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

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

the 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

Year	Eligible Patients	Number Using ADMAT	
		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.

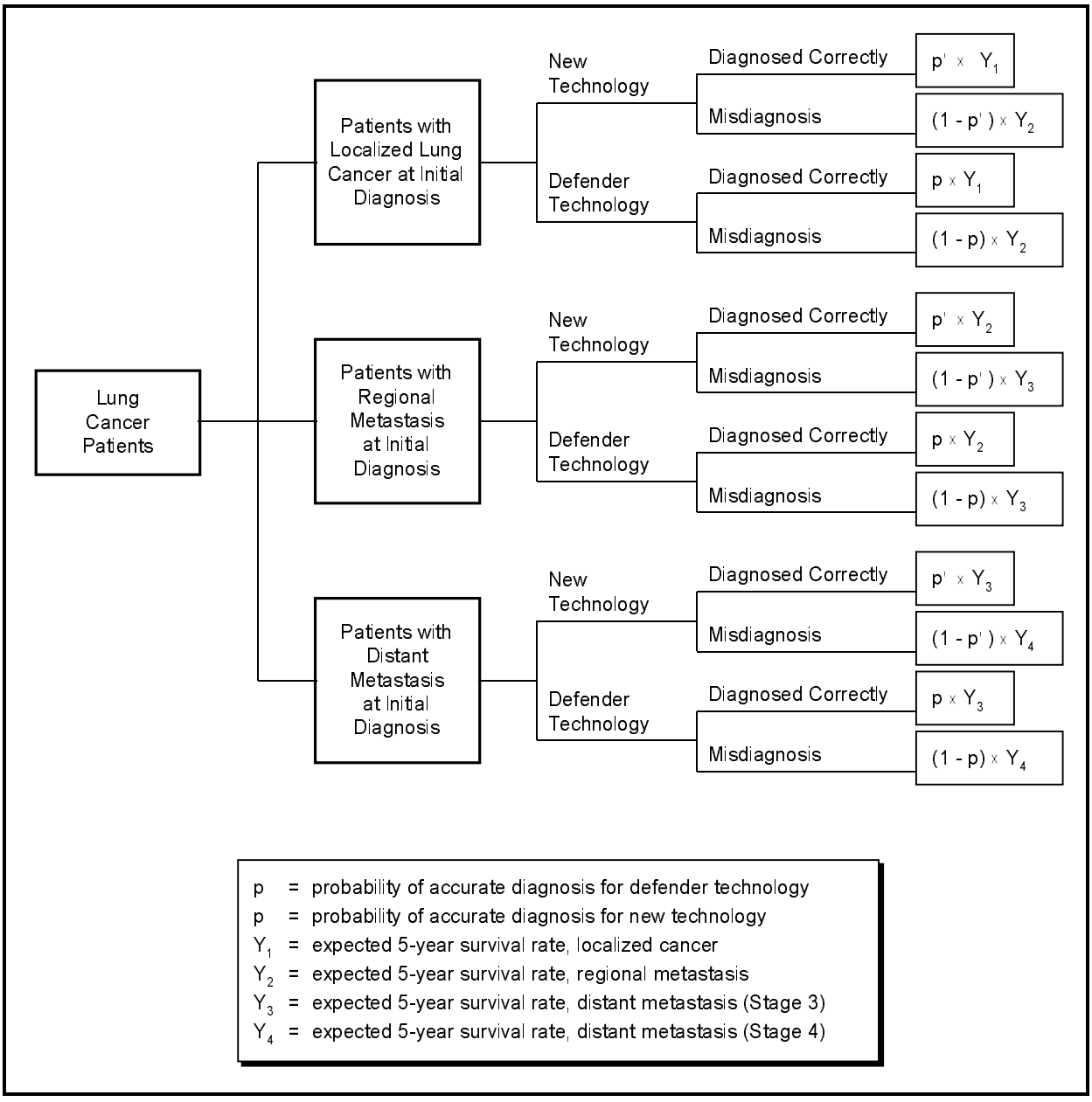
Defender Technology. Currently no technologies image soft tissue adequately to diagnose metastasis at a very early stage. Thus, Progenitor's product will not replace any current technologies but will supplement the current diagnostic techniques.

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.