2 Methodology

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

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

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

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

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

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

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

➤ medical benefits to patients,

➤ changes in the cost of health care, and

➤ costs and revenues to private companies.

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

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

2.1 THE TIMELINE OF R&D INVESTMENT COSTS AND BENEFITS

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

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

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

➤ R&D phase,

➤ commercialization phase, and

➤ production phase.

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

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

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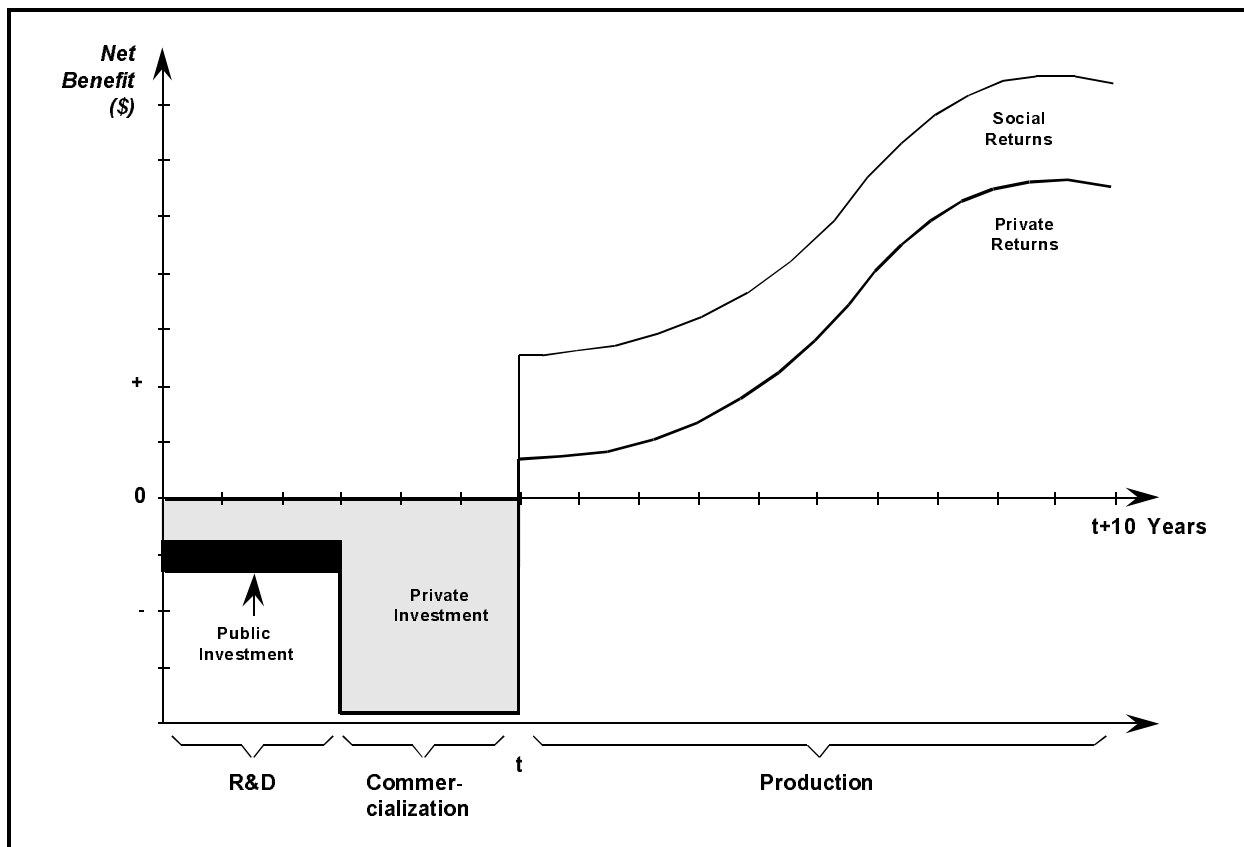
[1]We are speaking of the company narrowly as the business unit developing the new technology, under the assumption that it produces no other products.

