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## 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.

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## 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.

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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.<sup>1</sup>

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.

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<sup>1</sup>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.

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## 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.

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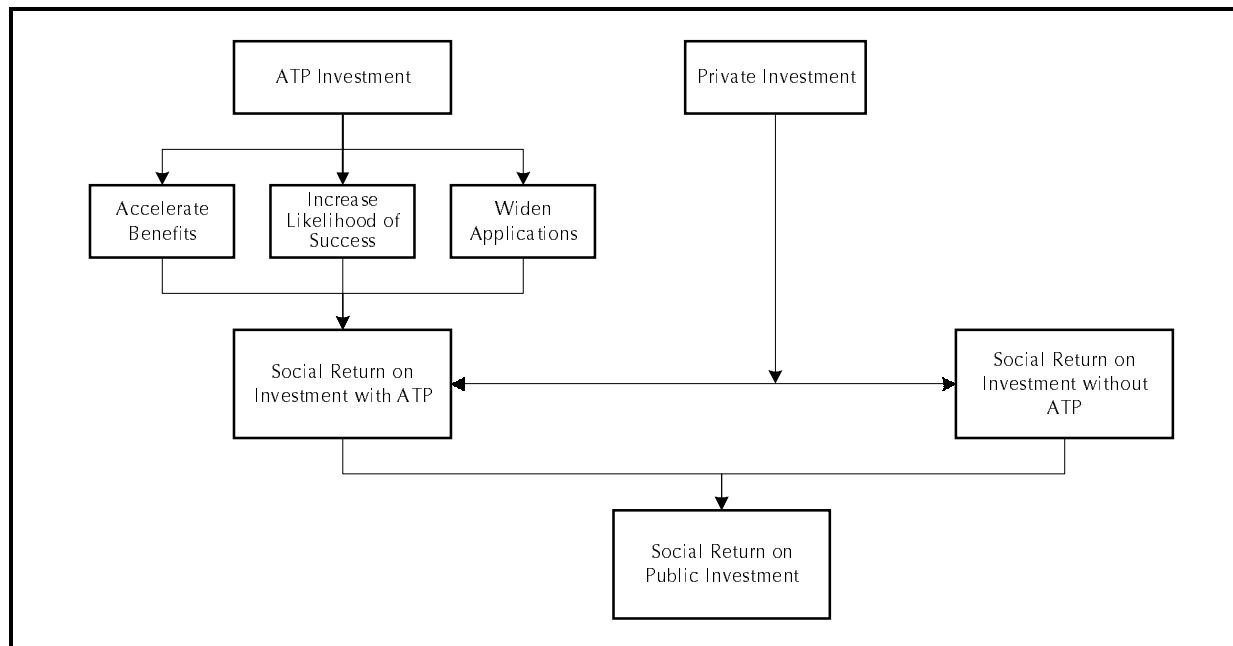
*From a public policy perspective, the social return on public investment is the central factor for determining the impact of ATP, because it quantifies the increment in expected social outcomes that is attributable to ATP's investment.*

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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.

