

# The Economics of Gene Therapy and of Pharmacogenetics

Patricia Danzon, PhD,<sup>1</sup> and Adrian Towse, MA, MPhil<sup>2</sup>

<sup>1</sup>Wharton School, University of Pennsylvania, Philadelphia, PA, USA; <sup>2</sup>Office of Health Economics, London, England, UK

## ABSTRACT

This paper focuses on the economic issues arising from two uses of genomics: 1) the development of gene therapy; 2) and use of pharmacogenetics to identify a patient's genotype before treatment to exclude those who will not benefit or who may be harmed. We conclude that private-sector investment aimed at developing gene therapy for monogenic diseases is likely to be socially suboptimal. Short-term administration regimens yielding long-term therapeutic benefits are likely to meet payer resistance to large "one-off" costs because of budget constraints or, in competitive systems, concerns that the savings would accrue to future insurers or would attract high-cost patients. For some monogenic diseases, patient numbers may be too small to support commercial development without changes to orphan drug legislation or payer willingness to accept higher cost-effectiveness

thresholds. In the case of pharmacogenetics, we conclude that it can often be socially optimal to test before treatment, particularly if the proportion of nonresponders is high, if there is a potential for serious adverse reactions, or if the test is inexpensive. Genetic testing that fragments the patient population could reduce incentives for R&D unless prices are adjusted to reflect the higher expected benefits of targeted treatment per patient. Even in situations where prices are adjusted, patient populations may be too small to make commercial development viable. This problem with small numbers is analogous to that associated with gene therapy for monogenic diseases and may require similar remedies if society values developing treatments for these diseases.

**Keywords:** gene therapy, monogenic disease, orphan drugs, pharmaceutical pricing, pharmacogenetics.

## Introduction

Genomics offers great promise for providing new and more effective therapies and diagnostic tests for patients. Many new medicines will arise from the use of pharmacogenomics in conventional drug discovery as knowledge of the human genome increases understanding of disease. This paper focuses on the economic issues arising from two relatively novel uses of genomics:

1. the development of gene therapy, where the aim is to insert genes that will produce or regulate the expression of proteins that are related to the patient's disease. This approach is most immediately relevant to monogenic diseases, many of which are currently incurable. The hope is that gene therapy will provide long-term therapeutic benefits;
2. the use of pharmacogenetics to identify a patient's genotype before treatment, to identify

those who will not benefit or who may be harmed. Here genomics is used to identify genetic traits that may lead either to nonresponse or to adverse reactions to specific medicines for any indication, including the great majority of diseases that are polygenic but in which genetic makeup can affect response to specific treatments.

We examine whether existing reimbursement and regulatory regimes will encourage the socially optimal development of these two uses of genomics and suggest possible policy changes. The high costs and uncertainties associated with gene therapy and its very novel modes of action, small patient numbers, and long-lived therapeutic effects may lead to suboptimal levels of commercial research. In the case of pharmacogenetics, testing could be socially beneficial but nevertheless reduce innovative firm's incentives to develop new drugs. This is in part due to the low numbers of patients treated—because drugs would be targeted at a subset of the patient population—and to the costs of testing. This may be offset by reduced R&D costs per drug developed or by unit price increases that reflect the greater specificity of use and consequent greater expected health gain per patient treated.

*Address correspondence to:* Adrian Towse, Director, Office of Health Economics, 12 Whitehall London SW1A 2DY. E-mail: atowse@ohe.org

The Office of Health Economics is supported by the Association of the British Pharmaceutical Industry.

### Formal Statement of the Problem

Assume that a new therapy (g) is considered cost-effective by payers for their patients relative to an existing treatment (0) if

$$\Delta C_{g,0}/\Delta E_{g,0} < k_p \quad (1)$$

where

$$\Delta C_{g,0} = P_g - P_0 + \Delta C_{g,0}^d + \Delta C_{g,0}^i$$

$P_g, P_0$  = respectively, the prices of the gene therapy and existing treatment;

$\Delta C_{g,0}^d$  = change in other direct treatment costs;

$\Delta C_{g,0}^i$  = change in indirect costs;

$\Delta E_{g,0}$  = change in quality-adjusted life years (QALYs) or other outcome measures; and

$k_p$  = threshold cost per QALY at which an intervention is considered cost-effective for the treatment of patient group p.

