric markets separately.

limited soft tissue coverage in this region. Stress shielding is also a significant concern and motivator for removal. Regions that are more difficult to access surgically are least likely for secondary device removal. Depending on fracture location, metal fixation devices can also have an adverse effect on the growth and maturity of bones in children; thus, the use of bioabsorbable devices may have special merit in children.

Although Integra believes their new material will improve fracture healing compared to metal fracture fixation devices, there are currently no human clinical trial data to quantify these impacts.

Differences in Health Outcomes. We were not able to model any differences in health outcomes between Integra's technology and the defender technology. Although Integra believes their new material will improve fracture healing compared to metal fracture fixation devices, there are currently no human clinical trial data to quantify these impacts. One recent study compared metal fixation devices to currently available bioabsorbable devices using several randomized trials (Böstman, 1996). This study found no significant difference between the ultimate results of treating these fractures with currently available (not Integra's) bioabsorbable fixation devices and metallic fixation devices. However, these results are not directly relevant to Integra's product, because Integra's material is different than the material used in currently available bioabsorbable devices.

Integra has developed data indicating that compared to currently available bioabsorbable fixation devices the Integra devices reduce the infection rate. However, these data are not relevant to our model because we are comparing the Integra devices to metallic devices.

We were able to quantify what will probably be the most important impact of this material in this application: the economic benefits of eliminating removal surgery. This surgery is often performed when metal pins and screws are used, especially when the patient is a child. As explained below, we used the acute illness and injury model to quantify differences in the health care costs of treating a fracture using conventional metal fixation devices and Integra's fixation devices, including the elimination of the second surgery. While some risk and discomfort to the patient are probably associated with the second surgery, we were not able to capture these effects.

Number of Beneficiaries

We divided the patient population into two groups—adults and children—because the impact of Integra's fracture fixation devices will be different for these two groups. Because removal surgery is more common in children, elimination of this surgery will affect these populations differently. Thus, it was important to model the market penetration of Integra's technology separately for children and adults.

Table 3-5 shows the expected number of adult and child patients who incur the type of injuries we are considering in this model. Table 3-6 shows the total number of eligible patients and the expected number of patients to be treated with the Integra product in the with-ATP and without-ATP scenarios. We developed these estimates of market penetration using the methodology explained in Section 2.3.2. We interviewed three physicians to obtain input for the diffusion model. Using these data, we estimated the Bass diffusion model and used the forecast equation (Eq. [2.7]) to determine the expected number of patients treated with the Integra materials for each year in the production phase for each population.

Changes in Health Care Costs

Table 3-7 lists the costs of procedures and materials relevant to our analysis of the impact of Integra's technology on health care costs. We obtained data regarding the hospital charges for most of the procedures of interest from the HCUP-3 Nationwide Inpatient Sample for 1992 Hospital Inpatient Stays (AHCPR, 1996). We inflated these charges to 1996 prices using the CPI index for medical care from the Statistical Abstract and used the standard hospital cost-to-charge ratio of 0.5 to determine costs. To estimate the charges for some removal surgeries we used the ratio of removal surgery costs to initial surgery costs for each procedure given in Böstman (1996).

To calculate the average per-patient change in cost, we considered the difference in the removal rates for the two therapies. According to the physicians we interviewed, metal fixation devices require removal surgery in 90 percent of the procedures performed on

Table 3-5. Number of Patients with Injuries Repairable with Integra's Fracture Fixation Materials

Injury Type	Number of Patients		Annual Change
	Adult[a,b]	Child[a,b]	
Shoulder or elbow	1,350	825	None
Wrist and hand	18,000	9,300	None
Knee	11,700	9,000	None
Ankle	9,000	14,800	None
Total	40,050	33,825	None

[a]Company and physician interviews
[b]National Hospital Discharge Survey (1994)

Table 3-6. Number of Patients Treated with Integra's Bioabsorbable Fracture Fixation Products

Year	Eligible Patients	Number Using Integra Product	
		With ATP	Without ATP
2000	73,875	8,173	0
2001	73,875	13,286	0
2002	73,875	20,007	0
2003	73,875	26,980	0
2004	73,875	31,977	0
2005	73,875	34,158	0
2006	73,875	34,744	0
2007	73,875	34,863	0
2008	73,875	34,885	0
2009	73,875	34,889	0

Table 3-7. Costs of Materials and Procedures for Fracture Fixation

Procedure	Cost	Source
Surgery to insert metal pins and screws		
Shoulder or elbow	$3,738	AHCPR (1996)
Wrist and hand	$3,620	AHCPR (1996)
Knee	$9,066	AHCPR (1996)
Ankle	$4,990	AHCPR (1996)
Surgery to remove metal pins and screws		
Shoulder or elbow	$852	Böstman (1996)
Wrist and hand	$1,148	Böstman (1996)
Knee	$2,176	Böstman (1996)
Ankle	$1,018	AHCPR (1996)
Metal pins and screws	$10	Physician interview

children and 10 percent of the procedures performed on adults. Based on conversations with physicians, we estimate that the removal rate for both children and adults may be about 1 percent using Integra's bioabsorbable devices. Thus, to calculate the average cost of treatment using the new and old technologies, we took a weighted average of the total procedure cost, including materials, and, when required, removal surgery. The average reduction in per-patient costs is $691.

Estimating Private Return on Investment

R&D Costs. Integra's contribution to the cost of the ATP project was $469,000. As explained above, we estimate that in the absence of ATP funding Integra would have spent $89,124 on this project.

Commercialization and Production Costs. Integra could not provide an estimate of the costs of commercialization or production of their fracture fixation products. Thus, we used data from the biotechnology industry described in Chapter 2 to assume that commercialization costs would be 37 percent of total revenue and that production costs would be 42 percent of revenue.

Summary

Our model assumes that Integra's bioabsorbable fracture fixation products will enter the U.S. market in 2000, following a 3-year commercialization phase and a 3-year R&D phase. In the absence of ATP funding, Integra estimates that the R&D phase would have been extended by at least 10 years. ATP funding also led to an increase in the total R&D spent on the project, increasing the probability of technical success by 171 percent.

Assuming technical success, Integra's materials will replace metal pins and screws for fracture fixation in patients with fractures to the shoulder, elbow, wrist, knee, and ankle. Using these bioabsorbable implants will eliminate the surgery that is required in many cases to remove metal pins and screws. Although this technology may also have significant effects on healing of these fractures, we were not able to quantify these effects.

Based on physician interviews and the diffusion model forecast, we expect that these materials will be used to treat over 8,000 patients

in the first year of production and almost 35,000 patients in 2009. The average per-patient cost of treating these fractures will fall by $691 (in 1996 dollars).

Integra will receive revenue from sales of its bioabsorbable fracture fixation products. Its costs include the R&D costs associated with the ATP project and commercialization and production costs, which we assume will be 37 percent and 42 percent of total revenue, respectively.

This model is limited by its failure to consider other applications of this technology and its failure to account for health effects.

The main limitation of this model is that it considers only the very first application of Integra's technology. Integra expects that other orthopedic applications, including additional orthopedic applications, wound care, cardiovascular repair, and drug delivery, will follow soon after this initial application.

The second limitation of this model is its failure to account for any differences in health outcomes between Integra's bioabsorbable fixation devices and metal fixation devices. Although no data currently support the estimation of these benefits, these data may become available as Integra proceeds with its animal models and human trials. At that time, it would be helpful to add health effects to this model.

3.1.3 Disease Treatment Using Living Implantable Microreactors

BioHybrid Technologies, Inc., is developing the capability to implant specific cells into the human body that produce hormones or other bioactive agents that the patient cannot produce or is not producing in sufficient quantity. BioHybrid's approach is to encase the transplanted cells in microspheres to isolate them from the immune system. These "microreactors" have pores large enough to permit glucose; nutrients; electrolytes; oxygen; and relatively small bioactive species, like insulin, to pass but are small enough to block the larger immunocytes and other relatively large molecules involved in transplant rejection. Isolating the implanted cells from the immune system opens up the possibility of using cells from sources other than the recipient, for treatment of diseases such as diabetes. Table 3-8 summarizes the assumptions of our analysis of the project.

Table 3-8. Model Assumptions for "Disease Treatment Using Living Implantable Microreactors"

Timeline of Costs and Benefits	With ATP	Without ATP
Year 1 of R&D phase	1994	1994
Year 1 of commercialization phase	1997	1999
Year 1 of production phase	2000	2002
Final year of market window	2009	2009
Impact of ATP		
ATP matching funds	$4,263,000	
Acceleration	2 years	
Probability of success		
Elasticity of marginal benefits curve	-0.5	
Total project R&D	$8,525,000 with ATP; $6,027,730 without ATP	
Probability of success	11 percent higher in the with-ATP scenario	
Scope effects	None reported	
Medical Benefits Per Patient		
Application	Diabetes	
Defender technology	Daily insulin injections	
Patient population	All Type I diabetics; insulin-dependent Type II diabetics	
Differences in health outcomes	Reduces the probability of retinopathy, nephropathy, and neuropathy as noted in the Diabetes Control and Complication Trial (DCCT) study (DCCTRG, 1996)	
Number of Beneficiaries	65,498 in 2000; 1,171,047 by 2009 (See Table 3-11)	
Changes in Health Care Costs	Annual procedure costs increase but costs of treating health effects of diabetes fall	
Private Company Costs and Benefits		
Private spending in R&D phase	$4,262,000 with ATP; $6,027,730 without ATP	
Commercialization cost	37 percent of revenue	
Production cost	42 percent of revenue	

Timeline of R&D Costs and Benefits

In our model, the relevant time horizon for this project is 1994 to 2009. BioHybrid's 3-year ATP project begins in 1994; the R&D phase is 1994 through 1997. (BioHybrid has recently been approved for a 2-year no cost project extension.) BioHybrid expects that its product will enter the U.S. market in 2000. Thus, the commercialization phase begins in 1997 and ends in 1999.

The production phase lasts 10 years, beginning in 2000 and ending in 2009.

BioHybrid estimates that ATP funding accelerated the project by 2 years. In our model, the R&D phase in the without-ATP scenario lasts 4, rather than 2, years; the commercialization phase begins in 1999 and the production phase begins in 2002. However, because the window of market opportunity ends in 2009, the production phase in the without-ATP scenario is only 8 years.

Impact of ATP on Social Returns

ATP awarded BioHybrid $4,263,000 in matching funds. Aside from the 2 years of project acceleration discussed above, ATP funding also increased the expected probability of technical success for this project. We discussed the impacts of ATP funding with BioHybrid officials who indicated that although ATP funding was important to securing private funding on the project BioHybrid would have proceeded with the project even in the absence of ATP funding. Thus, we assume that the marginal benefits function was relatively inelastic, with an elasticity of –0.5. Using this elasticity and Eq. (2.2), we estimate that in the absence of ATP funding total spending in the R&D phase would have totaled $6,027,730, rather than $8,525,000, which was spent in the with-ATP scenario. Applying this change in spending to Eq. (2.3), we estimate an 11 percent increase in the probability of technical success in the with-ATP scenario compared to the without-ATP scenario.

ATP funding helped BioHybrid attract the private-sector funding needed for the ATP match and the additional funding needed to bring the product to market.

BioHybrid reported no impact on the scope of the project; however, they did indicate that the ATP funding helped attract the private-sector funding for the ATP match and the additional funding that will be required to bring the product to market. This "halo effect" of ATP funding may have affected BioHybrid's cost of capital, their total R&D spending, and their probability of technical success. We did not explicitly quantify this effect; thus, we have probably underestimated the impact of ATP on the benefits of this technology.

Medical Benefits to Patients

Application. BioHybrid's technology has the potential to be applied to a number of therapeutic applications, including

hemophilia, Parkinson's disease, Alzheimer's disease, and hepatic failure. However, the most immediate application—the one considered for this study—is for diabetic patients who are unable to produce insulin to control blood glucose.

BioHybrid's technology will replace daily insulin injections in diabetic patients.

Defender Technology. This technology would be used in place of multiple daily insulin injections.

Differences in Health Outcomes. To receive the BioHybrid implants, patients will undergo an outpatient procedure under local anesthetic. Encapsulated islet cells will be injected into the peritoneal cavity under ultrasound control. Because the transplanted islet cells have a finite life, the patient will receive an injection once or twice a year. The dose and frequency of treatment have not yet been finalized but will be determined during the planned clinical trials.

If successful, the transplants will allow patients to achieve close to normal glycemic control, virtually eliminating many of the risks of long-term complications of diabetes, including retinopathy, nephropathy, and renal disease. To quantify the impact of these health impacts, we used the chronic disease model described in Chapter 2. We found much of the data required for the model in the results of a carefully controlled study of intensive insulin therapy on the long-term health outcomes of diabetic patients, the Diabetes Control and Complication Trial (DCCT). This study demonstrated that intensive insulin therapy would lead to tight glycemic control (DCCTRG, 1993; DCCTRG, 1995; DCCTRG, 1996). BioHybrid believes that the control provided by its technology will be at least as effective as intense insulin therapy. Thus, if BioHybrid is technically successful, our estimates of the long-term health impacts of its technology are conservative.

We examined the technology's impact on the three primary complications of diabetes: retinopathy, nephropathy, and neuropathy.

Health States. Our model includes three diseases—retinopathy, nephropathy, and neuropathy—which are the primary health complications of diabetes. For each of these diseases, a series of health states describes the seriousness of the disease. The DCCT defined these health states (DCCTRG, 1993). They are listed in Table 3-9.

Each of the health states is associated with a QALY and a cost. The cost includes the personnel, drug, equipment, and establishment

Table 3-9. Annual Health States, QALYs, and Cost for the Diabetes Model

	Cost	QALY
Retinopathy Model		
No retinopathy	$0	1.00
Background retinopathy	$0	1.00
Proliferative retinopathy	$0	1.00
Macular edema	$0	1.00
Blindness	$1,911	0.69
Nephropathy Model		
Normoalbuminuria	$0	1.00
Microalbuminuria	$0	1.00
Albuminuria	$0	1.00
End-stage renal disease (ESRD)	$46,207	0.61
Neuropathy Model		
No neuropathy	$0	1.00
Neuropathy	$0	1.00
Lower extremity amputation	$31,225	0.80

Source: DCCTG (1993, 1995, 1996).

cost of treating these disease states. The cost and QALY estimates listed in Table 3-9 were based on those reported by the DCCT study (DCCTRG, 1993; DCCTRG, 1995; DCCTRG, 1996). Note that no estimates are provided for intermediate health states.

Transition Probabilities. The transition probabilities indicate the probability of moving from one health state in one year to another health state in the next year. We developed the transition probabilities for nephropathy, neuropathy, and retinopathy based on the DCCT study (DCCTRG, 1993; DCCTRG, 1995; DCCTRG, 1996). The transition probability matrixes for the three models are found in Table 3-10.

Switching Probabilities. At the end of each year, part of the patient cohort will be switched from the defender technology to the new technology. The market diffusion forecast provides these switching probabilities.