2.1.1 The R&D Phase

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

$$Pr = f(R) \qquad\qquad (2.1)$$

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

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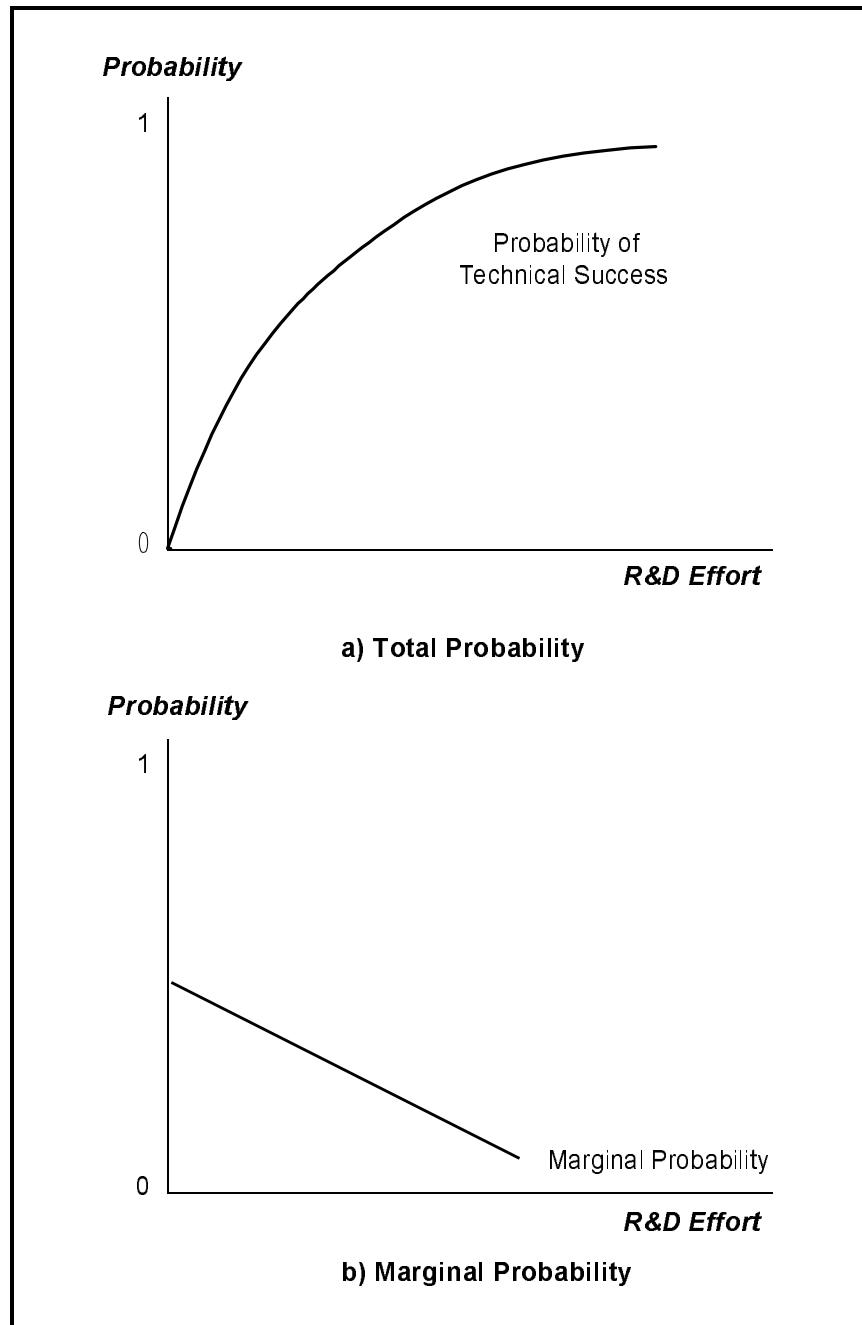
2.1.2 The Commercialization Phase