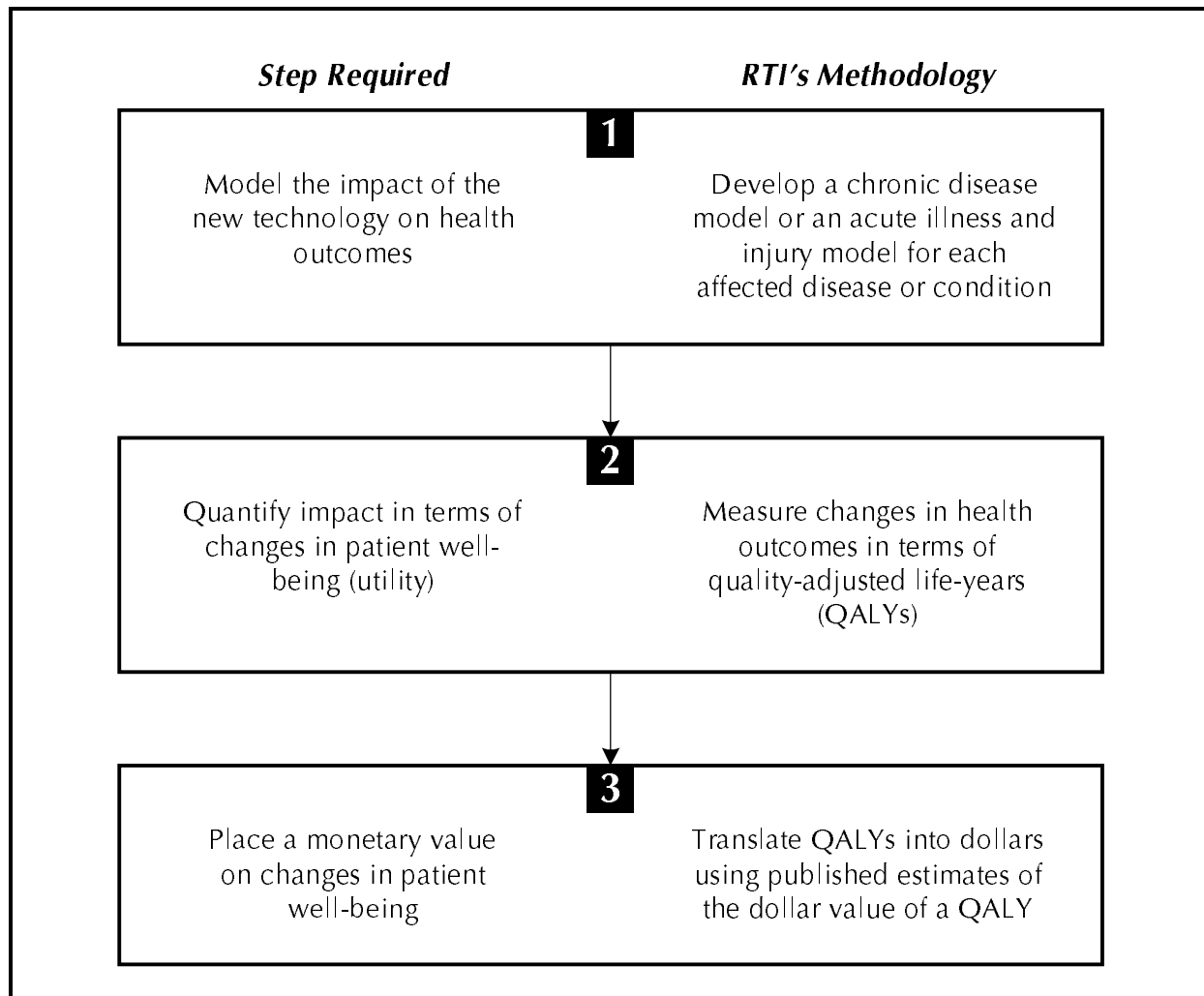
The second step is to assess how those changes in health outcomes affect the well-being of the patient (i.e., how the quality and length of life is affected). We use the *quality-adjusted life-year* (QALY) to measure the utility associated with different health states. The QALY combines morbidity and 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, commercialization, 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

$$\text{NPV} = \sum_{t=1}^n \frac{\text{NB}_t}{(1+r)^t} \quad (1.1)$$

where  $t$  indexes the year in which either benefits or cost occur,  $\text{NB}_t$  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

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

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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.

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.

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.

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

<sup>a</sup>Throughout this report, we refer to each project by the abbreviated title listed below the full title.

<sup>b</sup>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**

Astrom 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 Astrom 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 Astrom 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 periodontal 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 transgenic animals that express key human genes to eliminate the HAR response. They plan to develop organs, called UniGraft organs, from transgenic pigs.

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.

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.

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## 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 <sup>a,b,c,d</sup>	1992 to 2011	\$34,258	116%

<sup>a</sup>The composite measure of return is based on a sum of expected benefits and costs in each year across all projects.

<sup>b</sup>The time period for the composite measure includes all years from all the individual project periods.

<sup>c</sup>The composite NPV is not a simple sum of individual NPV because the time periods are different.

<sup>d</sup>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**

ATP Project	Expected Social Return on Investment		Expected Social Return on Public Investment	
	NPV (1996\$ millions)	IRR (%)	NPV (1996\$ millions)	IRR (%)
Stem Cell Expansion	\$134	20%	\$47	21%
Biopolymers for Tissue Repair <sup>a</sup>	\$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 <sup>b</sup>	\$109,229	115%	\$34,258	116%

<sup>a</sup>For Biopolymers, the two sets of figures are identical because all of the social return can be attributed to ATP investment.

<sup>b</sup>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.<sup>2</sup> 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.

<sup>2</sup>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 <sup>a</sup> (years)	Increase in the Probability of Success (percent)	Widening of Technology Applications <sup>b</sup>
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

<sup>a</sup>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.

<sup>b</sup>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.<sup>3</sup> 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<sup>a</sup>**

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

<sup>a</sup>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.

<sup>3</sup>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.

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**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.

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*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.*

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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.