Table 3-10. Transition Matrixes for the Diabetes Model: Conventional Treatment

	No Retinopathy	Background Retinopathy[a]	Proliferative Retinopathy[a]	Macular Edema	Blindness
No retinopathy	1 – P1	P1 = f(α=2.4862, β=0.008)			
Background retinopathy		1 – P2	P2 = f(α=1.8976, β = 0.004)		
Proliferative retinopathy			0.96	0.03	0.01
Macular edema				0.97	0.03
Blindness					1

	Normo-albuminuria	Micro-albuminuria	Albuminuria	ESRD	Death
Normoalbuminuria	1 – P1 – P2				P2 = 1.2 * disease-free mortality rate
Microalbuminuria		0.94 – P3	0.06		P3 = 1.4 * disease-free mortality rate
Albuminuria			0.95 – P4	0.05	P4 = 1.7 * disease-free mortality rate
ESRD				1 – P5	P5 = Age-specific ESRD mortality rate
Death					1

	No Neuropathy	Neuropathy	Lower Extremity Amputation
No neuropathy	0.98	0.02	
Neuropathy		0.99	0.01
Lower extremity amputation			1

[a]These entries represent the probability of moving between health state i and health state j as a function of α and β. The function is as follows:

$$P = 1 - \frac{e^{-\beta t^{\alpha}}}{e^{-\beta(t-1)^{\alpha}}}$$

Table 3-10. Transition Matrixes for the Diabetes Model: New Treatment (continued)

	No Retinopathy	Background Retinopathy[a]	Proliferative Retinopathy[a]	Macular Edema	Blindness
No retinopathy	1 – P1	P1 = f(α=1.487, β=0.018)			
Background retinopathy		1 – P2	P2 = f(α=1.651, β = 0.007)		
Proliferative retinopathy			0.97	0.02	0.01
Macular edema				0.97	0.03
Blindness					1

	Normo-albuminuria	Micro-albuminuria	Albuminuria	ESRD	Death
Normoalbuminuria	1 – P1 – P2				P2 = 1.2 * disease-free mortality rate
Microalbuminuria		0.94 – P3	0.06		P3 = 1.4 * disease-free mortality rate
Albuminuria			0.95 – P4	0.05	P4 = 1.7 * disease-free mortality rate
ESRD				1 – P5	P5 = Age-specific ESRD mortality rate
Death					1

	No Neuropathy	Neuropathy	Lower Extremity Amputation
No neuropathy	0.99	0.01	
Neuropathy		0.99	0.01
Lower extremity amputation			1

[a]These entries represent the probability of moving between health state i and health state j as a function of α and β. The function is as follows:

$$P = 1 - \frac{e^{-\beta t^{\alpha}}}{e^{-\beta(t-1)^{\alpha}}}$$

Number of Beneficiaries

Although there are many undiagnosed diabetics in the U.S., we do not include them in our patient cohort because they will not be treated.

The relevant patient population is Type I and insulin-dependent Type II diabetics because they depend on daily insulin injections. As shown in Table 3-11, there will be approximately 2,044,550 diagnosed insulin-dependent diabetics in the U.S. in 2000. Our model follows the progression of this cohort of diabetics from the time the new technology is introduced (2000) through the end of their lives.

Table 3-11. Expected Market Penetration for BioHybrid's Diabetes Treatment

		Number Using BioHybrid Technology	
Year	Eligible Patients[a]	With ATP	Without ATP
2000	2,044,550	65,498	0
2001	2,044,550	110,468	0
2002	2,044,550	183,271	65,498
2003	2,044,550	295,888	110,468
2004	2,044,550	457,310	183,271
2005	2,044,550	661,608	295,888
2006	2,044,550	874,437	457,310
2007	2,044,550	1,041,811	661,608
2008	2,044,550	1,134,485	874,437
2009	2,044,550	1,171,047	1,041,811

[a]Total eligible patients from ADA web site (1996) and Adams and Marano (1995). These numbers have been adjusted for the expected number of new diagnoses and deaths from 1996 to 2000.

Table 3-11 also shows the results of our analysis of the expected market penetration of BioHybrid's encapsulation technology. We developed these estimates of market penetration using the methodology explained in Section 2.3.2. We interviewed three physicians to obtain input for the diffusion model.

Using these data, we estimated the Bass diffusion model and the forecast equation (Eq. [2.7]) to determine the expected number of patients receiving BioHybrid's technology for each year in the production phase.

Changes in Health Care Costs

Each of the health states in the model is associated with an annual cost. The difference between the cost of treating a patient using daily insulin injections and BioHybrid's technology depends on both the cost of treatment (daily insulin injections or BioHybrid implants) and the cost of treating the complications of diabetes, which are defined by the health states shown in Table 3-9. As noted earlier, the cost estimates listed in Table 3-9 are based on those reported by the DCCT study (DCCTRG, 1993; DCCTRG, 1995; DCCTRG, 1996). The per-patient lifetime increase in health care costs is $42,996.

Estimating Private Return on Investment

R&D Costs. BioHybrid's contribution to the cost of the ATP project was $4,262,000. As explained above, we estimate that in the absence of ATP funding BioHybrid would have spent $6,027,730 on this project.

Commercialization and Production Costs. BioHybrid could not provide an estimate of the costs of commercialization or production. Thus, we used data from the biotechnology industry described in Chapter 2 to assume that commercialization costs would be 37 percent of total revenue and that production costs would be 42 percent of revenue.

Summary

Our model examines the costs and benefits of the development of BioHybrid's diabetes treatment technology from 1994 to 2009. In the with-ATP scenario, the R&D phase lasts 3 years, the commercialization phase lasts 3 years, and the production phase lasts 10 years. In the without-ATP scenario, the R&D phase lasts 5 years, and the production phase lasts only 8 years.

ATP funding accelerated the R&D phase of the project by 2 years, increased the level of total R&D spending by about $2.5 million and increased the probability of technical success by 11 percent.

BioHybrid's technology will be used in the treatment of diabetes in lieu of daily insulin injections. The treatment, if technically successful, will provide glycemic control at least as effective as that studied in the DCCT. Thus, we used data from that study to model the health impacts of this technology.

Based on the predictions of the experts we interviewed and our market diffusion model, we expect that in its first year of production, this technology will be used to treat over 65,000 patients; by 2009, it will be used to treat over one million diabetics annually. Although the costs of treating diabetes will rise, the costs of treating its complications will fall as the complications are reduced by the treatment.

In the with-ATP scenario, BioHybrid invests $4,262,000 in R&D for this project; our model predicts that without the ATP grant they would have invested over $6 million. Our model assumes that BioHybrid and its partners in commercialization and production will spend about 37 percent and 42 percent of revenue on commercialization and production, respectively.

This model does not take into account the following factors:

- patients diagnosed after 2000 whom we did not include in the fixed patient cohort;
- the change in quality of life for the patient from eliminating insulin injections;
- the improved health outcomes that may occur over and above what was found in the DCCT; and
- other health effects associated with diabetes that were not modeled by the DCCT, such as cardiovascular effects.

In addition, we could not find estimates of QALYs or costs for the intermediate health states of diabetes (see Table 3-9). The DCCT only estimates costs and QALYs for the end-stage diseases. Because these end-stage conditions occur late in life, most of the benefits of the diabetes model occur late in a patient's life. Consequently, the benefits are sensitive to the discount rate, especially because costs occur in each year, while benefits occur late in life.

3.1.4 Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules

VivoRx, Inc., is developing a new treatment for diabetes that will consist of transplanting human islets that have been encapsulated in immunoprotective membrane consisting of a novel material. This material protects the cells from the host's immune response. This technology has potential applications for liver disease, thyroid

VivoRx has tested the effectiveness of its diabetes treatment using islet cells from human cadaver pancreata. The success of these tests has encouraged VivoRx to take the next step in making this treatment widely available: providing proliferated human islets for transplant.

disease, Parkinson's disease, and Alzheimer's disease. However, the most immediate application—that examined for this study—is for the treatment of diabetes. It will eliminate the need for daily insulin injections and will enable patients to achieve tight glycemic control, reducing the risk of the common complications of diabetes.

The objective of VivoRx's ATP project is to make this therapy widely available by producing a source of human islet cells. VivoRx is developing the culture conditions and methods for proliferating human islets. They are simultaneously perfecting the polymers and biomaterials that are required to achieve immunoprotection and biocompatibility for the encapsulation technology. Table 3-12 summarizes the assumptions of our analysis of the project.

Timeline of R&D Costs and Benefits

The relevant time horizon for this project is 1995 to 2008.

In our model, the relevant time horizon for this project is 1995 to 2008. VivoRx's 3-year ATP project begins in 1995; the R&D phase of this project is 1995 through 1997. VivoRx expects that its product will enter the market in 1999. Thus, the commercialization phase occurs in 1998. The production phase lasts 10 years, beginning in 1999 and ending in 2008.

VivoRx estimates that ATP funding accelerated the project by 3 to 5 years. Using the median of this range (4 years), the R&D phase in the without-ATP scenario lasts 7, rather than 3, years. The commercialization phase occurs in 2002 and the production phase begins in 2003. The window of market opportunity is fixed; the production period in the without-ATP scenario lasts only 6 years.

Impact of ATP on Social Returns

ATP awarded VivoRx $2,000,000 in matching funds. Aside from the acceleration effect discussed above, we modeled how ATP funding affected the expected probability of technical success for this project. We asked VivoRx officials about how they would have proceeded in the absence of ATP funding. They indicated that although ATP funding was important to securing private funding on the project VivoRx would have proceeded with the project even in the absence

Table 3-12. Model Assumptions for "Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules"

Timeline of Costs and Benefits	With ATP	Without ATP
Year 1 of R&D phase	1995	1995
Year 1 of commercialization phase	1998	2002
Year 1 of production phase	1999	2003
Final year of market window	2008	2008
Impact of ATP		
ATP matching funds	$2,000,000	
Acceleration	4 years	
Probability of success		
Elasticity of marginal benefits curve	-0.5	
Total project R&D	$16,925,000 with ATP; $15,893,570 without ATP	
Probability of success	2 percent higher in the with-ATP scenario	
Scope effects	None reported	
Medical Benefits Per Patient		
Application	Diabetes	
Defender technology	Daily insulin injections	
Patient population	All Type I diabetics; insulin-dependent Type II diabetics	
Differences in health outcomes	As noted in the DCCT study (DCCTRG, 1996), about 0.6 QALY per patient over their lifetime	
Number of Beneficiaries	63,711 in 1999; 1,007,470 by 2008	
Changes in Health Care Costs	Annual procedure costs increase but costs of treating health effects of diabetes fall	
Private Company Costs and Benefits		
Private spending in R&D phase	$14,925,000 with ATP; $15,893,570 without ATP	
Commercialization cost	37 percent of revenue	
Production cost	42 percent of revenue	

of ATP funding. Thus, we assume that the marginal benefits function was relatively inelastic, with an elasticity of –0.5. Using this elasticity and Eq. (2.2), we estimate that in the absence of ATP funding total spending in the R&D phase would have totaled $15,893,570, rather than $16,925,000, which was spent in the with-ATP scenario. Applying this change in spending to Eq. (2.3), we

estimate a 2 percent increase in the probability of technical success in the with-ATP scenario compared to the without-ATP scenario.

Medical Benefits to Patients

Application. Although the proliferation of human islet cells will lead to advances in the treatment of many diseases, the most immediate application—that considered for this study—is to replace daily insulin injections in diabetic patients.

Defender Technology. This technology would be used in place of multiple daily insulin injections.

Differences in Health Outcomes. The application will involve an outpatient procedure and a local anesthetic. Proliferated, encapsulated human islet cells are injected into the peritoneal cavity. The procedure will be repeated once per year or perhaps once every 2 years to replenish the cells. The dose and frequency of treatment have not yet been finalized but will be determined during the current Phase I/Phase II trials.

If successful, the procedure will allow patients to achieve close to normal glycemic control, virtually eliminating many of the risks of long-term complications of diabetes, including retinopathy, nephropathy, and renal disease. Because the expected long-term health effects and the patient population are the same as for BioHybrid's technology, we used the same model and data to quantify the health impacts of this technology. VivoRx officials noted that it is appropriate to use the long-term health impacts reported in the DCCT to analyze the benefits of VivoRx's technology. Thus, the health states, the QALYs and costs associated with them, and the transition probabilities required for the model are the same as those used for the BioHybrid project. We derived the switching probabilities for each year from the market penetration analysis discussed below.

Number of Beneficiaries

The relevant patient population is Type I and insulin-dependent Type II diabetics. As shown in Table 3-13, there will be approximately 1,955,000 diagnosed insulin-dependent diabetics in the U.S. in 1999. Our model follows the progression of this cohort of diabetics from 1999 through the end of their lives.

Table 3-13 shows the expected total number of patients eligible to receive this treatment from 1999 to 2008. It also shows the results of our analysis of the expected market penetration of the VivoRx diabetes treatment. We developed these estimates of market penetration using the methodology explained in Section 2.3.2. We interviewed three physicians to obtain input for the diffusion model. Using these data, we estimated the Bass diffusion model and the forecast equation (Eq. [2.7]) to determine the expected number of patients receiving VivoRx's technology for each year in the production period.

Table 3-13. Expected Market Penetration for the VivoRx Diabetes Treatment Technology

		Number Using VivoRx Technology	
Year	Eligible Patients	With ATP	Without ATP
1999	1,955,000	63,711	0
2000	1,955,000	122,647	0
2001	1,955,000	202,286	0
2002	1,955,000	305,295	0
2003	1,955,000	430,677	63,711
2004	1,955,000	571,339	122,647
2005	1,955,000	713,520	202,286
2006	1,955,000	840,452	305,295
2007	1,955,000	939,509	430,677
2008	1,955,000	1,007,470	571,339

Changes in Health Care Costs

Each of the health states is associated with an annual cost. The difference between the cost of treating a patient using daily insulin injections and VivoRx's technology depends on both the cost of treatment (daily insulin injections or VivoRx implants) and the cost of treating the complications of diabetes, which are defined by the health states shown in Table 3-9. The cost estimates listed in Table 3-9 are based on those reported by the DCCT study

(DCCTRG, 1993; DCCTRG, 1995; DCCTRG, 1996). The per-patient lifetime increase in health care costs is $129,627.

Estimating Private Return on Investment

R&D Costs. VivoRx's contribution to the cost of the ATP project was $14,925,000. As explained above, we estimate that in the absence of ATP funding VivoRx's investment costs would have risen to $15,893,570; however, the total R&D funding would have fallen.

Commercialization and Production Costs. We used data from the biotechnology industry described in Chapter 2 to assume that commercialization costs would be 37 percent of total revenue and that production costs would be 42 percent of revenue.

Summary

Our model examines the costs and benefits of developing VivoRx's diabetes treatment technology from 1995 to 2008. In the with-ATP scenario, the R&D phase lasts 3 years, the commercialization phase lasts 1 year, and the production phase lasts 10 years. In the without-ATP scenario, the R&D phase lasts 7 years, and the production phase lasts only 6 years.

ATP funding accelerated the R&D phase of the project by 4 years, increased the level of total R&D spending by over $1 million, and increased the probability of technical success by 2 percent.

VivoRx's technology will be used in the treatment of diabetes in lieu of daily insulin injections. The treatment, if technically successful, will provide glycemic control at least as effective as that studied in the DCCT. Thus, we used data from that study to model the health impacts of this technology.

Based on the predictions of the experts we interviewed and our market diffusion model, we expect that in its first year of production, this technology will be used to treat over 63,000 patients. By 2008, it will be used to treat over one million diabetics annually. Although the costs of treating diabetes will rise, the costs of treating its complications will fall as the complications are reduced by the treatment.

In the with-ATP scenario, VivoRx invests $14,925,000 in R&D; our model predicts that without the ATP grant they would have invested

almost $16 million. Our model assumes that VivoRx and its partners in commercialization and production will spend about 37 percent and 42 percent of revenue on commercialization and production, respectively.

Because we used the same health benefits model for VivoRx's technology as we did for BioHybrid's, our estimates suffer from the same limitations, including the failure to consider

- patients diagnosed after 1999 whom we did not include in the fixed patient cohort;
- the change in quality of the patient's life from eliminating insulin injections;
- the improved health outcomes that may occur over and above what was found in the DCCT;
- other health effects associated with diabetes, such as cardiovascular effects; and
- the differences in cost on health effects of intermediate stages of each disease.