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

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

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

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

Probability

1

Probability of
Technical Success

0

R&D Effort

a) Total Probability

Probability

1

0

Marginal Probability

R&D Effort

b) Marginal Probability

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

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

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

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

2.1.3 The Production Phase

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

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

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

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

2.2 MEASURING THE IMPACT OF ATP ON TECHNOLOGY DEVELOPMENT

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

2.2.1 ATP's Acceleration of R&D

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

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

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

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

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

Figure 2-3. Impact of Acceleration on Social Returns
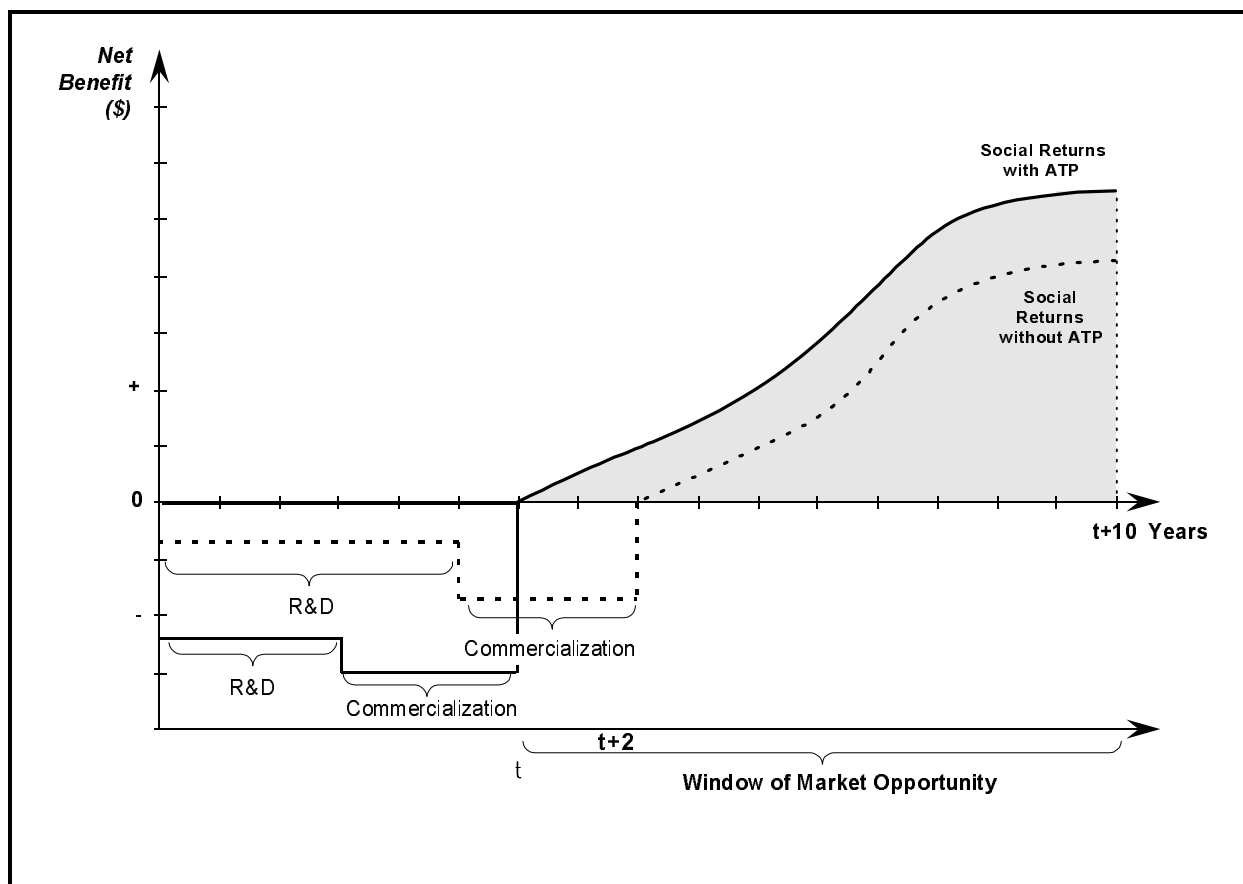
2.2.2   ATP's Impact on the Probability of Success

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

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

The degree to which ATP funding increases the probability of technical success depends on
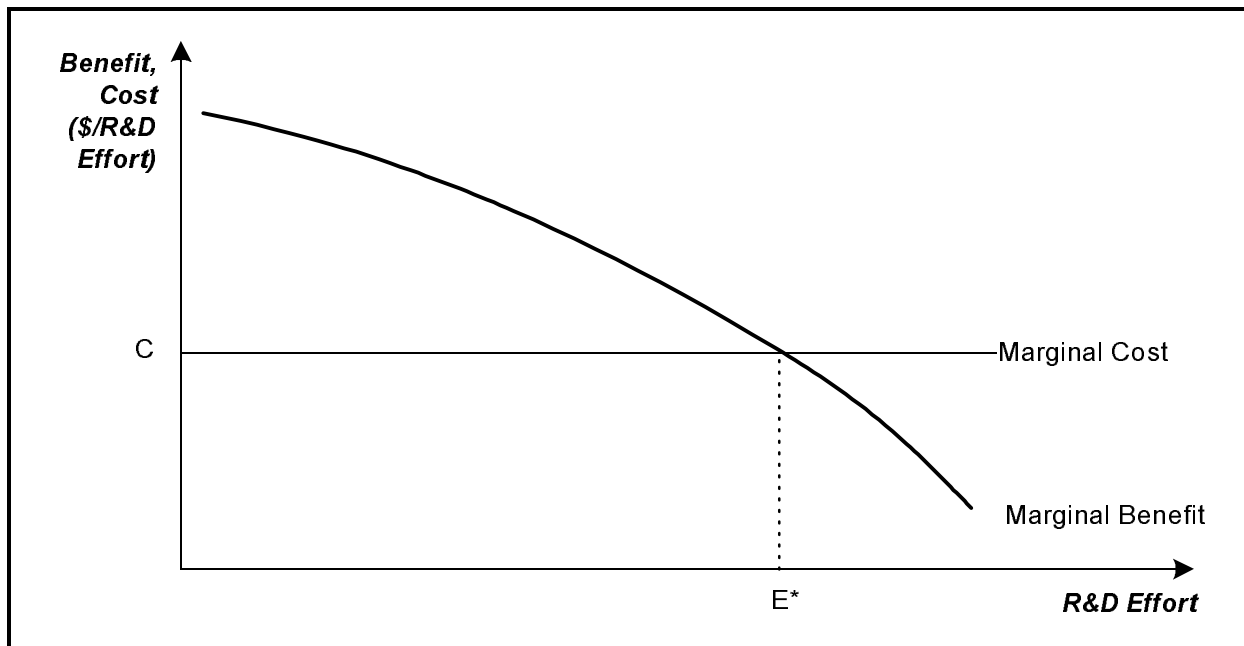
➤ ATP's impact on the cost of R&D to the firm,