We assume  $\Delta C_{g,0}$  and  $\Delta E_{g,0}$  are discounted at a socially optimal rate. If  $k_p$  is optimally chosen (i.e., reflects the willingness to pay for additional investment in treatment of patient group p), then equation 1 defines the condition for socially optimal reimbursement. We can use it to define the maximum price ( $P_g^{\max}$ ) at which the new therapy is cost effective:

$$P_g^{\max} = k_p \Delta E_{g,0} + (P_0 + \Delta C_{g,0}^d + \Delta C_{g,0}^i) \quad (2)$$

$$\text{or } P_g^{\max} = b \quad (2')$$

where  $b = k_p \Delta E_{g,0} + (P_0 + \Delta C_{g,0}^d + \Delta C_{g,0}^i)$  and represents the social benefits (positive or negative) from treatment g compared with treatment 0.

Assume that payers typically set the actual price at some fraction  $\alpha$  of the maximum price, where  $\alpha$  reflects the share of the social gain that accrues to the innovator firm and  $(1 - \alpha)$  is the share captured by the payer, so that

$$P_g = \alpha b = \alpha P_g^{\max} \quad (3)$$

Consider now the perspective of the firm planning to invest in developing a new therapy (g). We abstract from the fact that in practice  $\alpha$  and  $P_g^{\max}$  may not be known with certainty because of a lack of transparency in the price-setting process. Ignoring this uncertainty and using a net present value investment-valuation approach, the producer's break-even profit constraint can be written:

$$\Pi^T = \Sigma^T [(P_g - M)Q^i N^i (1+r)^{-i}] - F(r, L, p) \quad (4)$$

where

( $\Pi$ ) = discounted present value of net revenue over the T years of the product's market life ("profit");

M = variable cost per treatment to the producer, assumed to be invariant over time;

N = number of patients treated per year;

Q = number of treatments per patient per year, such that NQ is the number of treatments sold per year;

F = discounted present value of the firm's R&D cost, with  $F_r, F_L > 0, F_p < 0$ ;

r = cost of capital;

L = expected years from discovery to launch;

p = probability of success in showing safety and efficacy in clinical trials;

other fixed costs are zero.

To assess the implications of the payer's cost-effectiveness requirement on the producer's break-even constraint, we substitute the price from equation 3 into the firm's break-even constraint in equation 4. Therefore,

$$\Pi^T = \Sigma^T [(\alpha b - M)Q^i N^i (1+r)^{-i}] - F(r, L, p) \quad (4')$$

Equation 4' provides a framework in which to consider how the characteristics of gene therapy and pharmacogenetics may affect their commercial viability compared with other pharmaceutical R&D.

### Gene Therapy

Let us consider effects on revenue and R&D costs. The total operating net revenue depends on:

1. the social value of treatment b (the cost savings and gain in quality of life) and the producer's share,  $\alpha$ ;
2. the number of patients treated per year N, which may be low because most monogenic diseases (i.e., those involving only a single gene) affect a relatively small number of patients;
3. Q, which may be small because of the long-term benefits of gene therapies, implying that each patient may require treatment to be administered only once or twice a year rather than once or twice a day, the standard regimen for many pharmacotherapeutic agents administered to chronically ill patients; and
4. the variable cost of producing and delivering the treatment, M, which is likely to be significantly higher for gene therapies than for other drugs owing to both the novel delivery systems required and the small patient base over which to realize scale economies.

The extended duration of benefits and consequent reduction in frequency of administration

(low  $Q$  per patient for long-lasting therapies) would be irrelevant if payers were willing to assume that the cost of new therapies would be fixed relative to the full social benefits:  $P = \alpha P^{\max}$ . In this case, the price for gene therapy treatment would increase proportionately with the duration of its effects. A low  $Q$  would be associated with a relatively high benefit,  $b$ , per administered treatment compared with a once-a-day alternative therapy, thus preserving neutral incentives for efficient investment in R&D with respect to duration of benefits. This ideal may, however, be undermined in practice for several reasons.

First, payers tend to scrutinize and bargain aggressively over products that are priced relatively high per dose or per patient treated. If so, the producer's share is a decreasing proportion of the maximum price:  $d\alpha/dP^{\max} < 0$ . Second, turnover of patient populations could make competing health insurers reluctant to pay for long-lasting therapies because the insurer that pays for the initial treatment does not capture the full savings in future treatment costs if patients subsequently switch to other insurers. Thus the risk of adverse selection could reinforce the incentive of insurers to avoid offering long-lived therapies that target high-cost patients, such as gene therapy. This should be less of a problem in countries where patients have a limited choice of health plans, such as Canada and the United Kingdom. However, in these systems managers and doctors face annual budget constraints that limit their ability to invest in treatments that have higher immediate costs but longer-term benefits.