In addition, we did not consider the potential interaction between the VivoRx technology and the BioHybrid technology. Instead, we analyzed each technology in the absence of the other. If both technologies are technically successful, they may compete for market share. It is difficult to forecast how this competition might affect private and social returns.

3.1.5 Fabrication of Clinical Prosthesis from Biomaterials

The objective of Tissue Engineering's ATP project was to further the development of its new class of biomaterials. These biomaterials can be developed into prostheses that provide templates that mobilize the body's own cells and induce them to rebuild lost tissue, gradually replacing the prosthesis itself. With ATP funding, Tissue Engineering furthered the development of its basic ADMAT, or animal derived extracellular matrix. It can produce ADMAT in a variety of forms, has characterized the necessary properties of the ADMAT substrate to promote cell growth and differentiation, has characterized ADMAT for immunogenicity, and has developed cell banks to support five types of proposed cell-incorporating prostheses. Table 3-14 summarizes the assumptions of our analysis of the project.

Table 3-14. Model Assumptions for "Fabrication of Clinical Prostheses from Biomaterials"

Timeline of Costs and Benefits	With ATP	Without ATP
Year 1 of R&D phase	1993	1993
Year 1 of commercialization phase	1996	1998
Year 1 of production phase	2001	2003
Final year of market window	2010	2010
Impact of ATP		
ATP matching funds	$1,999,000	
Acceleration	2 years	
Probability of success		
Elasticity of marginal benefits curve	-0.01	
Total Project R&D	$4,127,000 with ATP; $4,099,750 without ATP	
Probability of success	1 percent higher in the with-ATP scenario	
Scope effects	None reported	
Medical Benefits Per Patient		
Application	Repair of the anterior cruciate ligament (ACL)	
Defender technology	Allogeneic banked tissue or autologous graft from patella tendon	
Patient population	Patients undergoing surgery for ACL repair	
Differences in health outcomes (Not quantified)	May reduce failure rates associated with both allogeneic banked tissue and autologous graft, risk of contamination associated with allogeneic tissue, and reduce morbidity compared to autologous graft	
Number of Beneficiaries	9,000 in 2001; 71,773 by 2010 (See Table 3-15)	
Changes in Health Care Costs	None	
Private Company Costs and Benefits		
Private spending in R&D phase	$2,128,000 with ATP; $4,099,750 without ATP	
Commercialization cost	37 percent of revenue	
Production cost	42 percent of revenue	

Timeline of R&D Costs and Benefits

Our model traces the benefits and costs of Tissue Engineering's ATP project from 1993 to 2010. The ATP project begins in 1993; the R&D phase of this project is 1993 to 1995. Tissue Engineering expects that its product will enter the U.S. market in 2001. Thus, the commercialization phase begins in 1996 and ends in 2000.

The production phase lasts 10 years, beginning in 2001 and ending in 2010.

Tissue Engineering estimates that ATP funding accelerated the project by 2 years. The R&D phase in the without-ATP scenario lasts 5, rather than 3, years. The commercialization phase begins in 1998 and the production phase begins in 2003. However, the window of market opportunity is fixed; the production period is 2 years shorter in the without-ATP scenario.

Impact of ATP on Social Returns

ATP awarded Tissue Engineering $1,999,000 in matching funds. Aside from the acceleration effect discussed above, ATP funding also had a very small impact on the probability of technical success for this project. We asked Tissue Engineering officials about how they would have proceeded in the absence of ATP funding. They indicated that the absence of ATP funding would have made no difference in their funding decisions. Thus, we assume that their marginal benefits function was very inelastic, with an elasticity of –0.01. Using this elasticity and Eq. (2.2), we determined that in the absence of ATP funding, total spending in the R&D phase would have totaled $4,099,750, rather than $4,127,000, which was spent in the with-ATP scenario. This results in a 1 percent increase in the probability of technical success in the with-ATP scenario compared to the without-ATP scenario.

Tissue Engineering reported no impact on the scope of the project; however, they did indicate that the ATP funding was important for peer recognition of their work.

Medical Benefits to Patients

ADMAT can be used for vascular grafts, ligament and tendon repair, and periodontal and similar reconstruction.

Application. ADMAT can be used to enhance collagen scaffolds for vascular grafts, ligaments, tendons, periodontal tissue, and similar reconstructions. ADMAT alone can be used as a matrix on which "glandular" cells such as insulin-producing cells, nerve cell precursors, thyroid cells, and others can grow and function. At the time of our survey, a likely early commercial application was thought to be reconstruction of ligaments, tendons, and articular cartilage. A specific sub-class of those therapies is the application

of ADMAT to repair the anterior cruciate ligament (ACL), which is the application modeled for this project.

Defender Technology. Two technologies are currently in use for surgical repair of the ACL: graft from cadaver tissue and autologous graft from the patient's patella tendon or hamstring. Many patients do not undergo surgical repair.

Differences in Health Outcomes. ACL repair currently suffers from a number of problems. Cadaver tissue is limited and carries a risk of viral infection. Autologous grafts often cause graft site morbidity, which may limit the patient's use of the area from which the graft was taken.

We spoke with several doctors who specialize in ACL repair and reviewed many papers on ACL repair procedures. These sources indicated that eliminating the risk of viral infection and graft site morbidity in patients undergoing ACL repair would certainly increase a patient's quality of life. Currently, a QALY instrument developed by Dr. Nicholas G.H. Mohtadi at the University of Calgary is being tested to determine the relative quality of life of patients before and after ACL surgery (Mohtadi, 1993). This research, which is being conducted by Dr. Mohtadi and his colleague Dr. P.H. Marks at the University of Toronto, will provide significant insight into the potential health benefits of eliminating complications of ACL repair (Marks and Mohtadi, 1996).

Until these estimates are available, we have only qualitative data to determine the potential gain from removing the complications of ACL surgery. Based on our conversations with a number of physicians, we assume that with the new technology a person would gain 0.025 QALY points per year (e.g., their QALYs would change from 0.90 to 0.925). For a person who lives 40 years past the time of surgery, this translates into 0.58 additional QALYs using a 3 percent discount rate.

Number of Beneficiaries

The patient population for Tissue Engineering's technology consists of the patients undergoing surgery for ACL repair. Jack Parr, of Wright Medical, a firm partnering with Tissue Engineering in marketing this application, estimated this population at 100,000 annually.

Table 3-15 shows the expected total number of patients eligible to receive this treatment from 2001 to 2010. It also shows the results of our analysis of the expected market penetration of the Tissue Engineering technology. We developed these estimates of market penetration using the methodology explained in Section 2.3.2. Because this was not one of our in-depth case studies, we obtained input for the diffusion model from one expert, a representative from Wright Medical.

Table 3-15. Expected Market Penetration for the Tissue Engineering's ADMAT Material for Repairing the ACL

		Number Using ADMAT	
Year	Eligible Patients	With ATP	Without ATP
2000	100,000	9,000	0
2001	100,000	19,493	0
2002	100,000	30,293	9,000
2003	100,000	40,629	19,493
2004	100,000	49,780	30,293
2005	100,000	57,277	40,629
2006	100,000	62,996	49,780
2007	100,000	67,102	57,277
2008	100,000	69,914	62,996
2009	100,000	71,773	67,102

Using these data, we estimated the Bass diffusion model and the forecast equation (Eq. [2.7]) to determine the expected number of patients receiving Tissue Engineering's technology for each year in the production period.

Changes in Health Care Costs

The additional cost of the ADMAT material will be outweighed by the savings resulting from eliminating the costs of obtaining the graft from a cadaver or from the patient's patella tendon.

We assume that the cost of repairing an ACL with the material provided by Tissue Engineering would be the same as current methods. Although the new technology requires the purchase of the ADMAT material developed by Tissue Engineering, other costs associated with the defender technology, such as obtaining the graft material from a cadaver or from another site on the patient, will be eliminated. According to a representative of Wright

Medical, these savings will at least outweigh the cost of the ADMAT material. Thus, there are no changes in health care costs in this model.

Estimating Private Return on Investment

R&D Costs. Tissue Engineering's contribution to the cost of the ATP project was $2,128,000. As explained above, we estimate that in the absence of ATP funding Tissue Engineering would have spent $4,099,750 on this project.

Commercialization and Production Costs. Tissue Engineering could not provide an estimate of the costs of commercialization or production of the ADMAT material for use in repairing the ACL. Thus, we used data from the biotechnology industry described in Chapter 2 to assume that commercialization costs would be 37 percent of total revenue and that production costs would be 42 percent of revenue.

Summary

We evaluated the benefits and costs of Tissue Engineering's ATP project from 1993 to 2010. In the with-ATP scenario, the R&D phase lasts 3 years, the commercialization phase lasts 5 years, and the production phase lasts 10 years. In the without-ATP scenario, the R&D phase is 2 years longer and the production phase is 2 years shorter.

Tissue Engineering stated that ATP funding accelerated the project by 2 years but had little impact on the level of funding or the scope of the project. Based on these qualitative remarks, our model estimated a 1 percent increase in the probability of technical success due to ATP funding.

If technically successful, Tissue Engineering's ADMAT material will replace allogeneic and autologous grafts for patients undergoing surgery for ACL repair. The reduction in failure rates, reduced risk of contamination, and reduced morbidity will increase the quality of life for these patients. The cost of treating these patients will not substantially change.

Based on the predictions of a company representative and our market penetration model, we expect that ADMAT will be used to

repair the ACL in 9,000 patients in its first year to market, and about 72,000 patients in 2010.

Tissue Engineering and its partners in commercialization and production will receive revenue from the sale of ADMAT. Tissue Engineering spent 2,128,000 in R&D on the ATP project. In our model, they will incur commercialization and production costs of 37 and 42 percent of these revenues, respectively.

The primary weakness of this model is the unavailability of clinical data to verify the qualitative estimates of the impact of this technology on patients' quality of life.

3.1.6 Application of Gene Therapy to Treatment of Cardiovascular Diseases

The objective of Progenitor, Inc.'s, ATP project was to develop a supply of transplantable endothelial cells from precursor stem cells that can be genetically engineered or otherwise modified for specific medical purposes. Progenitor originally envisioned that one application target would use these cells to repair damaged vascular tissue, with the most immediate application being the treatment of damage associated with coronary angioplasty. Other potential medical application areas originally identified by Progenitor were cancer treatments and bone development.

In the course of its research, Progenitor made an important discovery that provided an opportunity to strengthen the goals and activities related to cancer treatments. Progenitor believes that eventually this discovery will lead to a new treatment for solid tumor cancers. However, its most immediate application is the diagnosis, location, and staging of soft tissue metastases. The resulting improvement in diagnostic techniques will allow for more aggressive, effective cancer therapy at an earlier stage of metastasis, improving patients' prognosis. Table 3-16 summarizes the assumptions of this analysis of the project.

Timeline of R&D Costs and Benefits

We modeled the benefits and costs of Progenitor's ATP project from 1995 to 2011. The 3-year ATP project begins in 1995; the R&D phase is 1995 to 1997. Progenitor expects that its product will enter the U.S. market in 2002. Thus, the commercialization

Table 3-16. Model Assumptions for "Application of Gene Therapy to Treatment of Cardiovascular Disease"

Timeline of Costs and Benefits	With ATP	Without ATP
Year 1 of R&D phase	1995	1995
Year 1 of commercialization phase	1998	2000
Year 1 of production phase	2002	2004
Final year of market window	2011	2011
Impact of ATP		
ATP matching funds	$1,996,000	
Acceleration	2 years	
Probability of success		
Elasticity of marginal benefits curve	-0.5	
Total project R&D	$2,795,000 with ATP; $1,494,390 without ATP	
Probability of success	20 percent higher in the with-ATP scenario	
Scope effects	Some effects reported but not quantified	
Medical Benefits Per Patient		
Application[a]	Diagnosis, location, and staging of soft tissue metastases from lung cancer[a]	
Defender technology	Standard diagnostic techniques	
Patient population	Lung cancer patients	
Differences in health outcomes	Improve diagnosis of cancer metastasis; sensitivity and selectivity of diagnosis will be at least 85%	
Number of Beneficiaries	17,350 in 2002; 124,508 by 2011 (See Table 3-17)	
Changes in Health Care Costs	Procedure will be performed in conjunction with current techniques, adding to the cost of diagnosis; extending patient's life also adds to lifetime health care costs	
Private Company Costs and Benefits		
Private spending in R&D phase	$799,000 with ATP; $1,494,390 without ATP	
Commercialization cost	37 percent of revenue	
Production cost	42 percent of revenue	

[a]The technology will apply to all tissue metastases; we examined only lung cancer metastases as an illustration of the potential benefits on a portion of the applicable patient population.

phase begins in 1998 and ends in 2001. The production phase lasts 10 years, beginning in 2002 and ending in 2011. Progenitor estimates that ATP funding accelerated the project by 2 years. The R&D phase in the without-ATP scenario lasts 5, rather than 3, years. The commercialization phase begins in 2000 and the production phase begins in 2004. However, the window of market opportunity is fixed; the production period is 2 years shorter in the without-ATP scenario.

Impact of ATP on Social Returns

ATP funding accelerated the project by 2 years, increased total R&D spending by about $1.3 million, and increased the probability of technical success by 20 percent.

ATP awarded Progenitor $1,996,000 in matching funds. Aside from the acceleration effect discussed above, ATP funding also had an important impact on the probability of technical success for this project. Progenitor indicated that in the absence of ATP funding they would have proceeded with the project, although it would have had a lower priority, resulting in lower annual funding and the delay mentioned earlier. Thus, we assume that their marginal benefits function was relatively inelastic, with an elasticity of –0.5. Using this elasticity and Eq. (2.2), we determined that in the absence of ATP funding total spending in the R&D phase would have totaled $1,494,390, rather than $2,795,000, which was spent in the with-ATP scenario. This results in a 20 percent increase in the probability of technical success in the with-ATP scenario compared to the without-ATP scenario.

Progenitor stated that the ATP funding allowed them to explore endothelial cells in greater depth than they might have otherwise been able to. However, they were not able to state specifically how this affected the scope of the project. Thus, we were not able to model these scope effects in terms of changes in the applications or patient populations.

Medical Benefits to Patients

Application. Progenitor believes that eventually this technology will lead to a new treatment for solid tumor cancers. However, its most immediate application is the diagnosis, location, and staging of soft tissue metastases. The resulting improvement in diagnostic techniques will allow for more aggressive, effective cancer therapy at an earlier stage of metastasis, improving patients' prognosis. We chose to illustrate the potential benefits of Progenitor's product by

Progenitor's first application of its discovery will be the diagnosis, location, and staging of soft tissue cancer metastases. The resulting improvement in diagnosis of these metastases will allow more effective cancer therapy.

showing its impact on the diagnosis and treatment of lung cancer. The technology will be embodied in a diagnostic kit. The kit will be used to conduct an imaging procedure that will be used in conjunction with technetium bone scans.