➤ the expected marginal benefit of R&D effort, and

➤ the relationship between R&D effort and the probability of technical success.

The Firm's R&D Investment Decision

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

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

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

ATP's Impact on R&D Price and Investment

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

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

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

Figure 2-5. Impact of ATP Funding on R&D Effort
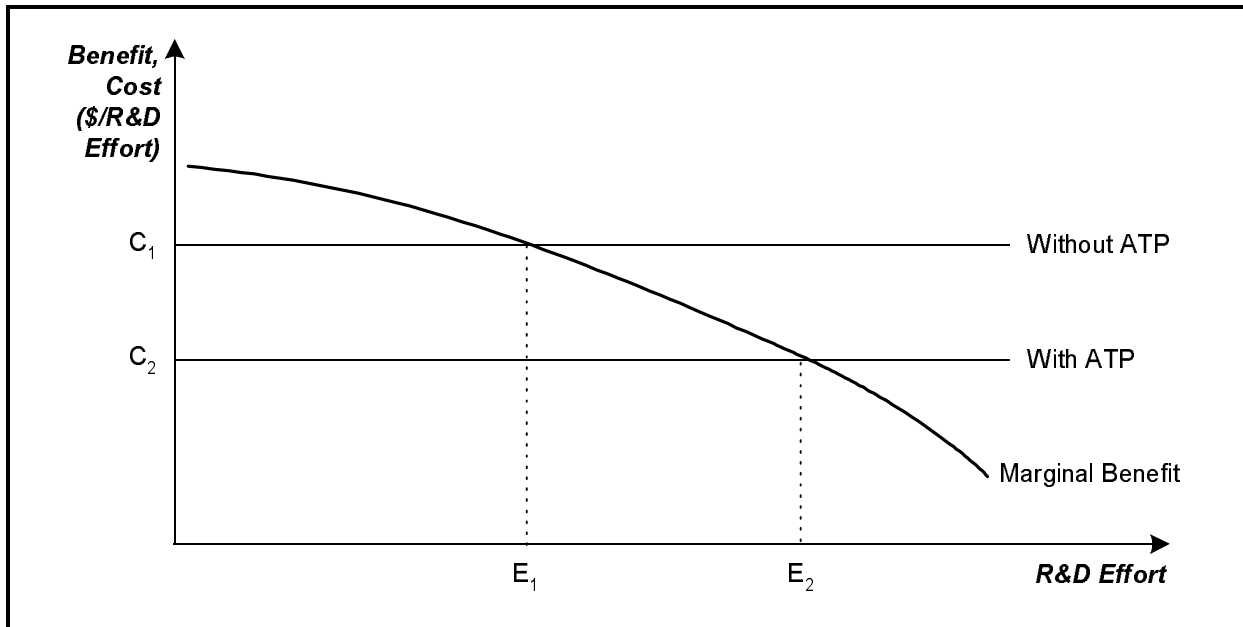
The impact of a change in the marginal cost of R&D effort on the quantity of R&D effort depends on the elasticity of the marginal benefits function:

$$\frac{\partial \ln E}{\partial \ln C} = \varepsilon, \tag{2.2}$$

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

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

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

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

➤ For companies that indicated a significant reduction in the funding for the project in the absence of ATP, we assume that their marginal benefit function is elastic with a value of -2.

➤ For companies that indicated that in the absence of ATP they would have proceeded with the project but under some possible funding constraints, we assume that their marginal benefit function is relatively inelastic with a value of -0.5.