The private cost of R&D,  $F(r, L, p)$ , may be atypically high for gene therapy compared with conventional therapy despite the relatively smaller requirements in terms of trial sizes. The extremely novel mode of action means that the probability of success,  $p$ , is very low and the expected duration of the R&D process,  $L$ , is relatively long. Several hundred clinical trials of gene therapy have been initiated but none has been successfully completed so far. The deaths in 1999 of two trial participants [1] have made expectations even more pessimistic.

Thus, values for each element of the expression for  $\Pi^T$  are likely to be lower in the case of gene therapies for monogenic diseases than corresponding values for conventional therapies for major diseases. The high risk and costs of R&D to companies are a reflection of real social costs arising from basic research into new technologies, the benefits of which cannot be fully expropriated by

the company. If reimbursement systems are biased against therapies providing long-term benefits, under-investment compared to the social optimum may result.

An examination of clinical trials in gene therapy tends to support our concerns that low patient numbers and investor perception of payer resistance to long-lived therapies may be influencing the allocation of R&D efforts. The majority of gene therapy trials are in cancer indications (oncology), followed closely by trials directed at cures for AIDS and HIV infection [2]. Many trials are focused on variants of treatment that would require repeat administration rather than providing a one-off cure. Only one monogenic disorder, cystic fibrosis, is the subject of significant clinical development, due in part to the early discovery of the gene for this disease. Unlike all other areas of drug development, most clinical trials in gene therapy are undertaken with at least partial public funding [3]. This suggests that the initial promise of gene therapy—that of delivering cures for monogenic diseases—is unlikely to be realized without changes in incentives or significant public investment.

The problem of insufficient commercial incentives for investment in drugs for small populations is not unique to gene therapy. Orphan drug legislation enacted in the United States in 1983 provides special incentives, including 5-year market exclusivity for the orphan indication and special tax credits, for drugs to treat diseases that affect fewer than 200,000 US patients. The European Union has now established an orphan drug regime. However, long-lived gene therapies are disadvantaged relative to conventional therapies by the current legislation if payers resist price increases in proportion to the duration of the effects. If the 200,000 patient threshold is the number of patients expected to use an orphan drug per day per year, then, arguably, this number should be adjusted for long-lasting gene therapies. For example, if the gene therapy lasts 5 years, then in steady state only one-fifth of the population with the disease would be treated per year. Thus, to provide neutral incentives the orphan drug threshold for long-lasting therapies should be  $n \times 200,000$ , where  $n$  is the average duration of benefits for one treatment with gene therapy relative to that of conventional therapies. This will increase the likelihood that a gene therapy receives orphan status and the associated benefit of market exclusivity, which should increase the price the company receives for the gene therapy, thereby in-

creasing  $\alpha$ , the share of the social benefit that the company obtains.

Thus, the characteristics of gene therapy—long and uncertain R&D, a small patient base, and infrequent treatment—may lead to suboptimal commercial investment in these therapies. Reimbursement systems introduce a bias against gene therapy if payers respond to budgetary or commercial pressures by focusing on short-term drug-budget costs without due weight to long-term health benefits and societal savings. Although society has signaled a willingness to pay additional subsidies to encourage treatments for orphan diseases, current legislation is not neutral between treatments administered on a daily basis and those administered sporadically or once or twice in a lifetime. We consider the public policy implications in the final section of the paper.

### Pharmacogenetics

Pharmacogenetic testing is designed to identify patients' genotypes so that drugs can be targeted to the subgroup whose genetic makeup makes them most likely to benefit. This raises the expected effectiveness per patient treated and hence the cost-effectiveness of the drug by eliminating the cost of treating patients whose genetic makeup makes them unlikely to benefit (nonresponders) or likely to suffer harm (adverse responders). For example:

1. New tests based on the ApoE gene may identify patients who are more likely to benefit from drugs designed to slow the symptomatic degeneration associated with Alzheimer's disease [4].
2. Testing for the human CysLT<sub>1</sub> receptor for cysteinyl leukotrienes may predict the effectiveness in individual patients of the three new cysteinyl leukotriene antagonists for asthma [5].
3. The presence of the B<sub>1</sub> variant of the CETP gene appears to predict the response of patients with coronary atherosclerosis to statin treatment. In a clinical trial statins slowed disease progression in B<sub>1</sub>B<sub>1</sub> carriers but not in B<sub>2</sub>B<sub>2</sub> carriers [6].