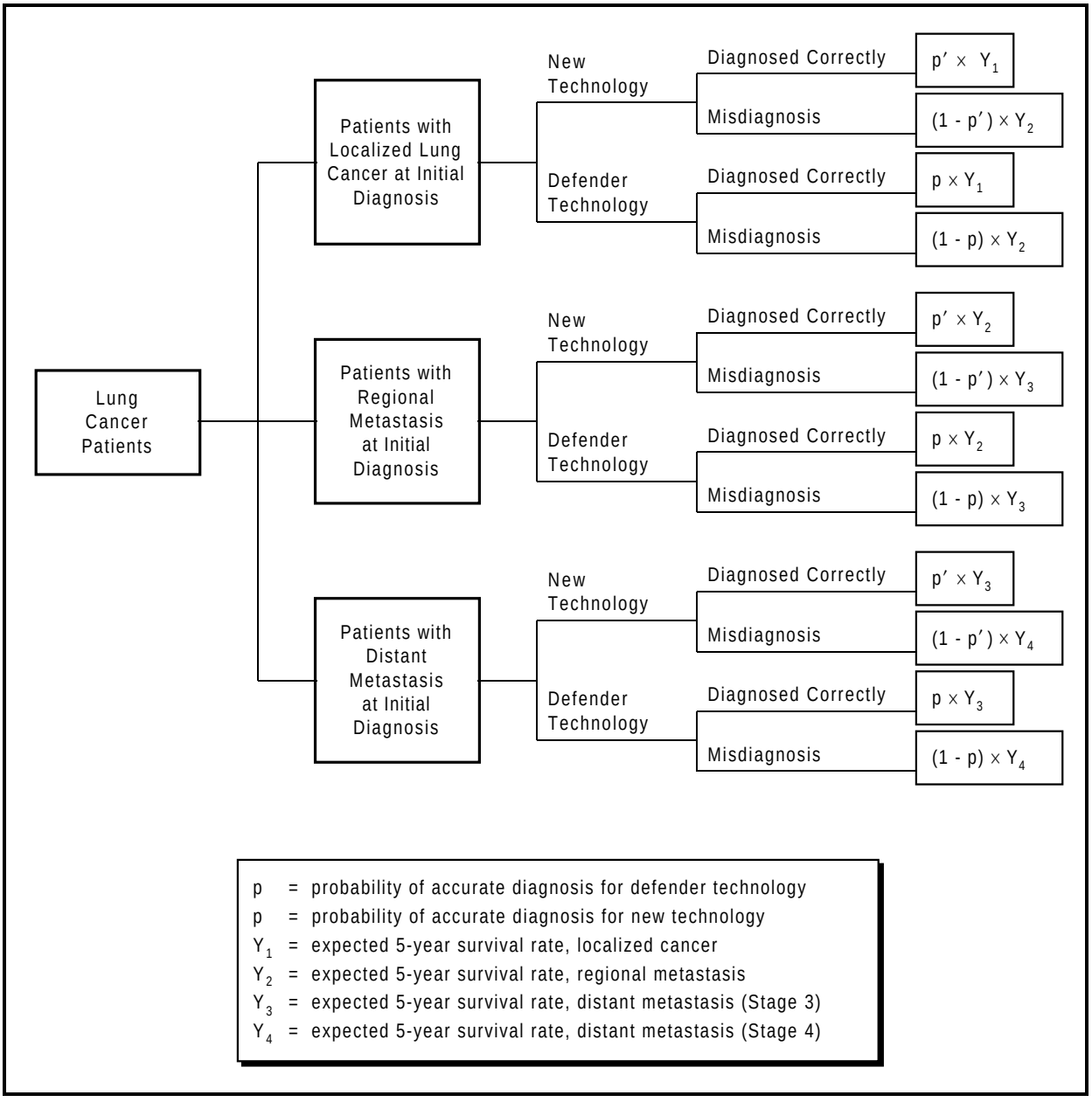
Defender Technology. Currently no technologies image soft tissue adequately to diagnose metastasis at a very early stage. Thus, Progenitor's product will not replace any current technologies but will supplement the current diagnostic techniques.

Differences in Health Outcomes. Progenitor's technology will improve the detection of metastasis once cancer has been diagnosed. We used the acute illness and injury model to develop a cancer diagnosis model to estimate the value of improved diagnosis of cancer metastasis.

Ideally, we would develop a Markov model for demonstrating the benefits of improved cancer diagnosis. In each year after being diagnosed with cancer, a patient has a probability of transitioning into another health state. The improved diagnosis provided by the Progenitor product would decrease the probability of progressing into more advanced health states because the correct diagnosis would lead to more appropriate treatment. Because the Progenitor project was not one of our in-depth case studies and because time for collecting data was limited, we opted for a simpler model, as illustrated in Figure 3-1.

The patient population includes all lung cancer patients. We allocated this population among localized, regional, and distant metastasis, using data on the incidence of different stages of cancer at diagnosis. For each stage of cancer, the defender technology provides probability, p, that the metastasis will be diagnosed correctly, while Progenitor's technology provides improved probability of correct diagnosis, p'. Metastases that are detected can be treated appropriately; left undetected, these metastases will progress to a more advanced stage before they are treated, costing the patient additional life-years. For example, if patients with regional metastasis are diagnosed correctly, we assume their 5-year survival rate is equal to Y_2, the 5-year survival rate for regional metastasis. If they are misdiagnosed, we assume their metastasis progresses, so we assigned them a 5-year survival rate for distant metastasis (Stage 3) of Y_3.

Figure 3-1. Cancer Diagnosis Model



We obtained data about the incidence of cancer, the initial allocation of patients among different stages of cancer, and expected life-years by stage of disease from *SEER Cancer Statistics Review, 1973-1992* (Kosary et al., 1995). We obtained data regarding the sensitivity of standard metastasis detection techniques (CT scans) from Buccheri and Ferrigno (1995). Progenitor provided an estimate of the expected sensitivity of their product.

Number of Beneficiaries

The patient population for this application of Progenitor's technology is all lung cancer patients. Table 3-17 shows the expected total number of patients eligible to receive this procedure from 2002 to 2011. It also shows the results of our analysis of the expected market penetration of Progenitor's product.

Table 3-17. Expected Market Penetration for Progenitor's Tumor Imaging Technology

		Number Using Progenitor's Technology	
Year	Eligible Patients	With ATP	Without ATP
2002	173,500	17,350	0
2003	174,021	43,505	0
2004	174,543	69,817	17,350
2005	175,066	87,533	43,505
2006	175,591	96,575	69,817
2007	176,118	96,865	87,533
2008	176,647	97,156	96,575
2009	177,176	97,447	96,865
2010	177,708	97,739	97,156
2011	178,241	98,033	97,447

Representatives of Progenitor were able to provide a 10-year forecast of market penetration; therefore, we did not use the Bass model to estimate market penetration for this technology. Appendix A contains the raw data we collected from company representatives.

Changes in Health Care Costs

Because Progenitor's technology will not replace a defender technology, but will augment existing diagnostic techniques, the cost of the diagnostic procedure represents an increase in the cost of treating a patient with lung cancer. In addition, some of the benefits derived from extending a patient's life are offset by the cost of caring for that person during these additional years. The per-patient increase in lifetime health care costs is about $452. We

obtained data on the average annual cost of treating lung cancer patients from Virgo et al. (1996).

Estimating Private Return on Investment

R&D Costs. Progenitor's contribution to the cost of the ATP project was $799,000. As explained above, we estimate that in the absence of ATP funding, Progenitor would have invested $1,494,390 on this project.

Commercialization and Production Costs. Progenitor could not provide an estimate of the costs of commercialization or production of its product; it plans to license the technology to another company that will conduct these activities. Thus, we used data from the biotechnology industry described in Chapter 2 to assume that commercialization costs would be 37 percent of total revenue and that production costs would be 42 percent of revenue.

Summary

We evaluated the costs and benefits of Progenitor's ATP project from 1995 to 2011. In the with-ATP scenario, the R&D phase lasts 3 years, the commercialization phase lasts 4 years, and the production phase lasts 10 years. In the without-ATP scenario, the R&D phase is 2 years longer while the production phase is 2 years shorter.

ATP funding accelerated the project by 2 years. Using our model of the impact of the cost of funding on total R&D and the probability of technical success, we estimate that ATP funding increased the total R&D effort by about $1.3 million and the probability of technical success by 20 percent.

Although this technology has a number of applications, the one examined for this case study is the diagnosis, location, and staging of soft tissue metastases from many kinds of cancer. To illustrate the potential impact of this technology on one patient population, we modeled the health benefits to lung cancer patients. By improving the diagnosis of metastasis, this technology will lead to more aggressive and effective treatment of lung cancer, improving patients' survival rate.

The procedure will add to the total cost of diagnosis because it will be performed in conjunction with currently used diagnostic techniques. Extending a patient's life also adds to the lifetime costs of their health care.

Based on Progenitor's estimates, our model assumes that Progenitor's technology will be used for over 17,000 diagnoses in its first year of production; by 2011, it will be used for over 98,000 diagnoses.

Progenitor and its partners in commercialization and production will earn revenues from the sale of diagnostic kits that will embody the Progenitor technology. Aside from R&D expenses, they will also incur commercialization and production costs, which, in our model, are 37 and 42 percent of revenue, respectively.

The accuracy of this model would be improved by using a Markov model and populating it with data regarding the probability of transitioning from one health state to the next, the cost of treating patients in each health state, and the QALYs associated with each health state. In addition, we considered only the sensitivity of diagnostic methods (the probability that a positive result is correct). We did not consider the impact of false positive diagnoses. If Progenitor's new diagnostic technique improves the specificity of cancer diagnosis, this may also contribute to social benefits to the extent that incorrect positive diagnoses lead to costly unnecessary treatment and cause patients pain and suffering. Finally, we have considered only one type of cancer; however, if successful, this product will improve diagnosis of soft tissue metastasis for many kinds of cancer.

3.1.7 Universal Donor Organs for Transplantations

The objective of Alexion Pharmaceuticals' ATP project is to develop transgenic animals that will provide a source of organs for xenogeneic transplants. In most cases, xenogeneic transplants fail because of hyperacute rejection (HAR), which causes graft failures within minutes to hours. To address this problem, Alexion is developing animals that express key human genes to eliminate the HAR response. Alexion plans to develop organs for human transplant, called UniGraft organs, from transgenic pigs. Table 3-18 summarizes the assumptions of our analysis of the project.

Table 3-18. Model Assumptions for "Universal Donor Organs for Transplantation"

Timeline of Costs and Benefits	With ATP	Without ATP
Year 1 of R&D phase	1995	1995
Year 1 of commercialization phase	1998	1999
Year 1 of production phase[a]	2002	2003
Final year of market window	2011	2011
Impact of ATP		
ATP matching funds	$1,999,000	
Acceleration	1 year	
Probability of success		
Elasticity of marginal benefits curve	-0.5	
Total project R&D	$3,203,000 with ATP; $1,963,770 without ATP	
Probability of success	16 percent higher in the with-ATP scenario	
Scope effects	None reported	
Medical Benefits Per Patient		
Application[b]	Standard heart disease treatment while awaiting transplant	
Defender technology	Heart transplants	
Patient population[a]	Patients who can benefit from a heart transplant but cannot receive one because supply is inadequate	
Differences in health outcomes	A large percentage of patients die while awaiting heart transplants; immediate availability of organs will improve survival rate because patients will not have to wait for organs; reduces deaths of patients awaiting organs	
Number of Beneficiaries	1,200 in 2002; 8,675 by 2011 (See Table 3-19)	
Changes in Health Care Costs	Recipients of UniGraft hearts incur the same costs as a human transplant recipient; annual treatment costs for transplant patients are higher; lifetime treatment costs rise due to increased life expectancy	
Private Company Costs and Benefits		
Private spending in R&D phase	$1,204,000 with ATP; $1,963,770 without ATP	
Commercialization cost	37 percent of revenue	
Production cost	42 percent of revenue	

[a]Alexion believes that ultimately the market may expand beyond traditional heart transplant candidates.
[b]UniGraft organs will be developed for hearts, kidneys, lungs, and islets. Our analysis considers heart transplants only.

Timeline of R&D Costs and Benefits

Our model assumes the relevant time horizon for this project is 1995 to 2011. Alexion's 3-year ATP project begins in 1995; the R&D phase is 1995 to 1997. Alexion expects that its product will enter the U.S. market in 2002. Thus, the commercialization phase begins in 1998 and ends in 2001. The production phase lasts 10 years, beginning in 2002 and ending in 2011.

Alexion estimates that ATP funding accelerated the project by 1 to 2 years. Using the conservative estimate of 1 year, the R&D phase in the without-ATP scenario lasts 4, rather than 3, years. The commercialization phase begins in 1999 and the production phase begins in 2003. However, the window of market opportunity is fixed; the production period is 1 year shorter in the without-ATP scenario.

Impact of ATP on Social Returns

ATP awarded Alexion $1,999,000 in matching funds. Aside from the acceleration effect discussed above, ATP funding also had an important impact on the probability of technical success for this project. Alexion representatives indicated that in the absence of ATP funding they would have proceeded with the project, although it would have progressed more slowly. Thus, we assume that their marginal benefits function was relatively inelastic, with an elasticity of –0.5. Using this elasticity and Eq. (2.2), we determined that in the absence of ATP funding total spending in the R&D phase would have totaled $1,963,770, rather than $3,203,000, which was spent in the with-ATP scenario. This results in a 16 percent increase in the probability of technical success in the with-ATP scenario compared to the without-ATP scenario.

Medical Benefits to Patients

Application. Although Alexion's technology may enable the xenogeneic transplant of hearts, kidneys, lungs, and islets, we modeled the medical and economic benefits of transplanted xenogeneic hearts only. This analysis illustrates the potential benefits of xenogeneic transplants for other organs.

Defender Technology. We assume that Alexion's UniGraft hearts will be used for patients who would otherwise not be able to obtain

a heart transplant because of a shortage of donor organs. Thus, the defender technology is standard heart disease treatment while awaiting a heart transplant.

Differences in Health Outcomes. Wider use of organ transplants could offer many patients significant improvement in the quality and duration of their lives while improving the cost-effectiveness of treatment. Patients with prolonged waiting times are at risk for end-organ deterioration, have an increased risk of transplant failure, or may die before a donor organ becomes available (Mehta et al., 1995).

To estimate the health effects of the availability of xenogeneic hearts, we examined the life expectancy of patients who are candidates for heart transplants. We assume that xenogeneic heart transplant patients will have the same survival rate as human heart transplant recipients. This is Alexion's benchmark for technical success. Therefore, the per-patient change in QALYs for patients receiving UniGraft hearts is equal to the expected life-years for heart transplant patients minus the expected life-years for patients who are treated with standard heart disease therapy but do not receive a transplant. We used data from Evans (1993) and the United Network for Organ Sharing (UNOS, 1996; 1997) to determine the change in life expectancy.

Number of Beneficiaries

We defined the patient population for this technology very conservatively. We assume that the relevant population is patients who are placed on the heart transplant waiting list maintained by the UNOS but who do not receive a heart. This definition is narrow because Alexion believes that if xenogeneic organs are available the criteria for being placed on the waiting list will be relaxed, increasing the eligible population. We chose to make a more conservative assumption because we cannot predict what these relaxed criteria might be and how many patients might qualify under them.

Table 3-19 shows the expected total number of patients eligible to receive this treatment from 2002 to 2011. It also shows the results of our analysis of the expected market penetration of UniGraft hearts. We developed these estimates of market penetration using

Table 3-19. Expected Market Penetration of UniGraft Hearts

Year	Eligible Patients[a]	Market Penetration	
		With ATP	Without ATP
2002	11,998	1,200	0
2003	11,998	2,361	1,200
2004	11,998	3,610	2,361
2005	11,998	4,852	3,610
2006	11,998	5,982	4,852
2007	11,998	6,919	5,982
2008	11,998	7,631	6,919
2009	11,998	8,132	7,631
2010	11,998	8,465	8,132
2011	11,998	8,675	8,465

[a]We used a very broad definition of heart transplant candidates that includes all patients who could benefit from a heart transplant below age 65 but cannot receive one because organs are unavailable (AHA, 1996).