➤ For companies that told us that the absence of ATP funding would have made little or no difference in the project's funding level, we assume that the cost of R&D was immaterial to their decision to proceed with the project and that the elasticity of the marginal benefit function is -0.01.

Chapter 3 explains our assumptions for each company.

R&D Effort and the Probability of Technical Success

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

$$\frac{\partial \ln P_r}{\partial \ln E} = 0.3. \tag{2.3}$$

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

2.2.3 Widening the Scope of an ATP Project

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

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

2.3 EVALUATING MEDICAL BENEFITS TO PATIENTS

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

2.3.1 Valuing Per-Patient Changes in Health Outcomes

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

➤ Step 1: Model the technology's impact on health outcomes

➤ Step 2: Quantify changes in health outcomes in terms of patient well-being

➤ Step 3: Determine the monetary value of patient changes in well-being

Modeling Differences in Health Outcomes

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

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

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

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

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

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

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

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

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

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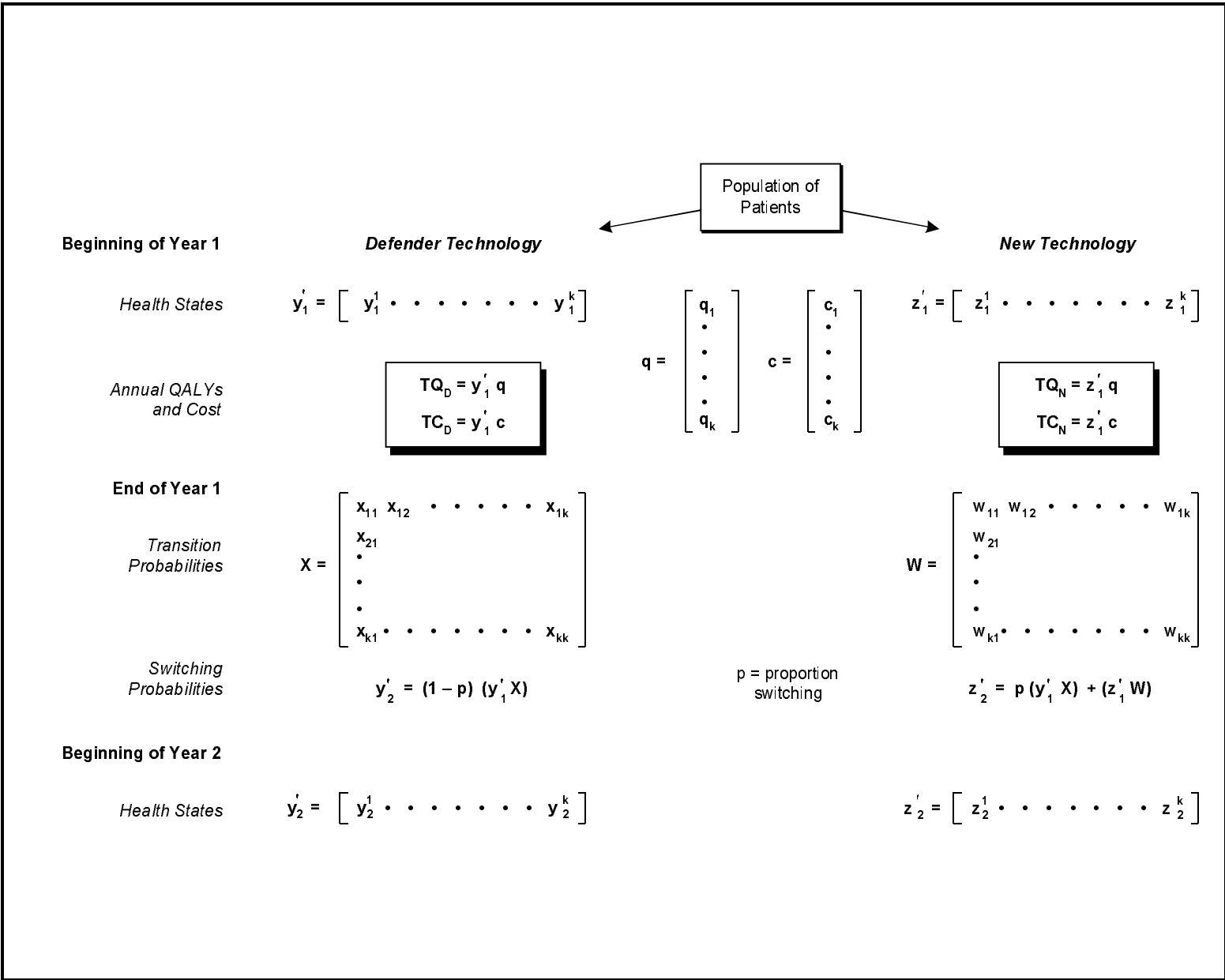
Figure 2-6. Chronic Disease Model of Health and Cost Impacts of New Technologies