Payers would rationally adopt pharmacogenetic testing before treatment if the savings from treating fewer patients and avoiding complications exceeded the costs of testing. For drug companies pharmacogenetic testing means lower patient volume and hence lower revenues per drug, other things being equal. This reduction in gross sales may be exacerbated if payers subtract the costs of the genetic screening from the price that they are

willing to pay or reimburse for the drug. A key issue, therefore, is the extent to which we might expect drug prices to increase as a consequence of testing, as might be the case if the innovator were able to get a share of any increased societal benefit arising from testing.

To examine the potential impact of testing from societal, payer, and company perspectives we adapt the formal model set out earlier to introduce responders and nonresponders, adverse reactions, and testing costs.

Let  $N_1$  be the number of patients who benefit from the drug.  $N_2$  is the number who do not benefit but who cannot be identified without testing, so

$$N = (N_1 + N_2)$$

Let  $b_1 = k_p \Delta E_{1g,0} + (P_0 + \Delta C_{1g,0}^d + \Delta C_{1g,0}^l)$  i.e., the health gain plus cost savings per patient relative to current treatment. Only the responders,  $N_1$ , obtain these benefits.

Let  $a_2 = k_p \Delta E_{2g,0} + (P_0 + \Delta C_{2g,0}^d + \Delta C_{2g,0}^l)$  denote the adverse health effect ( $\Delta E_2 < 0$ ) plus the consequential costs of the adverse reaction for each patient in group  $N_2$ .

We let  $P_{g1}^{\max}$  be the maximum price of the drug without testing,  $P_{g2}^{\max}$  be the maximum price of the drug with testing, and  $P_t$  be the price of the test. Thus, adapting equation 2', the maximum price of the drug without testing is

$$P_{g1}^{\max} = (b_1 N_1 - a_2 N_2)/N. \quad (5)$$

With testing, the payer's maximum price for a drug targeted solely at the responders is

$$P_{g2}^{\max} = b_1 - P_t N/N_1. \quad (6)$$

The change in the maximum price, which is the social value of testing, is therefore

$$\begin{aligned} \Delta P_{g2}^{\max} &= P_{g2}^{\max} - P_{g1}^{\max} \\ &= b_1(1 - N_1/N) - P_t N/N_1 + a_2 N_2/N \\ &= (b_1 + a_2)(N_2/N) - P_t N/N_1. \end{aligned} \quad (7)$$

This social value of testing reflects three factors:

1. the expected health benefit per patient treated, which is equal to  $b_1$  (the benefit per responder) times the proportion of nonresponders  $N_2/N$ ;
2. the averted costs of treating the adverse effects of the drug on nonresponders,  $a_2$ , times the proportion of nonresponders  $N_2/N$ ;
3. a cost of testing the whole patient population,  $P_t N$ , amortized over the  $N_1$  responders.

The first two components will be non-negative and testing will be beneficial if these effects exceed

the third element, the cost of testing. Formally, testing offers benefit to society if  $\Delta P_g^{\max} > 0$ , or

$$(b_1 + a_2)(N_2/N) > P_t N/N_1. \quad (8)$$

Thus testing is of benefit if the savings from avoiding treatment and side effects for the  $N_2$  nonresponders exceeds the cost of testing all patients. In the simplest case, if  $a_2$  is zero (no side effects) and we substitute for  $P_{g1}^{\max}$  from equation 5 this can be rewritten:

$$N_2/(N_1 + N_2) > P_t/P_{g1}^{\max}. \quad (9)$$

Testing is worthwhile from a societal perspective if the ratio of nonresponders to the total population exceeds the ratio of the cost of the test to the social value of the drug in the absence of testing.