The immediate availability of UniGraft organs would change the use of organ transplantation by

- eliminating long waiting times for donor organs and the associated negative medical effects,
- allowing surgeries to be scheduled optimally,
- eliminating the cost of maintaining a recipient in the hospital while awaiting a donor organ, and
- eliminating the need to keep a donor alive on life support.

the methodology explained in Section 2.3.2. Company representatives provided market penetration estimates for the first 5 years. Using these data, we estimated the Bass diffusion model and the forecast equation (Eq. [2.7]) to determine the expected number of patients receiving UniGraft hearts for each year in the production period.

Changes in Health Care Costs

We assume that the cost of a heart transplant using a xenogeneic heart will be the same as the cost of a heart transplant using a human donor. This is a very conservative assumption. Alexion believes that the availability of xenogeneic organs will decrease costs of transplants by

- eliminating the need to keep donors on life support,
- reducing hospitalization during recipient waiting time, and
- transplanting organs to recipients and scheduling surgeries more effectively.

As with the cancer diagnosis model, the improvements in life-years will be partially offset by the cost of caring for a person who has

had a transplant. We assume that the lifetime cost of treating a patient who receives a UniGraft heart is equal to their expected life-years times the annual cost of treatment after transplant, plus the cost of the transplant procedure. The lifetime treatment cost for a patient who does not receive a UniGraft heart is equal to the annual cost of treating a patient before transplant times their expected life-years. For patients who receive Unigraft hearts, lifetime health care costs rise because the expected life-years, the annual cost of treatment, and the procedure costs are all higher for UniGraft transplant patients. We used data from Votapka et al. (1995) to determine the annual cost of treating a patient before and after heart transplant. We used data from AHCPR (1996) to determine the cost of a heart transplant. The per-patient increase in lifetime health care costs is $102,661.

Estimating Private Return on Investment

R&D Costs. Alexion's contribution to the cost of the ATP project was $1,204,000. As explained above, we estimate that in the absence of ATP funding Alexion would have spent $1,963,770 on this project.

Commercialization and Production Costs. Alexion could not provide an estimate of the costs of production and commercialization. These activities will be handled by Alexion's partner in commercialization and production. Thus, we used data from the biotechnology industry described in Chapter 2 to assume that commercialization costs would be 37 percent of total revenue and that production costs would be 42 percent of revenue.

Summary

In the with-ATP scenario, Alexion's 3-year ATP project begins in 1995. The R&D phase is 3 years, the commercialization phase is 4 years, and the production phase is 10 years. In the without-ATP scenario, the R&D phase lasts 1 year longer and the production phase is 1 year shorter.

ATP funding led to a 1-year acceleration of the project. It also induced an increase in total R&D spending of over $1.2 million, leading to a 16 percent increase in the probability of technical success.

Alexion's transgeneic UniGraft organs will probably be developed for hearts, kidneys, lungs, and islets. To illustrate the potential benefits of the development of these organs, we developed a model of its impact on heart transplants. In our model, these hearts will be used for patients who are awaiting a heart transplant but cannot receive one because of a shortage of donor organs. The defender technology is the standard heart disease treatment while awaiting a donor organ. We modeled the health benefits of the availability of UniGraft organs by comparing the expected life-years of patients receiving heart transplants with those who do not.

We defined the patient population conservatively as the patients who are placed on the heart transplant waiting list but do not receive a heart. Using information from company representatives our diffusion model estimates that 1,200 patients will receive Unigraft hearts in the first year of production; 8,674 patients will receive UniGraft hearts in the year 2009.

We assume that the cost of transplanting a UniGraft heart will be the same as the cost of a human heart transplant. The annual cost of treatment for a heart patient that has received a transplant is higher than a pre-transplant patient. Furthermore, increases in life expectancy increase the lifetime treatment costs for those patients receiving UniGraft hearts.

Alexion and its partners in commercialization and production will receive revenues from the sale of UniGraft hearts and incur R&D, commercialization, and production costs. We assume that commercialization and production costs will be 37 percent and 42 percent of revenue, respectively.

This model has a number of limitations. First, it considers only heart transplants, although, if successful, Alexion may develop other organs as well. Second, the relevant population is defined conservatively, according to current guidelines for acceptance of a patient on the transplant waiting list. Finally, we assume that only patients who cannot get a human heart will be candidates for a UniGraft heart; thus, the model does not consider the potential savings from xenogeneic transplants as compared to human donor transplants.

3.2 CASE STUDY RESULTS

Each of the technologies discussed in Section 3.1 offers unique benefits to society and specific challenges to modeling their potential economic benefits. This section reports the results of our analysis of each project and discusses why they differ among the seven projects. It also discussed the limitations of each analysis.

3.2.1 Private and Social Return on Investment in ATP Tissue Engineering Projects

The composite social return on public investment represents the returns on all of the projects taken together.

Table 3-20 shows the expected social return on public investment for each of the ATP projects examined in this study and for all of the projects taken together (the composite). These projects demonstrate a wide range of NPV and SRR. As a group, they provide over $35 billion in social return on public investment and an SRR of 116 percent over 20 years. These results imply that the ATP funding invested in these projects provides an expected net benefit of over $35 billion dollars to the nation.

Table 3-20. Expected Social Return on Public Investment: ATP Tissue Engineering Projects for a Single Preliminary Application

ATP Project	Project Time Horizon	NPV (1996$ millions)	IRR (%)
Stem Cell Expansion	1992 to 2009	$47	21%
Biopolymers for Tissue Repair	1994 to 2009	$98	51%
Living Implantable Microreactors	1994 to 2009	$17,750	148%
Proliferated Human Islets	1995 to 2008	$1,297	34%
Biomaterials for Clinical Prosthesis	1993 to 2010	$15,058	128%
Gene Therapy Applications	1995 to 2011	$945	111%
Universal Donor Organs	1995 to 2011	$783	92%
Composite[a,b,c,d]	1992 to 2011	$34,258	116%

[a]The composite measure of return is based on a sum of expected benefits and costs in each year across all projects.

[b]The time period for the composite measure includes all years from all the individual project periods.

[c]The composite NPV is not a simple sum of individual NPV because the time periods are different.

[d]The composite IRR is not an average of the individual project IRRs because IRR is not additive.

Table 3-21 shows how the expected social return on public investment compares to the expected social return on investment for each project. This comparison provides a perspective on the importance of ATP funding in catalyzing the social return on investment. As demonstrated by the composite return, ATP funding is responsible for inducing about 31 percent of the total social returns from all of these projects over 20 years. For the individual projects, the effect of ATP on social returns ranges from a low of 24 percent to 100 percent of social returns.

Table 3-21. Social Return on Investment and Social Return on Public Investment: ATP Tissue Engineering Projects for a Single Preliminary Application

		Expected Social Return on Investment		Expected Social Return on Public Investment	
ATP Project	Time Horizon	NPV (1996$ millions)	IRR (%)	NPV (1996$ millions)	IRR (%)
Stem Cell Expansion	1992 to 2009	$134	20%	$47	21%
Biopolymers for Tissue Repair	1994 to 2009	$98	51%	$98	51%
Living Implantable Microreactors	1994 to 2009	$74,518	149%	$17,750	148%
Proliferated Human Islets	1995 to 2008	$2,252	36%	$1,297	34%
Biomaterials for Clinical Prosthesis	1993 to 2010	$32,855	118%	$15,058	128%
Gene Therapy Applications	1995 to 2011	$2,411	106%	$945	111%
Universal Donor Organs	1995 to 2011	$2,838	91%	$783	92%
Composite[a]	1992 to 2011	$109,229	115%	$34,258	116%

[a]See notes to Table 3-20 for an explanation of the derivation of the composite measure of return.

Social return on investment in these projects vary with respect to the number of patients that will be treated, the value of the health benefits of the new technology, the changes in health care costs, and the probability of technical success. For example, the two projects, "Living Implantable Microreactors" and "Proliferated Human Islets" are very similar in many respects. They have similar medical benefits to the same patient population. The main differences between these two projects are the probability of technical success, as reported by the companies, and the changes in health care cost. BioHybrid Technologies, Inc., projects a lower

annual cost for the islet transplant procedure and a higher probability of technical success.

The two projects "Biopolymers for Tissue Repair" and "Biomaterials for Clinical Prosthesis" further demonstrate the sources of differences among projects. The size of the market for these two technologies is similar. However, for "Biomaterials for Clinical Prosthesis," market penetration during the production phase is expected to be more complete. Furthermore, while we did develop an estimate of the reduction in health care costs for "Biopolymers for Tissue Repair," we were not able to quantify any health benefits for patients because we could not find any relevant health outcome data. By comparison, we did quantify a substantial per-patient health benefit for "Biomaterials for Clinical Prosthesis" because we were able to collect information regarding the potential health benefits.

Table 3-22 demonstrates how ATP funding induced increases in social returns. Recall that in our model, ATP might affect the development of medical technologies by accelerating the technology's development, increasing the probability of success (by stimulating additional R&D investment), or widening the technology's applications (scope). Table 1-4 shows the magnitude of these impacts for each project. ATP funding accelerates the projects by 1 to 10 years, increases the probability of success by 1 to 171 percent, and wideness the scope of two projects.

The acceleration effect has a much greater impact on the social return on public investment than the probability effect. Table 3-23 demonstrates the relative impact of the acceleration effect on the social return on public investment. To determine the impact of the acceleration effect only, we calculated the social return on public investment assuming that the probability of technical success in both scenarios is the same as it is in the with-ATP scenario. Then we compared the NPV considering both the probability and acceleration effects to the NPV considering the acceleration effect only. The table shows that the acceleration effect is responsible for 81 percent of the social return on public investment.

Table 3-22. Impact of ATP Funding on the Development of Medical Technologies for Seven Tissue Engineering Projects

ATP Project	Project Acceleration[a] (years)	Increase in the Probability of Technical Success (percent)	Widening of Technology Applications[b] (scope effects)
Stem Cell Expansion	1 to 2	9%	None reported
Biopolymers for Tissue Repair	At least 10	171%	Significant but not quantified
Living Implantable Microreactors	2	11%	None reported
Proliferated Human Islets	3 to 5	2%	None reported
Biomaterials for Clinical Prosthesis	2	1%	None reported
Gene Therapy Applications	2	20%	Some effects reported but not quantified
Universal Donor Organs	1	16%	None reported

[a]This is the number of years of acceleration reported by the ATP-funded companies. When they reported a 2-year range, we assume the lower number for our analysis. For "Proliferated Human Islets," we used the middle number, 4 years, for our analysis.

[b]Our model allows conceptually for a widening of scope effect of ATP. In practice, for the applications examined in this study, there was little or no impact in all but one case, which we did not quantify.

Table 3-23. Impact of Acceleration Effect on Social Return on Public Investment

	NPV (1996$ millions)		
ATP Project	Acceleration and Probability Effects	Acceleration Effect Only	Acceleration, Percent of Total
Stem Cell Expansion	$47	$38	82%
Biopolymers for Tissue Repair	$98	$98	100%
Living Implantable Microreactors	$17,750	$11,528	65%
Proliferated Human Islets	$1,297	$1,278	99%
Biomaterials for Clinical Prosthesis	$15,058	$15,022	100%
Gene Therapy Applications	$945	$642	68%
Universal Donor Organs	$783	$458	58%
Composite[a]	$34,258	$27,759	81%

[a]See notes to Table 3-20 for an explanation of the derivation of the composite measure of return.

The results demonstrate that by accelerating R&D and increasing the probability of technical success, ATP can have an important impact on the social return on investment.

Clearly, ATP provided the greatest leverage for social returns for the second project, "Biopolymers for Tissue Repair." ATP accelerated the benefits from this project by at least 10 years, had a significant impact on the probability of success, and affected the scope of the project.[3] According to company officials, in the absence of ATP funding, the company might not have developed this technology at all or might have developed it so slowly that the market opportunity for this technology would have passed before it was ready for commercialization. Although the impact of ATP on social returns was less dramatic for the remaining projects, it is clear that these two potential sources of ATP's impact on the R&D process have provided important increases in social returns.

Table 3-24 shows the composite private returns for all of the ATP projects in tissue engineering.[4] The private returns for all projects are significantly lower than their social returns. Although the composite NPV is about $1.5 billion, the individual expected NPV varies widely from over $1 billion to less than zero. Individual PRRs (not reported) range from about 14 percent to less than zero.

Table 3-24. Composite Private Returns: ATP Projects in Tissue Engineering for a Single Preliminary Application[a]

	NPV (1996$ millions)	IRR (%)
Project returns	$1,564	12%
Increment attributable to ATP	$914	13%

[a]See notes to Table 3-20 for an explanation of the derivation of the composite measure of return.

From the data we had available for this study, we estimated expected NPV for four of the seven ATP projects in tissue engineering is positive; thus we expect the ATP-sponsored companies and their partners in commercialization and production to earn profits on the development, commercialization, and sales of these technologies. However, because we have modeled these

[3]Although we were not able to quantify the scope effects, this does not affect the results because the 10-year acceleration of benefits virtually attributes all benefits of the technology to ATP funding.

[4]Although the model calculated the private returns on each project, they are not disclosed to preserve the confidentiality of the companies.

activities together, we do not know how these profits will be distributed among the companies.

Three of the seven projects have negative expected private NPV, implying that the ATP-sponsored companies and their partners in commercialization and production will suffer a loss from the development of these applications of these technologies. However, this result is not surprising given the limitations of our analysis. Recall that the applications considered in this study are only the first of many possible applications of ATP-funded technologies. Although three of the seven projects show an expected negative NPV, ATP-sponsored companies base their investment decisions on the potential long-term profitability of these technologies in all of their applications. Thus, investments in future application will probably may be more profitable because of the spillovers between the first and future applications.

The substantial differences between private and social returns for these projects provide a rationale for encouraging private-sector investment through the ATP program.

ATP funding has a dramatic impact on the private return on investment in some projects. Although the magnitude of ATP's contribution to private returns varies by project, our estimate of the total contribution to NPV is about $914 million, which is about 58 percent of the total. This means that ATP's funding stimulates additional private-sector investment and research that yield returns that will be significantly higher than they would be without ATP funding.

Two of the companies reported that ATP funding helped them attract other forms of capital. To the extent that this "halo effect" reduced their cost of capital, ATP funding may have had an additional impact on private returns that we did not measure. In Section 3.3, we discuss how we could extend our model to capture these impacts.

The wide disparity between social and private returns indicates the importance of ATP's incentives to the private sector to pursue these technologies. Because the social returns far outweigh the returns to the companies developing, commercializing, and producing these technologies, the private sector is less likely to fund these kinds of high-risk projects. Hence, ATP funding serves to provide the incentives needed to stimulate the private sector's investments in these activities.

3.2.2 Sources of Project Variations

Tables 3-20 through 3-22 demonstrate a wide variation in the social return on public investment and in the social return on investment, in terms of both the NPV and the IRR. Some of the characteristics of projects that provide a relatively higher expected social return on investment have the following characteristics:

- **Broad application.** Technologies that apply to more patients and diffuse more quickly throughout the patient population have a greater expected social return on investment.
- **Significant health benefits.** Technologies that lead to more significant improvements in the health of patients over and above the defender technology will have a greater expected social return on investment.
- **Cost-effectiveness.** Technologies that offer health care improvements at relatively lower costs provide greater expected social return on investment.
- **Higher probability of technical success.** Technologies with a greater expected probability of technical success have a higher expected social return on investment.