Population of Patients

Defender Technology

Beginning of Year 1

New Technology

Health States

$$y_1' = \begin{bmatrix} y_1^1 \cdot \cdot \cdot \cdot \cdot \cdot \cdot y_1^k \end{bmatrix}$$

$$q = \begin{bmatrix} q_1 \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ q_k \end{bmatrix} \qquad c = \begin{bmatrix} c_1 \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ c_k \end{bmatrix}$$

$$z_1' = \begin{bmatrix} z_1^1 \cdot \cdot \cdot \cdot \cdot \cdot \cdot z_1^k \end{bmatrix}$$

Annual QALYs and Cost

$$TQ_D = y_1' \, q$$
$$TC_D = y_1' \, c$$

$$TQ_N = z_1' \, q$$
$$TC_N = z_1' \, c$$

End of Year 1

Transition Probabilities

$$X = \begin{bmatrix} x_{11} & x_{12} & \cdot & \cdot & \cdot & \cdot & x_{1k} \\ x_{21} & & & & & & \\ \cdot & & & & & & \\ \cdot & & & & & & \\ x_{k1} & \cdot & \cdot & \cdot & \cdot & \cdot & x_{kk} \end{bmatrix}$$

$$W = \begin{bmatrix} w_{11} & w_{12} & \cdot & \cdot & \cdot & \cdot & w_{1k} \\ w_{21} & & & & & & \\ \cdot & & & & & & \\ \cdot & & & & & & \\ w_{k1} & \cdot & \cdot & \cdot & \cdot & \cdot & w_{kk} \end{bmatrix}$$

Switching Probabilities

$$y_2' = (1 - p) \, (y_1' \, X)$$

$$p = \text{proportion switching}$$

$$z_2' = p \, (y_1' \, X) + (z_1' \, W)$$

Beginning of Year 2

Health States

$$y_2' = \begin{bmatrix} y_2^1 \cdot \cdot \cdot \cdot \cdot \cdot \cdot y_2^k \end{bmatrix}$$

$$z_2' = \begin{bmatrix} z_2^1 \cdot \cdot \cdot \cdot \cdot \cdot \cdot z_2^k \end{bmatrix}$$

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

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

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

The chronic disease model quantifies differences between the new and defender technologies with respect to
➤ the proportion of patients in each health state and
➤ the patient's probability of moving from one health state to the next.

It also incorporates the expected penetration of the new technology.

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

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

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

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

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

Figure 2-7. Acute Illness and Injury Model of Health and Cost Impacts of New Technologies
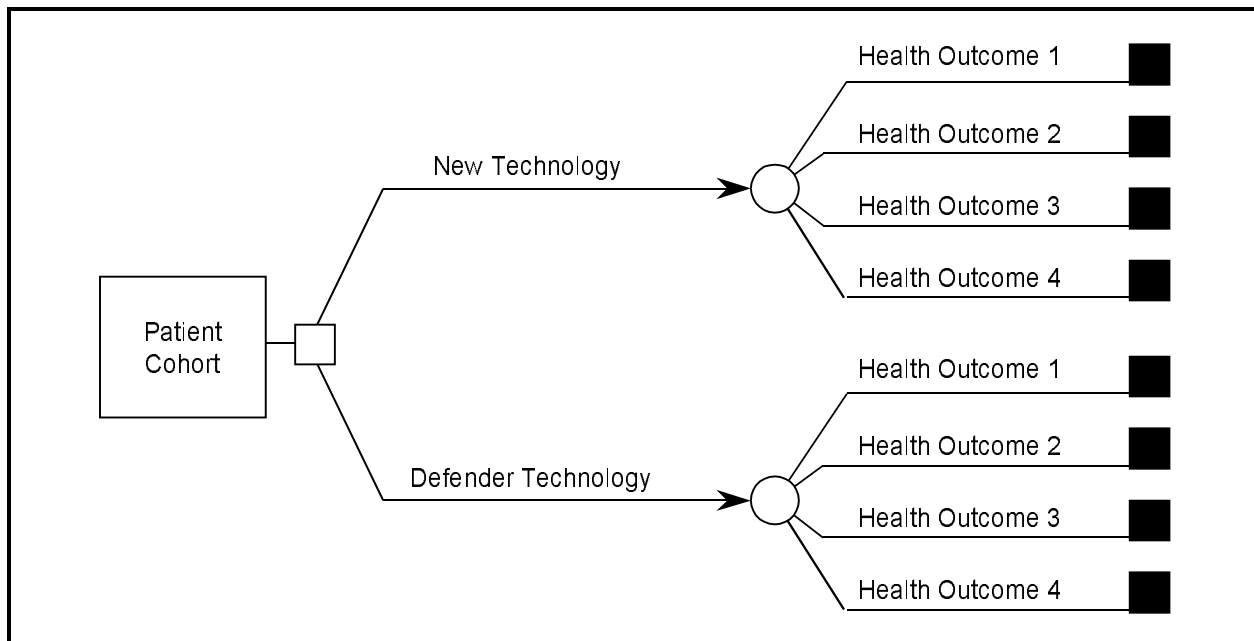
The acute illness and injury model describes how the new and defender technologies leads to different health outcomes and their associated QALYs costs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Quantifying Changes in Patient Well-Being