Returning to the general case where there may be adverse events ( $a_2 \geq 0$ ), and assuming that the price obtained by the company reflects the same share  $\alpha$  of the social benefit of the drug with and without testing, then equation 7 shows that testing increases the price of the drug obtained by the company:

$$\alpha \Delta P_g^{\max} = \alpha (b + a)(N_2/N) - \alpha P_t N/N_1. \quad (10)$$

The company gets a share  $\alpha$  of the social gain of avoiding the drug costs and adverse events associated with treating nonresponders but also bears the share of  $\alpha$  of the costs of testing. It is rewarded and motivated to produce more specific drugs. In this case only the share  $\alpha$  of the cost of the test  $P_t$  is borne by the company, with the payer accepting to pay the remainder  $(1 - \alpha)$ . This follows from the assumption that the cost of the test is deducted to arrive at social benefit before it is divided between the producer and the payer. Note that in the simplest case of zero adverse reactions and test costs (i.e., if  $a_2 = 0$ ,  $P_t = 0$ ) the price would rise in proportion to the increase in proportion of patients expected to benefit:

$$\alpha \Delta P_g^{\max} = \alpha b_1 (N_2/N) \text{ or } P_{g2}/P_{g1} = N/N_1.$$

In practice, payers may be unlikely to permit the price of the drug, adjusted for the cost of testing and of side effects averted, to increase in proportion to its expected benefit per patient. We suggested above that payers scrutinize most stringently those products that are priced relatively high; actual price is then a decreasing proportion of the maximum price:  $d\alpha/dP^{\max} < 0$ , in which case  $P_g$  would be lower than that suggested by equation 10. The cost of the test,  $P_t$ , the ratio of nonresponders to responders,  $N_2/N_1$ , the severity of the adverse reactions, and the value of  $\alpha$  are all

crucial to the ability of a company to obtain a price premium for a more targeted product and to face, *ex ante*, neutral incentives for developing targeted products versus more indiscriminate products with lower expected benefits per patient treated. We consider in turn the payer and company perspectives.

### The Payer Perspective

We can note the general conditions in which testing is of benefit to the payer. Let  $B_1$  denote the potential payer benefit per period with no test,  $B_2$  denote the potential payer benefit with testing,  $P_{g1}$  be the price the payer is paying for the drug in the absence of a test, and  $P_{g1} + \Delta P$  be the price with a test. Note that we assume that payers focus on health effects and all costs. Adapting equations 5 and 6 above yields

$$B_1 = N_1 b_1 - N_2 a_2 - N P_{g1} \quad (11)$$

$$B_2 = N_1 b_1 - N_1 (P_{g1} + \Delta P) - N P_t. \quad (12)$$

In assessing the cost-effectiveness of testing to the payer, potential savings from avoiding adverse events and not paying for drugs to treat nonresponders have to be offset by the costs of testing and any higher price that is charged by the innovator. The protocol with testing offers greater benefit to the payer than does indiscriminate treatment of all patients if

$$B_2 - B_1 > 0, \text{ or}$$

$$N_2 (a_2 + P_{g1}) > N_1 \Delta P_g + N P_t. \quad (13)$$

If there are no adverse effects, i.e.,  $a_2 = 0$ , and if the payer does not give the company a price increase following the introduction of testing, so that  $\Delta P_g = 0$ , then equation 13 reduces to

$$N_2/N > P_t/P_{g1}. \quad (14)$$

Testing is worthwhile for the payer if the ratio of nonresponders to the total population exceeds the ratio of the price of the test to the price of the drug. More generally, the extent to which payers are prepared to award higher prices, i.e.,  $\Delta P_g > 0$  is crucial to creating consistent incentives for companies to develop new products using pharmacogenetics given society's cost-effectiveness threshold  $k_p$ . Of course if companies are able to develop other products that treat nonresponders at prices that result in a positive incremental cost-effectiveness below the cost-effectiveness threshold  $k_p$ , overall payer expenditures will rise. This may give rise to rationing issues if payer budgets are constrained (so  $k_p$  will rise) or to more aggressive bar-

gaining by payers seeking to reduce  $\alpha$ . We do not consider this issue further. We now consider the impact on the company.