The impact of ATP funding on the magnitude of social returns also varies from one project to the next. The primary factors affecting these differences include the following:

- **ATP's impact on project timing.** The number of years by which ATP funding accelerates the R&D phase of the project has an important impact on social returns. Conditions that lead to high estimates of the acceleration effect from ATP funding are the absence of alternative capital sources and the risk of the project, as perceived by the company and its potential sources of capital.
- **ATP's impact on R&D funding and the probability of technical success.** The impact of ATP funding on the total R&D investment has an important effect on the social return on public investment because it affects the project's expected probability of technical success. The impact of ATP funding depends on the company's motivation and ability to pursue the project in the absence of ATP funds. For all but two projects, ATP stimulated increases in R&D investment sufficient to make a significant difference in the probability of technical success. In addition, ATP funding may have further reduced the company's cost of capital by helping them to attract other sources of private funding. We did not quantify this impact of ATP funding.

- **ATP's impact on project scope.** If ATP funding encourages the company to pursue additional applications and patient populations, the social return on the public investment will increase. Our study investigated only one application of each of the technologies studied. We did not explicitly model any scope effects for the projects we examined. The scope effects may be evident in the number of applications for which the technology is eventually used.

3.2.3 Methodological Limitations

The results of this study are subject to a number of methodological limitations and assumptions that may affect the results. Some of the limitations of our analysis include

- analyzing only a single application of each technology,
- omitting the value of some medical benefits that could not be quantified,
- failing to quantify ATP's impact on a company's ability to attract other sources of capital, and
- basing assumptions about costs and benefits on the expectations of informed individuals.

Single-Application Analysis

This study analyzes only one preliminary application for each project. Because these technologies provide basic scientific platforms for many applications, their long-term impact may be much greater than suggested here, as companies apply their discoveries to a wide variety of medical applications. In addition, the knowledge generated by these initial applications may lead to advances in unrelated areas by other companies.

Limitations of the Health Benefits Models

The models we used to quantify the health benefits of each technology have limitations that might affect the results of the study. As shown in Table 3-25, some analyses included only a portion of the entire population of patients that might benefit from the technology. In other cases, we did not consider all of the potential health benefits of the technologies, usually because data to support these estimates were not available. Similarly, some of the cost savings associated with the technologies may be underestimated because of our inability to quantify them.

Table 3-25. Limitations of the Health Benefits Models

ATP Project	Patient Population	Benefits per Patient	Cost per Patient
Human Stem Cell and Hematopoietic Expansion Systems	Does not consider the European market	Does not consider decreases in the probability of reintroducing cancer, benefits due to convenience, or potential benefits of eliminating mobilization drugs	Cost of instruments and procedure is very uncertain
Structurally New Biopolymers Derived from Alpha-L Amino Acids	Considers only the first application of this technology	Does not account for differences in healing rates	Price of new device subject to uncertainty
Disease Treatment Using Living Implantable Microreactors	Considers only patients diagnosed as diabetics by the first year of commercialization	Does not account for changes in QALYs for intermediate health states	Does not account for changes in cost for intermediate health states
Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules	Same as above	Same as above	Same as above
Fabrication Using Clinical Prosthesis from Biomaterials	Considers only patients who currently undergo ACL repair	Estimate of QALY change is speculative	Assumes that the cost of using the new material would be the same as current technologies
Application of Gene Therapy to Treatment of Cardiovascular Diseases	Includes only lung cancer patients	Cannot capture the QALY impacts of health states other than death	Does not consider the cost impact of eliminating false positive diagnoses
Universal Donor Organs for Transplantations	Considers only the market for heart transplants; considers only patients eligible under current criteria	Cannot capture the QALY impacts of health states other than death	Does not consider potential savings of xenogeneic transplants compared to human transplants

Our method for quantifying the health benefits of a disease may also tend to underestimate the total benefits. The economic burden of a disease is usually divided into three components: direct medical costs, indirect costs, and intangible costs. Direct medical costs are the costs of medical treatment. Indirect costs are the societal costs associated with the loss in productivity due to illness and unpaid caregiver time. Intangible costs are due to the patient's pain and suffering.

Because we measured the health benefits of these technologies in terms of QALYs, our estimates capture how ATP-funded technologies change both the direct medical costs and the intangible costs of a disease. However, they may not capture changes in the indirect costs. Improvements in the health of a patient population with a particular illness or injury may reduce the indirect costs of the disease, allowing those receiving an improved treatment to lead more productive lives. These benefits to society may not be captured by QALYs.

Health economists disagree about whether QALYs actually do capture changes in indirect costs. While the standard assumption is that QALYs do not capture indirect costs, some health economists argue that QALY estimates do include these costs. Assuming that the standard assumption is correct, if we were able to fully capture the changes in indirect costs due to these technologies, our estimates of the social returns to investment in some of these technologies would be higher.

ATP's Impact on Availability of Capital

Two companies in our study reported that ATP funding influenced their ability to attract private funding. This "halo effect" may have reduced the companies' cost of capital. Conceptually, reducing the companies' cost of capital would affect the cost of R&D in the same way ATP funding affects it. That is, as the cost of R&D effort falls, the level of effort rises, increasing the probability of technical success. Although we did not quantify the benefits of this mechanism of ATP impact, we could modify our methodology to incorporate this effect as explained below.

Data Limitations

Because none of these technologies have yet reached the commercial market—though several are in clinical trials—the results of this analysis are based, in part, on the expectations of the innovators and other informed individuals. We do not know at this time whether these expectations will be realized. However, the methodology we employed can be used to update our estimates as better data on the actual costs and benefits of the technologies become available.

We examined the sensitivity of our results to our assumptions about some of the most uncertain parameters in our model. The results of the sensitivity analyses are reported in Appendix B. We examined the sensitivity of social returns to the following parameters:

- discount rate,
- per-patient treatment costs and QALYs, and
- probability of technical success.

We examined the sensitivity of private returns to several key parameters:

- discount rate,
- commercialization cost percentage,
- production cost percentage,
- product price, and
- probability of technical success.

We found that the results are fairly sensitive to the predictions about the technologies' costs and effectiveness by doctors and company representatives. As these technologies develop, estimates of their costs and effectiveness may change dramatically, or their technical success may prove impossible. As better information becomes available, we should consider adjusting these estimates to incorporate more accurate forecasts of these costs and benefits.

3.3 CONCLUSIONS AND POTENTIAL IMPROVEMENTS

The objectives of this project were to

- develop a methodology for estimating the expected social economic return on public investment in ATP-funded projects with medical applications,

- ➤ illustrate this methodology by applying it to seven ATP-funded projects in tissue engineering,
- ➤ estimate the social return on public investment in these seven ATP projects, and
- ➤ provide insight regarding the factors that affect the social return on public investment in ATP-funded projects with medical applications.

This section offers conclusions about the suitability of this methodology for estimating the private and social return on investment in medical and other technologies and ways this methodology might be improved. It also discusses our conclusions with respect to the social and private returns on investments in each of the case study technologies and offers observations about why these results differ among the case studies.

3.3.1 Developing, Applying, and Improving the Methodology

To address the specific methodological challenges of modeling and estimating the economic return on investment in new medical technologies, we extended the currently accepted framework for calculating private and social returns. We incorporated nonmarket methods for valuing the benefits of these technologies to patients. We illustrated this methodology by applying it to seven ATP-funded projects in tissue engineering.

Applicability of this Methodology

This methodology is useful for analyzing ATP-funded medical technologies, particularly under the following conditions:

- ➤ One or several primary applications are apparent.
- ➤ The health outcome and resource cost differences between the new and defender technologies can be quantified (e.g., because some clinical trials or other studies have produced the required data).
- ➤ The impact of changes in health outcomes on patients' well-being has been quantified by other studies (e.g., QALYs for health outcomes or health states are available).
- ➤ The market potential for the new technology is apparent.
- ➤ The technology is sufficiently close to commercialization to enable company representatives to project the costs of commercialization and production.

Aside from medical technologies, this methodology is also applicable to other situations in which the technology affects goods and services whose values are not adequately reflected in market prices. For example, technologies that improve environmental quality or reduce the crime rate provide benefits that are not priced in the market.

Aside from medical technologies, this methodology is also applicable to other situations in which the technology affects goods and services whose values are not adequately reflected in market prices. For example, technologies that improve environmental quality or reduce the crime rate provide benefits that are not priced in the market. Nonmarket valuation methods are required to value these kinds of social benefits. As in this study, valuation of these social benefits requires determining the beneficiaries' willingness to pay for these improvements.

Potential Methodological Improvements

The methodology we developed and applied in this study might be improved in several ways. These potential improvements involve

- improving our model of the impact of ATP funding on company investment behavior,
- forecasting the impact of distant applications, and
- modeling the decline in market penetration.

Modeling the Impact of ATP Funding on Company Investments. Constructing a without-ATP scenario is the most challenging task in calculating social and private returns. Because the without-ATP case is the counterfactual, we must rely on the company's conjectures about what they might have done in the absence of an ATP grant. Clearly, better information about how companies respond to ATP grants could improve our estimates of the without-ATP scenario.

ATP funding may reduce the cost of R&D effort by reducing the cost of other sources of funding. We could improve the model by incorporating empirical estimates of these differences in cost to demonstrate how they further encourage R&D effort and improve the probability of technical success.

First, ATP needs to understand how companies react to changes in the real cost of R&D. ATP seeks to identify projects that would not be funded to the same degree by the private sector. Information about how a company's size, scope, ownership structure, age, and R&D portfolio affect its R&D investment decisions could shed some light on these issues. An *ex post* empirical analysis of the private return on investment in projects funded with alternative sources of funds could identify points on the marginal benefits curve relating the cost of R&D to its returns.

Second, ATP needs to understand exactly how its funding affects the cost of R&D. In this study, we assume that in the absence of ATP the cost of an R&D dollar is equal to $1, and that with ATP the cost of an R&D dollar is the ratio of the company's ATP match to

the total project budget. But the difference between the price of R&D in the with-ATP scenario versus without-ATP scenario depends on the cost of alternative funding. ATP funding may reduce the cost of R&D effort not only by subsidizing the project's budget, but also by helping the company attract other sources of funding and reducing the cost of capital. If companies could provide an empirical estimate of the impact of ATP funding on the cost of capital, it could be incorporated into the model, and we could demonstrate how these decreases in the cost of capital further encourage company R&D and improve the probability of technical success.

Existing or prospective studies of project spillovers may provide a general guideline for forecasting the return on investment in later applications of ATP-funded technologies.

Forecasting Impacts of Distant Applications. Analyzing the most immediate and probable application of an ATP project provides the most reliable data regarding its potential impacts. However, ignoring the later applications probably underestimates the project's benefits.

The challenge of collecting data regarding these distant applications can be significant. Because the expected benefits lie farther into the future, all of the data required to calculate social returns, including the size of the expected patient population, the appropriate defender technology, and the costs of health care resources, become more and more uncertain. Data regarding expected private returns may be even more difficult to gather, since the companies will be very reluctant to forecast spending on R&D, commercialization, and production for applications that are relatively remote.

A potential approach to this problem may be to draw from existing or prospective studies of project spillovers. An empirical analysis of trends in the returns to the application of an enabling technology as it ages may provide a general guideline for forecasting the returns from later applications. For example, a retrospective study of the medical applications resulting from the development of ultrasound techniques might show that the return on investment in each successive application of the techniques rise at first, then decline as the enabling technology ages and is replaced by a new technique. Analyzing this pattern could help ATP determine how many distant applications should be examined to capture the majority of the returns.

We know very little about how quickly the value of new medical technologies depreciates through the emergence of treatments and technologies that render them obsolete.

Improving Market Penetration Forecasts. While the Bass model is a generally accepted model for forecasting the diffusion of new technologies, it has one important drawback for studying ATP-funded enabling technologies. The cumulative number of adopters predicted by the Bass model is strictly increasing over time. Yet technologies depreciate over time as new technologies emerge and consumer needs and tastes change. Thus, a diffusion model is needed that accounts for the future emergence of technologies that will replace the ATP-funded technology. One way to think of such a model is that it actually forecasts the diffusion of two technologies: the ATP-funded technology and its replacement.

Our ability to determine what these replacement technologies might be and their pattern of diffusion limits our ability to implement the double-diffusion method outlined above. However, we could develop empirical data about the likely pattern of obsolescence of ATP-funded technologies by analyzing the diffusion patterns of existing medical technologies. For example, we could examine the diffusion patterns of two drugs introduced at different times but with the same application. The objective of this analysis would be to examine the factors that affect how quickly a new technology is superseded by an even newer technology.

3.3.2 Summary of Social Returns from Seven ATP Projects in Tissue Engineering

If successful, these technologies and their applications will improve the quality of life for thousands of people every year. Among the technologies we examined, the medical benefits include

- a less painful, invasive, and expensive system for transplanting bone marrow cells;
- a bioabsorbable fracture fixation device that will eliminate the need for removal surgery and improve healing of fractures;
- a virtual cure for the negative health effects of diabetes;
- a system for making donor organs more widely available;
- a diagnostic technique that improves the detection of cancer metastasis, which increases the effectiveness of cancer treatment; and
- a material that will improve the effectiveness of ligament repair.

Our analysis of the social and private benefits of these technologies yields the following findings:

- The expected *social return on ATP public investment* in these technologies, or the increment to social returns attributable to ATP funding, is estimated at $34 billion in net present value.
- The expected *social rate of return on ATP public investment* in these technologies is estimated at an annual rate of 116 percent.
- The expected total *social return* on public and private investment in these technologies is estimated at $112 billion in net present value, or an annual rate of 115 percent.
- The expected total *private return* on investment in these technologies to ATP-award companies and their partners in commercialization and production is estimated at $1.6 billion in net present value, or an annual rate of 12 percent. Of the $1.6 billion in net present value of private returns, $914 million is estimated to be attributable to ATP funding.
- To the extent that the technologies will yield applications in addition to those we investigated, it is likely that public and private returns on these projects will be higher.

These results illustrate two important points about the role of ATP in funding these technologies:

- ATP plays a significant role in increasing the expected social and private returns on these projects.
- The social returns far outweigh the benefits to the private sector. Private companies will therefore tend to underinvest in these technologies compared to what would be optimal from society's perspective. The wide disparity between social and private returns indicates the importance of ATP's incentives to the private sector to pursue these technologies.

Three factors affect the social return on public investment in projects with medical applications:

- the number of years by which ATP funding accelerates the R&D phase of the project,
- the impact of ATP funding on the probability of technical success, and
- the impact of ATP funding on the scope of the project.

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Appendix A
Market Diffusion Interview Materials, Summaries, and Results

This appendix contains materials used to complete the forecasts of technology penetration for each of the seven tissue engineering projects we analyzed in this study. For the four in-depth case studies listed in Table 1-1, we conducted more in-depth case studies than for the remainder of the projects. For the in-depth case studies, we interviewed physicians to obtain data for the Bass diffusion model, as explained in Section 2. For the remainder of the companies, we collected diffusion estimates for the Bass model from the companies' representatives.

A.1 INTERVIEW MATERIALS

Figures A-1 through A-4 contain the clinical profiles we developed and provided to physicians prior to the interviews. We did not identify the company, either on the profile or during the interview.

Figure A-5 is a sheet of questions that we sent to the physicians along with the clinical profile. It was designed to prepare the physicians to answer our questions. Figure A-6 contains the informal interview guide that we used while interviewing the physicians over the telephone.

Table A-1 provides information about the physicians we interviewed. These physicians were recommended to us as experts in the treatment of the relevant diseases by ATP-sponsored companies, by associations such as the American Diabetes Association, or by other physicians.