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

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

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

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

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

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

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

> ➤ expressed preference, in which individuals are surveyed directly to elicit their WTP/WTA for the desirable change or to prevent an undesirable change, and

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

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

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

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

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

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

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

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

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

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

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

Determining the Monetary Value of Changes in Well-Being

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

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

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

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

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

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

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

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

Table 2-2. Alternative QALY Values

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

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

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

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

2.3.2 Determining the Number of Beneficiaries

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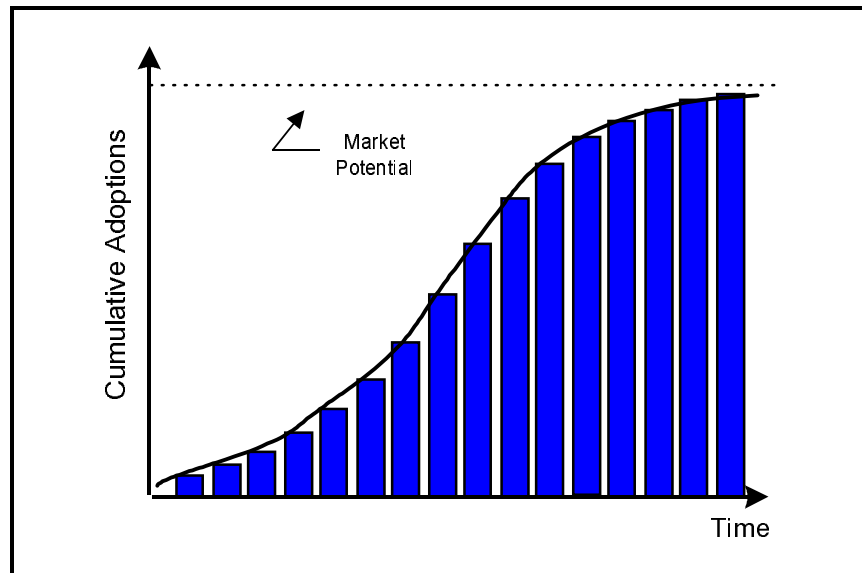
The total medical benefits of a new technology and the revenues to private companies depend on the speed of the new technology's market penetration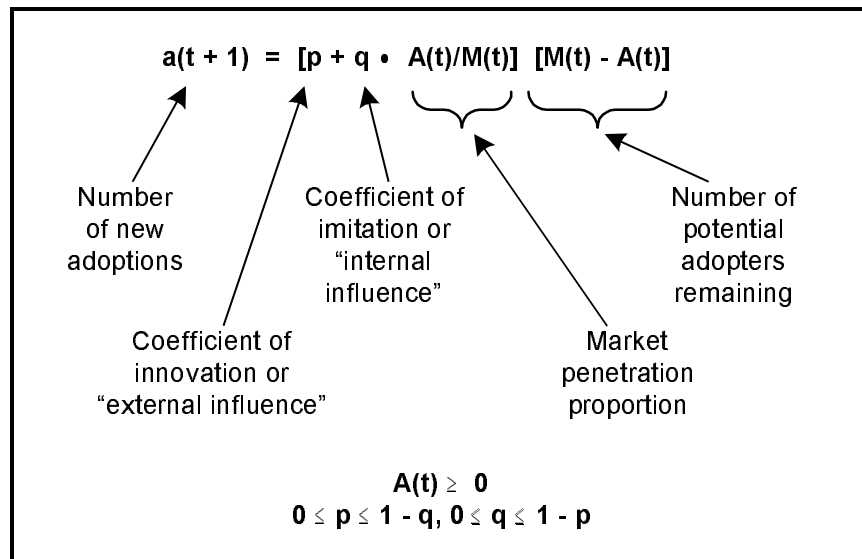. The adoption of a new technology is typically a function of the benefits of adoption to firms or consumers using the technology. Typically, firms and consumers do not adopt new technologies simultaneously; instead, innovations "diffuse" into use over time (Reinganum, 1989).