### The Company Perspective

Assume that the innovative firm faces two choices. It could ignore the possibility of pharmacogenetic testing and develop a traditional drug. This drug would be targeted indiscriminately to all patients with the disease in question, of which a proportion receives no benefit and may be harmed. The innovative firm's alternative choice is to develop and sell a genetic test that would identify the  $N_1$  patients who will benefit and produce a drug targeted to them. Assume that the test can be sold at a price  $P_t$  and produced at constant marginal cost  $C_t$ . Adapting equation 4, assuming that  $Q = 1$  for simplicity, let  $\Pi_1$ ,  $P_g$  be the producer's profit and price, respectively, with no testing, and  $\Pi_2$ ,  $P_g + \Delta P_g$ , the profit and price with testing, and  $F_2$ , the R&D cost with testing. Therefore,

$$\Pi_1^T = \Sigma^T[(P_{g1} - M)N_1^t(1+r)^{-1}] - F_1 \quad (15)$$

$$\Pi_2^T = \Sigma^T[(P_{g1} + \Delta P_g - M)N_1^t(1+r)^{-1}] - F_2 + N_1^t(P_t - C_t)(1+r)^{-1}. \quad (16)$$

The producer's profit is greater with the test than without only if  $\Pi_2^T - \Pi_1^T > 0$ , or

$$\begin{aligned} & \Sigma^T(P_{g1} + \Delta P_g - M)N_1^t(1+r)^{-1} + \\ & (F_1 - F_2) + N_1^t(P_t - C_t)(1+r)^{-1} > \\ & \Sigma^T[(P_{g1} - M)N_1^t](1+r)^{-1}. \end{aligned} \quad (17)$$

Equation 17 shows that if the final drug price is unchanged, i.e.,  $\Delta P_g = 0$ , the innovative firm has no incentive to invest in pharmacogenetic testing in development that will result in a narrower indication unless there are savings in R&D costs ( $F_1 - F_2$ ) or profits to be made on the provision of the tests. Savings in R&D costs may be possible if, for example, genetic testing permits phase III trials to be targeted to fewer patients who are more likely to benefit. Thus, efficacy may be demonstrated with much smaller trials. However, there may be additional costs if either the link between the gene and the response or the reliability of the test has to be validated. It is also possible that with genetic testing the drug could be designed such that it is effective for a larger fraction of the patient population. In that case, the tendency for pharmacogenetics to reduce the average size of the target population per drug would be mitigated. Moreover, if the proportion of patients  $N_2/N$  who fail to benefit is expected to be relatively large, an untargeted

drug might fail to qualify for reimbursement because of poor cost-effectiveness.

More realistically, with free entry to the business of developing genetic tests, pretreatment tests are likely to be developed irrespective of the actions of the innovator when they can yield a net saving to the payer. This occurs when the cost of testing the entire patient population  $N$   $P_t$  is less than the savings from avoiding treatment of non-responders  $P_g N_2$  plus any savings from averting harm,  $a_2 N_2$ . It is likely, therefore, that drug producers will have incentives to do this testing themselves as part of drug development rather than wait for others to do it after drugs reach the market. In the latter case, the producer suffers the loss of sales but gets none of the potential benefits of smaller trials or an improved drug design. Nevertheless, to the extent that pharmacogenetic testing tends to reduce the patient population per drug, some drugs may not be worth developing once testing becomes an option if the reduction in expected revenues due to population fragmentation exceeds the reduction in R&D costs.

The key issue, then, is what happens to drug prices. If pre- and post-testing prices reflect expected social benefits, the price of the drug will increase in proportion to the expected benefits (net of testing costs) as specificity increases and the risk of zero benefit or positive harm declines as a consequence of genetic testing.

The willingness of payers to award higher prices for targeted benefits (i.e., maintaining a constant value of  $\alpha$ ) will be essential to retaining neutrality in investment incentives.

### Examples

Two drug launches illustrate the potential impact of testing on manufacturers and payers. In one case, nebacumab (Centoxin™, Centocor, Malvern, PA) no test was available, whereas in the case of trastuzumab (Herceptin, Genentech, San Francisco, CA), tests are available.

*Nebacumab.* Nebacumab was launched in 1991 in most European countries [7] as a treatment for sepsis. However, it only worked in those cases where the sepsis was due to Gram-negative bacteremia, or approximately one-third of all sepsis cases. With a cost of \$4000 per patient, doctors found themselves under pressure to use the drug on all cases of sepsis, despite knowing that for every 1000 patients treated, \$2.67 million was being spent on

drugs for patients who could not benefit. It eventually became clear that nebacumab was harmful to patients without Gram-negative bacteremia. A trial in which nebacumab was given to 538 sepsis patients showed that, although the 28-day mortality of the 200 patients with Gram-negative bacteremia was reduced to 30%, overall mortality was not significantly different from the 49% mortality in the placebo group. This implies that mortality in the other 338 patients was 60%, an increase of 11%. Centocor withdrew the product from the European market and withdrew its FDA application. In the absence of a bedside diagnostic test to promptly identify patients with Gram-negative bacteremia, the product was of no value to sepsis patients as a group and of no value to payers.