A.2 DATA COLLECTED

Table A-2 contains the data that we collected from the physicians and company representatives for input to the model. For some of the projects, the physicians identified and provided market penetration estimates for a number of different populations. In these cases, we divided the eligible population into these segments and developed weighted averages for input to the Bass diffusion model. For example, for the project "Biopolymers for Tissue Repair," the total eligible population was 73,875; 33,825 adults and 40,050 children. Expert 1 forecasted a market cap of 25 percent for adults and 75 percent for children as his estimate for the market cap. Therefore, we used 38,494 as his forecast of the market cap for this technology.

Figure A-1. Clinical Profile for "Human Stem Cell and Hematopoietic Expansion Systems"

Many patients with dose-sensitive cancers are treated with high-dose chemotherapy and/or radiation. To enable the patient to survive this treatment, patients are treated with stem cell therapy to repair the damage to their hematopoietic system. In many cases, the stem cells are harvested from the patient prior to the myelotoxic treatment or from a donor via peripheral blood progenitor cell (PBPC) collection. PBPC requires the use of mobilization drugs that may have side effects for the patient or donor.

Assume that a new method for stem cell harvest is now available. This new method involves extracting a small quantity of bone marrow (a single aspirate) in a doctor's office under local anesthesia. The aspirate is placed in a Cell Production System (CPS) which is fully automated for growing stem cells outside the human body. This method may reduce the probability that certain tumor cells will be reintroduced via the graft.

Please examine the clinical profile below and think about the current stem cell harvest techniques versus the new treatment we described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient, including all resources required for stem cell harvest:	No more than $12,000.
Likely alternative treatment and treatment cost:	Peripheral blood progenitor cell (PBPC) mobilization. $12,000-$20,000
Risks/side-effects:	No drugs or procedures required to prepare the patient for the procedure prior to the time of the aspirate.
Ease of use:	It is very easy to use and requires limited training.
Expected outcomes of new treatment compared to likely alternative treatment:	May reduce tumor cells in a graft by 10- to 70-fold versus the conventional methods. Other differences noted below.

Cell Source	Care Episodes[a]	Procedure Time (Hours)	Needle Sticks[b]
PBPC mobilization and collection[c]	21	39	22
CPS[d]	2	1-3	4-10

Note: The numbers in the table include all procedures associated with stem cell procurement and administration.

[a]Includes all outpatient, inpatient, and home care episodes.

[b]Includes bone marrow aspirates, blood samples, catheter placements, and subcutaneous injections.

[c]Based on an average of three rounds of apheresis following cell mobilization injections.

[d]Based on data accumulated during confidential company's pre-clinical research and trials.

Figure A-2. Clinical Profile for "Structurally New Biopolymers Derived from Alpha-L Amino Acids"

Currently, fractures of the shoulder, elbow, wrist and hand, knee, and ankle are fixed with metallic devices. Some fractures are also fixed with bioabsorbable materials. Assume that new devices—pins and screws made from a newly developed bioabsorbable material—have just become available. The new bioabsorbable material is made from a novel synthesis of tyrosine that avoids the problems associated with acids produced by the breakdown of existing bioabsorbable polymers. Also, the new pins and screw are stiffer than the current bioabsorbable alternative. The primary application for the pins and screws is orthopedic repair (fracture fixation).

The new bioabsorbable pins and screws are intended for use in the following types of fractures:

- *shoulder (distal clavicle, acromion, glenoid rim, proximal humerus)*
- *elbow (humeral condyles or capitellum, olecranon, radial head or neck)*
- *wrist and hand (distal radius, carpal and metacarpal bones)*
- *knee (femoral and tibial condyles, patella)*
- *ankle (uni or bimalleolar, and severe with syndesmotic disruption)*

Source: Böstman, O., E. Hirvensalo, E. Partio, P. Törmälä, and P. Rokkanen. 1991. "Impact of the Use of Absorbable Fracture Fixation Impacts on Consumption of Hospital Resources and Economic Costs." *The Journal of Trauma* 31(10):1400-1403.

Please examine the clinical profile below and think about the current treatment for fracture fixation versus the new bioabsorbable treatment described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient:	Surgery cost identical to defending treatment. Material cost expected to be $50-$150 per pin or screw.
Likely alternative treatment and treatment cost:	Surgery with metallic fixation devices (pins and screws): $8-$20 per device.
Expected outcomes of new treatment compared to likely alternative treatment:	➤ Reduction in stress shielding and secondary fractures due to screw holes ➤ Elimination of removal surgery ➤ Reduced potential for tissue abrasion or device loosening and migration

Figure A-3. Clinical Profile for "Disease Treatment Using Living Implantable Microreactors"

Currently, most insulin-dependent diabetics are treated with daily insulin injections. Assume that a new treatment has just become available that uses porcine pancreatic transplant cells encased in microspheres to achieve tight glycemic control in insulin-dependent diabetics. The cells permit glucose, nutrients, electrolytes, oxygen, and bioactive products to pass but block immunocytes involved in transplant rejection. As the cells cease to function, the patient will require a booster injection of new cells. The cells are intended for treatment of all Type I diabetics and Type II diabetics who require daily insulin injections.

Please examine the clinical profile below and think about the current treatment for insulin-dependent diabetics versus the new treatment described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient:	$12,000 for initial implant and $6,000/year for booster implants, which are required once or twice a year.
Likely alternative treatment and treatment cost:	Daily insulin injections: $1,666/year
Expected outcomes of new treatment:	The new treatment will achieve equal or superior outcomes as realized in the Diabetes Control and Complications Trial (DCCT). The DCCT demonstrated the benefits of tight glycemic control for insulin-dependent diabetics. Results of the trial showed: ➤ 76% reduced risk of eye disease ➤ 50% reduced risk of kidney disease ➤ 60% reduced risk of nerve disease ➤ 35% reduced risk of cardiovascular disease
Other benefits:	➤ Improved quality of life ➤ Reduces glucose monitoring to once a week ➤ Eliminates daily insulin injections ➤ Automatic insulin response to glucose ➤ No immunosuppression required ➤ Simple to administer
Ease of use:	Procedure will be an injection under ultrasound control, similar to amniocentesis; done on an outpatient basis. Requires a simple syringe.

Figure A-4. Clinical Profile for "Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules"

Currently, most insulin-dependent diabetics are treated with daily insulin injections. Assume that a new treatment has just become available that uses proliferated insulin-secreting human islet cells combined with a unique encapsulation technology to help patients achieve tight glycemic control. The encapsulation technology ensures adequate immunoprotection and biocompatability with the human body. The cells are intended for treatment of Type I diabetics and Type II diabetics who require daily insulin injections. This new treatment eliminates the need for daily insulin injections.

Please examine the clinical profile below and think about the current treatment for insulin-dependent diabetics versus the new treatment described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient:	$10,000-$15,000 per year
Likely alternative treatment and treatment cost:	Daily insulin injections: $1,666/year
Expected outcomes of new treatment:	The new treatment will achieve similar outcomes as realized in the Diabetes Control and Complications Trial (DCCT). The DCCT demonstrated the benefits of tight glycemic control for insulin—dependent diabetics. Results of the trial showed: ➤ 76% reduced risk of eye disease ➤ 50% reduced risk of kidney disease ➤ 60% reduced risk of nerve disease ➤ 35% reduced risk of cardiovascular disease
Other benefits:	➤ Improved quality of life ➤ Reduces glucose monitoring to once a week ➤ Eliminates daily insulin injections ➤ Automatic insulin response to glucose ➤ No immunosuppression required ➤ Simple to administer
Ease of use:	Product is injectable, an in-office treatment. Patient is placed under local anesthesia, sits for 3 hours, and then goes home. Patient makes a monthly visit to the doctor for monitoring. Treatment is once a year or once every two years.

Figure A-5. Questions about the Clinical Profile

1. In thinking about the application that this therapy is intended for according to the profile you just read, what group of patients do you believe will be eligible to *receive* the treatment?

   Please list by group, defining each group. For example, one group might consist of "Type II diabetic patients currently requiring daily insulin injections." Use as many groups as necessary.

   Group A:

   Group B:

   Group C:

2. Given that Group A is eligible for this treatment, what percentage of patients in this group do you think will actually *receive* the treatment?

   Please provide this percentage for each of the first 5 years that the treatment is available.

   Group A:

_____%	_____%	_____%	_____%	_____%
(year 1)	(year 2)	(year 3)	(year 4)	(year 5)

   Group B:

_____%	_____%	_____%	_____%	_____%
(year 1)	(year 2)	(year 3)	(year 4)	(year 5)

   Group C:

_____%	_____%	_____%	_____%	_____%
(year 1)	(year 2)	(year 3)	(year 4)	(year 5)

Figure A-6. Physician Interview Guide

This interview is part of a study that RTI is doing for the National Institute of Standards and Technology (NIST). NIST has asked us to talk with clinical experts about the expected market acceptance of a number of new biotechnologies.

Introduction

1. First, can you please tell me about your particular affiliation?
   a. research organization, hospital or clinic, private or group practice, government, etc.

   b. type of patient base you see (if appropriate)

   c. number of years you have been in your present position, current title

   d. your affiliation with the biotechnology company

Estimating the Eligible Population

Please examine the clinical profile of the treatment, including the target patient profile and the expected costs and outcomes of the treatment.

1. In thinking about the application that this therapy is intended for according to the profile we sent you, what group or groups of patients do you believe are eligible to receive the treatment?

   ✓ describe patient cohorts (e.g., by age, severity of disease, type of disease, receiving a certain treatment, etc.)

   ✓ Would these patients all be eligible for the defending treatment as we have defined it on the profile?

2. Do you think the population of eligible patients will change over time, or will the number of eligible patients remain constant over the next 10 years? How will it change?

(continued)

Figure A-6. Physician Interview Guide (continued)

Potential Barriers to Market Penetration and Market Penetration

1. What do you view as some of the barriers to this treatment's widespread use? For example,
   - ✓ physicians
   - ✓ insurance companies
   - ✓ patients
   - ✓ hospitals
   - ✓ costs

2. Who do you think will be most influential in determining whether this treatment becomes widely used or not (e.g., physicians, hospitals and managed care formularies, insurance companies, patients)?

3. Given that patients in group A (as you have defined it) are eligible for this treatment, and taking into account the barriers we just discussed, what percentage of the patients in group A do you think will actually *receive* the treatment?

   Please provide this percentage for each of the first 5 years that the treatment is available.

_____%	_____%	_____%	_____%	_____%
(year 1)	(year 2)	(year 3)	(year 4)	(year 5)

4. Given that patients in group B (as you have defined it) are eligible for this treatment, and taking into account the barriers we just discussed, what percentage of the patients in group B do you think will actually *receive* the treatment?

   Please provide this percentage for each of the first 5 years that the treatment is available.

_____%	_____%	_____%	_____%	_____%
(year 1)	(year 2)	(year 3)	(year 4)	(year 5)

Table A-1. Physicians Interviewed for Each Case Study Company

Company	Date of Interview	Physician	Vocation or Title	Hospital or Work Affiliation(s)	Location	Nature of Work
Aastrom Biosciences, Inc.	Feb. 6, 1997	Dr. Sam Silver	Director of Adult Bone Marrow Transplants	University of Michigan Hospital	Ann Arbor, MI	60% patient contact 20% administrative 20% clinical research
	Feb. 20, 1997	Dr. Randy Broun	Clinical Associate Professor of Medicine	The Jewish Hospital of Cincinnati, University of Cincinnati, and private practice	Cincinnati, OH	80% patient contact 20% other
	Feb. 25, 1997	Dr. Richard Champlin	Chairman ad interim, Dept. of Hematology and Chief, Section of Blood and Marrow Transplantation	University of Texas M.D. Anderson Cancer Center	Houston, TX	Not covered in interview
Integra LifeSciences	Feb. 7, 1997	Dr. Barry Eppley	Plastic and Oral Surgeon	Indiana University Medical Center	Indianapolis, IN	95% patient contact 5% lab and clinical research
	Feb. 10, 1997	Dr. Richard Freidman	Professor of Orthopedic Surgery	Medical University of South Carolina	Charleston, SC	80% clinical 20% research and other
	Feb. 12, 1997	Dr. Robert Bucholz	Professor and Chairman of Orthopedic Surgery	University of Texas Southwestern Medical Center	Dallas, TX	90% patient contact 10% clinical research
VivoRx, Inc./ BioHybrid Technologies, Inc.	Feb. 11, 1997	Dr. John Buse	Director, Diabetes Center	University of North Carolina-Chapel Hill	Chapel Hill, NC	70% patient contact 30% clinical research and administrative
	Mar. 7, 1997	Dr. John Deller	Endocrinologist	The Heart Institute of the Desert—Eisenhower Medical Center	Rancho Mirage, CA	95% patient contact 5% other
	Mar. 11, 1997	Dr. Ann Brown	Assistant Professor of Medicine, Endocrinology; Medical Director, Diabetes Education Program	Duke University Medical Center	Durham, NC	50% clinical 20% research 30% administrative

Table A-2. Data Collected from Physician and Company Interviews

Eligible Population	Percentage of Population Receiving Treatment					
	Year 1	Year 2	Year 3	Year 4	Year 5	Market Cap
Stem Cell Expansion						
Autologous BMTs	4%	10%	15%	25%	—	—
Multicyclic chemotherapy	10%	20%	25%	30%	40%	—
Autologous BMTs	1%	5%	10%	10%	10%	100%
Multiple-course cancer therapy	1%	5%	10%	20%	20%	20%
Cord blood transplants	1%	10%	20%	50%	50%	100%
Chemotherapy + autologous stem cell support	3%	8%	15%	25%	35%	—
Chemotherapy + cord blood support	3%	8%	15%	20%	20%	100%
Dose intensive therapy	3%	8%	15%	25%	40%	100%
Chemotherapy and allogeneic stem cell support	3%	8%	15%	20%	20%	100%
Biopolymers for Tissue Repair						
Adults (five fracture sites)	1%	3%	5%	10%	15%	25%
Pediatric (all fractures)	2%	6%	10%	20%	30%	75%
Adults (five fracture sites)	25%	40%	55%	70%	75%	75%
Adults	10%	10%	10%	20%	20%	20%
Pediatric	10%	10%	10%	10%	10%	10%
Living Implantable Microreactors						
Type I diabetics	1%	5%	10%	10%	10%	10%
10% Type II diabetics	1%	10%	15%	15%	15%	15%
Type I children under 10 years of age	2%	2%	2%	5%	10%	100%
Type I over puberty and with complications	20%	25%	30%	40%	50%	100%
Type I over puberty with no complications	10%	10%	10%	20%	30%	100%
Type II insulin-dependent with disease for ≥10 years	2%	2%	2%	5%	10%	100%
Type I diabetics	3%	7%	15%	30%	50%	95%
Type II diabetics (ins-dep.) < age 50	1%	2%	4%	20%	25%	25%

(—) denotes missing value.

(continued)

Table A-2. Data Collected from Physician and Company Interviews (continued)

Eligible Population	Percentage of Population Receiving Treatment					
	Year 1	Year 2	Year 3	Year 4	Year 5	Market Cap
Proliferated Human Islets						
Type I diabetics	1%	5%	10%	10%	10%	10%
10% Type II diabetics	2%	10%	15%	20%	20%	20%
Type I children under 10 years of age	2%	2%	2%	5%	10%	100%
Type I over puberty and with complications	20%	25%	30%	40%	50%	100%
Type I over puberty with no complications	10%	10%	10%	20%	30%	100%
Type II insulin-dependent with disease for ≥10 years	2%	2%	2%	5%	10%	100%
Type I diabetics	3%	7%	15%	30%	50%	95%
Type II diabetics (ins-dep.) < age 50	1%	2%	4%	20%	25%	25%
Biomaterials for Clinical Prostheses	9%	20%	30%	40%	50%	75%
Gene Therapy Applications	10%	25%	40%	50%	55%	55%
Universal Donor Organs	10%	20%	30%	40%	50%	75%

(—) denotes missing value.