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

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

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

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

Figure 2-8. The Classic Diffusion Curve

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

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

Number of new adoptions

Coefficient of imitation or "internal influence"

Number of potential adopters remaining

Coefficient of innovation or "external influence"

Market penetration proportion

$$A(t) \geq 0$$
$$0 \leq p \leq 1 - q, 0 \leq q \leq 1 - p$$

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

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

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

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

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

Collecting Model Data

The following data are required to estimate the Bass model:

➤ M(t) = potential market size in year t and

➤ A(t) = the cumulative number of early adopters in year t.

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

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

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

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

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

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

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

Estimating the Diffusion Model

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

$$a(t + 1) = [p+q \bullet A(t)/M(t)] \; [M(t) - A(t)] \tag{2.5}$$

where

➤ a(t+1) is the number of new adopters in the next year,

➤ A(t) is the cumulative number of adopters in year t,

➤ M(t) is the total market potential in year t, and

➤ A(t+1) = A(t) + a(t+1).

Rewriting Eq. (2.5) provides the estimated equation:

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

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

The forecast equation is

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

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

2.4 ESTIMATING CHANGES IN HEALTH CARE COSTS

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

$$TC_D^1 = \mathbf{y}_1' \mathbf{c} \text{ and } TC_N^1 = \mathbf{z}_1' \mathbf{c} \quad (2.8)$$

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

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

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

2.5 CALCULATING RETURNS TO PRIVATE COMPANIES

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

➤ probability of technical success;

➤ expected investments and costs for

✓ R&D,

✓ commercialization, and

✓ production; and

➤ expected revenues.

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

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

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

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

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

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

2.5.1 Determining R&D Investment

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

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

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

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

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

2.5.2 Determining Costs of Commercialization and Production

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

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

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

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

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

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

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

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

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

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

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

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

2.5.3 Calculating Revenues

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

2.5.4 Estimating the Probability of Technical Success

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

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

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

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

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

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

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

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

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

2.6 CALCULATING MEASURES OF ECONOMIC RETURN

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

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

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

1. Construct the time profile of benefits and costs for the with-ATP and without-ATP scenarios.

2. Choose measures of economic return.

3. Choose a discount rate.

4. Conduct sensitivity analysis on key parameters.

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

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

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

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

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

$$\text{IENB}_t = \text{ENB}^{\text{w}}_t - \text{ENB}^{\text{wo}}_t \qquad (2.12)$$

where IENB_t is the incremental expected net benefit in year t, ENB^{w}_t is the with-ATP expected benefit in year t, and ENB^{wo}_t is the

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

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

2.6.2 Choosing Measures of Economic Return

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.6.3 Choosing a Discount Rate

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

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

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

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

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

➤ first convert all uncertain costs and benefits into "certainty equivalents," expressed in real terms, and

➤ discount at a selected riskless real discount rate (Gold et al., 1996).

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

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

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

The Panel also recommends the following:

➤ discounting costs and benefits at the same rate and

➤ conducting sensitivity analysis at 5 percent because many other studies have used 5 percent as their base case.

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

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

➤ discounted costs and benefits at the same rate,

➤ discounted social and private returns at the same rate (since they have been risk-adjusted),

➤ used the 3 percent discount rate, and

➤ conducted sensitivity analysis for discount rates of 1 and 5 percent.

2.6.4 Conducting Sensitivity Analysis

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

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

➤ discount rate,

➤ per-patient treatment costs and QALYs,

➤ probability of technical success,

➤ commercialization cost parameters,

➤ R&D cost parameters,

➤ production cost parameters, and

➤ product price.

Appendix B contains the results of these sensitivity analyses.

2.7 METHODOLOGICAL CHALLENGES AND LIMITATIONS

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

2.7.1 Characterizing New and Defender Technologies

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

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

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

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

2.7.2 Modeling Medical Benefits

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

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

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

2.7.3 Forecasting Market Penetration

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

2.7.4 Estimating Company Costs and Revenues

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

may be misleading because they do not account for the specific circumstances of each company. Furthermore, the biotechnology industry is very young. As the industry matures and becomes more profitable, the ratios between sales and these costs will probably change.

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

2.7.5 Calculating Social and Private Returns

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