Recall that the necessary condition for testing to be beneficial for the payer as compared with not testing is  $B_2 - B_1 > 0$ . Taking equation 13 and letting  $\Delta P_g = 0$ , then

$$N_2/N > P_t / (a_2 + P_{g1}). \quad (18)$$

In these circumstances testing is worthwhile from a payer perspective if the ratio of nonresponders to the total population exceeds the ratio of the price of the test to the price of the drug plus the cost of the adverse reactions experienced by the nonresponders. The maximum price at which a test is worthwhile to a payer is therefore

$$P_t < [N_2/N](a_2 + P_{g1}). \quad (19)$$

In the nebacumab case, using the data above we obtain the following rough values:  $N_2/N = 0.67$ ,  $a_2 = [0.11 (20 \times \$10,000)] = \$22,000$  if we assume that each death costs 20 QALYs,  $\Delta E = 20$ , and  $k_p$  is \$10,000. We ignore extra treatment costs, and  $P_{g1} = \$4000$ . Thus the maximum value of a test is  $P_t < 0.67 \times \$26,000$ , or  $P_t < \$17,420$ .

However, this assumes that at a drug price of \$4000, nebacumab was cost-effective and that the benefit to the payer,  $B_2$ , as set out in equation 12, was positive. If we assume that the health gains per patient and the marginal cost per QALY threshold are as in the case of the adverse reactions, then  $b_1 = [0.19 (20 \times \$10,000)] = \$38,000$ .

From equation 11, the payer benefit per patient treated with no testing is

$$\begin{aligned} B_1 &= 0.33 \times \$38,000 - 0.67 \times \$22,000 - \$4000 \\ &= \$12,540 - \$14,740 - \$4000 = -\$6200 \end{aligned}$$

Thus, at the price of \$4000, the drug is not cost-effective without testing. For the drug to be cost-effective with testing and with treatment confined

to patients with Gram-negative bacteremia, from equation 12,

$$B_2 > 0$$

$$\$38,000 - \$4000 - N/N_1 P_t > 0$$

$$P_t < 0.33 \times \$34,000$$

$$P_t < \$11,333$$

Thus, using these assumptions, with a bedside diagnostic test costing up to \$11,333 per test, nebacumab would have been cost-effective to payers at a price of \$4000. Without the test the product was not cost-effective at any price.

*Trastuzumab.* Trastuzumab is a new product for the treatment of breast cancer. It benefits only those patients with lesions that express increased quantities of the HER-2 protein, or approximately 25% of patients [8]. Three diagnostic tests have been approved by the FDA [9]. Each costs less than \$100 per test. There are no adverse reactions in the patient group that does not respond. Thus, equation 14 shows that, conditional on the decision to use the product, using the test is of benefit to payers if  $P_g > P_t/[N_2/N]$ . This means that  $P_g > 100/0.75$ ,  $P_g > \$133$ .

The price of trastuzumab in the United States is \$1382 for a 440-mg injection, and patients need to take therapy throughout the period in which the disease is being treated. Thus, testing clearly makes economic sense compared to not testing. However, this analysis does not consider whether there is an overall payer benefit from using the product with testing, i.e., if  $B_2 > 0$ . We do not have the information on which to make that assessment, nor do we know if the product will provide positive returns to the company.

We can also use equation 14 to ask what proportion of nonresponders would represent breakeven for the payer. If we assume that the total treatment cost per patient is \$7000 (five sets of treatment) then  $P_t/P_{g1} = 0.015$ ; i.e., it is worthwhile from the payer's perspective to test if more than 1.5% of patients are nonresponders. Thus testing is highly worthwhile because the test is very inexpensive relative to the price of the drug.