A.3 KEY FINDINGS FROM INTERVIEWS

We highlight key findings from the physician interviews by project.

Stem Cell Expansion

- In addition to autologous bone marrow transplants (BMTs), physicians believed this procedure would be useful for patients receiving multicyclic subablative chemotherapy and umbilical cord stem cell transplants.
- Two physicians stated that there are technical barriers to using this treatment for allogeneic transplants due to graft rejection, graft versus host disease, and the inability to restore blood cells to the level they need to be.
- Barriers to this treatment's market success cited by physicians interviewed include the cost of capital equipment for health maintenance organizations (HMOs), hospitals, and BMT centers; the ease of training; and physicians' belief in the procedure's reliability to grow stem cells. One physician said that a disadvantage of the treatment is that once the cell expansion has started, the

cells will have to be used on a given date and cannot be "saved" until a later date, in the event that a patient is unable to undergo the transplant.

- Physicians and CEOs of hospitals and managed care organizations were cited as being most influential in determining whether the treatment will become widely used.
- Physicians stated that the possibility of reducing tumor cells in a graft will be extremely important in determining the treatment's market acceptance; however, this factor will not be important in terms of modeling health outcomes.

Biopolymers for Tissue Repair

- Physicians noted the differences between the pediatric orthopedic market and the adult orthopedic market. The pediatric market has a high removal rate for pins (95 percent) because physicians are reluctant to leave pins in growing bone. However, the removal rate for adults is closer to 10 to 15 percent.
- One physician said that the only adult population this would be applicable for is healthy adult patients with low-load nondiaphyseal fractures.
- Barriers to this treatment that were cited included physicians' concern, even if it is misinformation, about possible reactions to bioabsorbable materials versus inert metals; the ability to use bioabsorbables mechanically as easily as metals are used; the fact that biodegradable devices may not have the same degree of interfragmental compression; and the higher cost of bioabsorbable materials.
- One surgeon said that surgeons will be most influential in determining whether these devices become widely used *if* they find the devices comparable to the metal devices.

Living Implantable Microreactors

- Physicians believed that the eligible population is identical to that for VivoRx's technology.
- The biggest barriers cited to this treatment's widespread use are the fact that human and porcine islets are good reservoirs for retroviruses, and the long-term effects of porcine retroviruses are not known. Cost was also cited as a barrier.

Proliferated Human Islets

- Physicians confirmed that the eligible populations for this treatment are Type I diabetics and 10 percent of Type II diabetics (those who are insulin-dependent). The only group not eligible for this treatment is women who are pregnant or considering getting pregnant.

- One physician believes that children and young adults who are beyond puberty *and* have already shown some complications related to diabetes will be the ideal group for both VivoRx's and BioHybrid's treatments, since the medical community will do anything to prevent further complications in such young patients.
- One physician stated that if we can clone human cells, these should be better than porcine cells; however, there is a big reservoir of porcine cells, so availability should not be an issue.
- The biggest barriers cited to this treatment's widespread use include
  - ✓ cost, which far exceeds current diabetes therapy, especially for young parents with young (less than 10 years of age) diabetic children;
  - ✓ availability of tissue for transplantation;
  - ✓ the government, which may be overly restrictive in regulating the number of patients able to receive either therapy (VivoRx or BioHybrid);
  - ✓ pharmaceutical companies that are large producers of insulin and insulin-related products;
  - ✓ concerns about unrecognized malignant cell transmission; and
  - ✓ long-term immunological effects of this type of transplantation.
- Physicians predicted that the American Diabetes Association and professional endocrine societies will be influential in determining how widespread this treatment becomes. One physician believed it will be primarily patient-driven, because many patients will be willing to pay more for improving lifestyles (i.e., reduction in glucose monitoring).

A.4 RESULTS OF MODEL ESTIMATES

Table A-3 summarizes the results of our diffusion modeling. The forecasted estimate is the quantity of patients used in the model for estimating returns. The "high" and "low" columns are the end points of the 95 percent confidence intervals for the forecasts.

Table A-3. Summary Results

ATP Project	Year	Number of Patients: Forecast Estimate	95% Confidence Interval: High	95% Confidence Interval: Low
Human Stem Cell and Hematopoietic Expansion Systems in Tissue Engineering	1	665	665	665
	2	1,060	1,162	958
	3	1,674	2,002	1,373
	4	2,606	3,371	1,953
	5	3,976	5,477	2,750
	6	5,890	8,424	3,823
	7	8,384	11,996	5,224
	8	11,334	15,537	6,986
	9	14,424	18,318	9,098
	10	17,251	20,172	11,489
Structurally New Biopolymers Derived from Alpha-L-Amino Acids	1	8,173	8,173	8,173
	2	13,286	13,889	12,683
	3	20,007	21,525	18,500
	4	26,980	29,056	24,763
	5	31,977	33,494	29,942
	6	34,158	34,718	33,002
	7	34,744	34,874	34,289
	8	34,863	34,889	34,715
	9	34,885	34,890	34,840
	10	34,889	34,890	34,876
Disease Treatment Using Living Implantable Microreactors	1	65,498	65,498	65,498
	2	110,468	130,376	90,560
	3	183,271	252,047	124,436
	4	295,888	460,182	169,546
	5	457,310	755,608	228,401
	6	661,608	1,043,557	303,100
	7	874,437	1,175,873	394,507
	8	1,041,811	1,187,567	501,178
	9	1,134,485	1,187,113	618,454
	10	1,171,047	1,187,135	738,431

(continued)

Table A-3. Summary Results (continued)

ATP Project	Year	Number of Patients: Forecast Estimate	Number of Patients: 95% Confidence Interval: High	Number of Patients: 95% Confidence Interval: Low
Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules	1	63,711	63,711	63,711
	2	122,647	175,059	70,234
	3	202,286	339,115	78,109
	4	305,295	552,472	87,592
	5	430,677	779,403	98,978
	6	571,339	958,064	112,598
	7	713,520	1,053,241	128,820
	8	840,452	1,087,586	148,042
	9	939,509	1,097,188	170,678
	10	1,007,470	1,099,607	197,136
Fabrication of Clinical Prosthesis from Biomaterials	1	9,000	9,000	9,000
	2	19,493	22,777	16,209
	3	30,293	37,258	23,397
	4	40,629	50,442	30,376
	5	49,780	60,631	36,974
	6	57,277	67,321	43,050
	7	62,996	71,152	48,506
	8	67,102	73,145	53,292
	9	69,914	74,124	57,400
	10	71,773	74,591	60,862
Application of Gene Therapy to Treatment of Cardiovascular Diseases[a]	1	17,350		
	2	43,505		
	3	69,817		
	4	87,533		
	5	96,575		
	6	96,865		
	7	97,156		
	8	97,447		
	9	97,739		
	10	98,033		

(continued)

Table A-3. Summary Results (continued)

ATP Project	Year	Number of Patients		
		Forecast Estimate	95% Confidence Interval	
			High	Low
Universal Donor Organs for Transplantations				
	1	1,200	1,200	1,200
	2	2,361	2,638	2,084
	3	3,610	4,203	3,020
	4	4,852	5,705	3,968
	5	5,982	6,949	4,883
	6	6,919	7,832	5,726
	7	7,631	8,379	6,464
	8	8,132	8,684	7,082
	9	8,465	8,843	7,579
	10	8,675	8,923	7,964

[a]We did not estimate a model for this project because the company representative gave us a 10-year forecast.

Appendix B
Sensitivity Analysis

This appendix describes the sensitivity of our estimates of the social return on public investment, the social return on investment, and the private return on investment to changes in key parameters.

B.1 SENSITIVITY OF SOCIAL RETURNS

We examined the sensitivity of the social return on public investment and the social return on investment to the following parameters:

- discount rate,
- per-patient treatment costs and QALYs, and
- probability of technical success.

B.1.1 Sensitivity to the Discount Rate

Changing the discount rate has a complex effect on the social NPV. First, if the technology has a QALY impact, it affects the total number of QALYs gained per patient, since QALYs that occur later in life are discounted. Second, it affects the value of a QALY, as explained in Section 2. Finally, it affects the rate at which the expected net benefits are discounted.

Table B-1 shows the value of the social NPV when the discount rate is 5 percent and 1 percent. The composite social returns on all projects are about 40 percent lower than baseline at a 5 percent discount rate and about 75 percent higher than baseline at a 1 percent discount rate. For most projects, decreasing the discount rate increases the NPV of social returns. For one project, "Proliferated Human Islets," the social benefits are negative at a 5 percent discount rate because at this rate the discounted value of the lifetime health-related benefits per patient is less than the discounted lifetime cost of treatment. Because the per-patient net benefits are negative for this project, the impact of ATP on the return on investment from this project is also negative, because the with-ATP scenario includes more patients. The increase in the discount rate decreases the value of improvements in the quality of life, which occur late in life relative to the cost of treatment.

Table B-1. Social Return on Investment and Social Return on Public Investment: ATP Projects in Tissue Engineering for a Single Application: 5 and 1 Percent Discount Rates (NPV 1996$ millions)

	5 Percent		1 Percent	
ATP Project	Expected Social Return on Investment	Expected Social Return on Public Investment	Expected Social Return on Investment	Expected Social Return on Public Investment
Stem Cell Expansion	$94	$33	$190	$65
Biopolymers for Tissue Repair	$77	$77	$125	$125
Living Implantable Microreactors	$39,930	$10,461	$138,866	$29,634
Proliferated Human Islets	($924)	($313)	$8,165	$4,029
Biomaterials for Clinical Prosthesis	$24,339	$11,493	$45,092	$20,041
Gene Therapy Applications	$449	$990	$2,278	$866
Universal Donor Organs	$3,568	$1,001	$1,866	$504
Composite	$63,961	$21,992	$193,036	$54,321

B.1.2 Sensitivity to Estimates of Health Benefits

Social returns are relatively insensitive to changes in per-patient treatment cost and QALYs, except for one project.

The health benefits models estimate the benefits of ATP-funded technologies in tissue engineering by calculating the change in the cost of treating patients and the change in the benefits to patients in terms of QALYs. Table B-2 demonstrates the sensitivity of the results with respect to the change in the cost of treatment and the QALYs gained by using the new technology. The table shows the percentage change in each project's social NPV when the per-patient cost or the per-patient change in QALYs is varied by 25 percent. With the exception of "Proliferated Human Islets," none of the results are overly sensitive to our data regarding these benefits and costs. However, the results for this project are very sensitive to both of these estimates partly because the percentage changes are calculated on a small base. If the company revises its estimates of the cost of the diabetes treatment, or if we can develop more accurate estimates of the QALYs gained by this treatment, the social returns from this project may be substantially larger or smaller.

Table B-2. Sensitivity of Social NPV to a 25 Percent Change in Per-Patient Treatment Cost and QALYs

ATP Project	Percentage Change in Expected Social Return on Investment (NPV)	
	Cost	QALYs
Stem Cell Expansion	25%	N/A
Biopolymers for Tissue Repair	25%	N/A
Living Implantable Microreactors	11%	36%
Proliferated Human Islets	362%	381%
Biomaterials for Clinical Prosthesis	N/A	25%
Gene Therapy Applications	1%	26%
Universal Donor Organs	7%	18%

NA = not applicable

B.1.3 Sensitivity to the Probability of Technical Success

Table B-3 shows how the results of our analysis change if we assume that the probability of technical success is equal to 1. Note that in our model, the expected benefits and costs *following the R&D phase* are multiplied by the probability of technical success. The table shows how our estimates of the social return on public investment, NPV, and IRR would be different if there was no uncertainty about the technical success of these projects. Although the NPV is significantly higher in some cases, the IRR does not change a great deal because both costs and benefits in the commercialization and production phases are multiplied by the probability of technical success.

B.2 SENSITIVITY OF PRIVATE RETURNS

This section describes the sensitivity of private returns to several key parameters:

- discount rate,
- commercialization cost percentage,
- production cost percentage,
- product price, and
- probability of technical success.

Table B-3. Sensitivity of Expected Social Return on Investment to Probability of Technical Success

Project	NPV (millions)		IRR	
	Under Baseline Assumption	When Prob of Success = 1	Under Baseline Assumption	When Prob of Success = 1
Stem Cell Expansion	$134	$168	20%	21%
Biopolymers for Tissue Repair	$98	$131	51%	55.36%
Living Implantable Microreactors	$74,518	$78,441	149%	149%
Proliferated Human Islets	$2,252	$6,787	36%	37%
Biomaterials for Clinical Prosthesis	$32,855	$41,070	118%	121%
Gene Therapy Applications	$2,411	$6,971	106%	129%
Universal Donor Organs	$2,838	$6,310	91%	101%

For the discount rate, we calculated the value of composite NPV for 5 percent and 1 percent discount rates. For the probability of technical success, we compared the value of composite NPV under the baseline assumptions to the NPV when the probability of success is 1. For the other variables, we varied them from their baseline values by 25 percent and calculated the percentage change in composite NPV.

B.2.1 Sensitivity of Results With Respect to the Discount Rate

As shown in Table B-4, our estimates of private return on investment are fairly sensitive to the discount rate assumption. Increasing the discount rate from 3 percent to 5 percent changes composite private returns by about 38 percent from the baseline result. Decreasing the discount rate from 3 percent to 1 percent increases composite NPV by about 54 percent.

Table B-4. Private NPV for ATP Projects in Tissue Engineering for a Single Preliminary Application: 5 and 1 Percent Discount Rates (1996$ millions)

	5 Percent	1 Percent
Project returns	$977	$2,409
Increment attributable to ATP	$589	$1,369

B.2.2 Sensitivity of Results with Respect to Cost Parameters

As explained in Section 2, we had very little data on costs that companies would incur during commercialization and production. In the absence of information from the companies, we developed assumptions for these variables based on average values in the pharmaceutical and biotechnology industries. We assumed that the

- commercialization cost is 37 percent of expected revenue and
- variable cost of production is 42 percent of revenue.

Composite private return on investment is most sensitive to changes in assumptions about the commercialization cost and the cost of production.

We also made various assumptions about product price, based on our interviews with company representatives. Table B-5 shows the percentage change in composite NPV given a 25 percent change in these parameters. The sensitivity of the NPV estimates varies widely across projects. For some projects, the NPV is very sensitive to these assumptions. The composite returns are most sensitive to changes in our assumptions about production cost and commercialization cost. Thus, our confidence about our estimates of private returns depends largely on our certainty about these assumptions. Given that we used secondary industry information, we believe these estimates can be improved in the future by updating them with data from the companies when it is available.

Table B-5. Sensitivity of Results with Respect to Key Parameters

Parameter	Percentage Change in Composite NPV
Commercialization cost	67%
Production cost	72%
Product price	28%

B.2.3 Sensitivity to the Probability of Technical Success

Table B-6 shows how the composite private return on investment changes if we assume that the probability of technical success is equal to 1. The table shows how our estimates of the composite NPV and IRR would be different if there was no uncertainty about the technical success of these projects. The composite NPV is about 66 percent higher when we assume that all projects are successful. However, the IRR does not change because the costs of commercialization and production are higher, as are the benefits, when we are certain of success.

Table B-6. Sensitivity of Composite Private Return on Investment to Probability of Technical Success

	NPV of ATP Project (thousands)	IRR of ATP Project
Under baseline assumptions	$1,564	12%
When probability of success = 1	$2,605	12%