The nebacumab example clearly illustrates the potential gains to payers and manufacturers afforded by diagnostic tests that can distinguish potential responders from nonresponders so that treatment is targeted solely to the responders. In this case, an appropriate test was not available and the product had to be abandoned, at least for the purpose for which it was originally developed. If a

test had been available to distinguish patients who would benefit from those who would be harmed, the price of the drug could have been higher, depending on the cost of the test, and would still have been cost-effective for payers. Of course we do not know if nebacumab would have earned a commercial return for its developers even in these circumstances. The trastuzumab example again indicates the value of a test to payers. It shows that with a low test cost, testing makes sense even when nonresponders are a small fraction of potential patients, suggesting that manufacturers could benefit from having such tests at the time of drug development. Such knowledge can be used either to design the drug to fit a broader spectrum of patients or to abandon products early if they can only benefit a small fraction of patients and hence will never cover their development costs. Of course the implication is that with testing becoming feasible and, in all probability, supplied competitively by third parties, drug producers will face smaller target populations. In some cases the resulting target population may be too small for the drug to be commercially viable unless payers increase prices to reflect the increase in expected benefits per patient treated. In the absence of such price adjustments, patients who would have benefited may forgo treatment unless R&D costs for targeted drugs can be significantly reduced. Even with such adjustments, the patient population may be too small to enable R&D costs to be recovered.

### Implications for Public Policy

In the case of gene therapy, we concluded that private sector investment in developing cures for monogenic diseases is likely to be socially suboptimal for several reasons:

1. Long-lived therapies were likely to meet payer resistance to large one-off costs because of budget constraints or, in competitive systems, concerns that the savings would accrue to other insurers or that such therapies would attract high-cost patients.
2. Current orphan drug legislation to encourage development of treatments for diseases with low patient numbers is therefore not neutral as between once-a-day and long-lived therapies.
3. The novel nature of the treatment implies an atypically high risk of failure and a long delay to success, making these therapies unattractive to private investors.

Evidence on trial activity appears to confirm our assessment. Public investment is already playing a major role in the development of gene therapies for monogenic diseases, and this may be the best policy to address the development risk. However, adjusting reimbursement norms and orphan drug laws so that they are neutral between long-lived and once-a-day therapies might be a better way of achieving the appropriate mix of private and public funds once public funding has established proof of concept. In addition to the benefits offered by orphan drug status and public funding of trials to establish proof of concept, one must also consider the issue of whether payer cost-effectiveness thresholds for monogenic diseases should be higher than for other diseases. It is therefore important that the full social benefit of such an adjustment is obtained by signaling to companies that this is the case.

In the case of pharmacogenetics, testing will often be socially optimal, particularly if the proportion of nonresponders is high, if serious adverse reactions can arise, or if the test is inexpensive. The problem of patient fragmentation that results from genetic testing is most appropriately addressed by adjusting prices to reflect higher benefits of targeted treatment. However, two potential problems remain:

1. Payers may be reluctant to adjust prices upward for targeted treatments to reflect the increase in expected benefits per patient treated that results from treating only those patients who are genetically appropriate candidates. Doing so requires companies and payers to use economic evaluation to identify the higher value associated with such targeting.
2. If genetic testing reduces populations eligible for treatment but does not significantly reduce the costs of R&D through smaller trials required to show efficacy, and if prices are not adjusted, then an increasing number of potential treatments may be shelved for lack of commercial viability at normal payer thresholds.

Even where prices are adjusted, patient populations may be too small to make commercial development viable. The problem with small numbers is analogous to that associated with gene therapy for monogenic diseases and may require similar solutions if society wishes to find cures for these diseases.

### References

- 1 Langreth R. Gene therapy is dealt a set back by the FDA. *Wall Street Journal*. October 11, 1999.
- 2 Lehman Brothers. *Gene Therapy: the Ultimate Ap-*

- plication of Genomics. New York: Lehman Brothers Inc., 1997.
- 3 Martin PA, Thomas SM. The commercial development of gene therapy in Europe and the USA. *Hum Gene Ther* 1998;9:87-114.
  - 4 Bell J. The human genome. In: Marinker M, Peckham M. eds. *Clinical Futures*. London: BMJ Books, 1998.
  - 5 Lynch KRO, Neill GP, Liu Q, et al. Characterisation of the human cysteinyl leukotriene Cys LT<sub>1</sub> receptor. *Nature* 1999;399:789-93.
  - 6 Kuivenhoven JA, Jukema JW, Zwinderman AH, et al. The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. *N Eng J Med* 1998; 338:86-93.
  - 7 Centoxin: a lesson on patient selection? *Pharm Pricing Rev* 1999;4:34.
  - 8 Wisecarver JL. HER-2/neu Testing Comes of Age. *Am J Clin Path* 1999;111:229-301.
  - 9 McNeil C. How should HER-2 status be determined? *J Nat Cancer Inst* 1999;91:10.