The Economics of Gene Therapy and of Pharmacogenetics

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Introduction

Genomics offers great promise for providing new and more effective therapies and diagnostic tests for patients. Many new medicines will come from the use of pharmacogenomics in conventional drug discovery, as knowledge of the human genome increases understanding of disease mechanisms and so enables new and better targets for treatment to be identified. As of 1996, genomics was predicted to generate 3,000 – 10,000 interesting targets, compared to the 500 identified molecular targets then available[1]. This paper, however, focuses on the economic issues arising from two other, more novel uses of genomics:

- 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
- the use of pharmacogenetics to identify a patient's genotype prior to treatment, in order to identify those who will benefit from those who either will not benefit or who may be harmed.

We examine whether existing reimbursement and regulatory regimes are well-designed to encourage the socially optimal development of these two uses of genomics, and suggest possible policy changes.

Gene therapy

Gene therapies focus on correcting the gene causing or regulating a disease, through inappropriate expression of a protein, rather than on merely treating the disease symptoms. The hope is that gene therapies will offer the possibility of treating diseases that are currently incurable, and provide long-term therapeutic benefits. The initial focus of many gene therapy trials was on monogenic diseases involving only a single gene. However, most of these monogenic diseases affect a relatively small number of patients. The number of patients treated per year would be further reduced if therapeutic effects were long-lived. Small patient numbers, combined with the uncertainties associated with very novel modes of action may lead to suboptimal levels of commercial research for reasons we now discuss.

Payers currently appear to be concerned about the potential cost of gene therapies. A plausible assumption is that payers will only pay for these therapies if they are deemed cost-effective. There will exist some positive price at which an effective gene therapy is cost-effective from a payer perspective. Let us assume that this price is defined in terms of a societal perspective of cost-effectiveness. The critical question

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for commercial feasibility is whether this price is also one at which the firm developing the therapy can expect to break even. This assumes that investors will only develop a new therapy if the expected revenue, that is, the discounted present value of price times volume over the therapy's economic life, is sufficient to cover the costs of production and delivery and the fixed cost of R&D, to yield a return on funds invested commensurate with other possible uses of funds, adjusted for risk. A formal statement of the problem follows.

Formal Statement of the Problem

Assume that the new gene therapy is considered cost-effective by payers for their patients relative to an existing treatment if:

$$(C_g - C_0) / (E_g - E_0) < k, \qquad (1)$$

where

$C_i = P + C^d + C^I \qquad i = g, 0$

Subscripts g and 0 denote, respectively, the gene therapy and the status quo alternative treatment.

P_i = the price of the therapy (gene therapy or other treatment)

C_i^d = other direct treatment costs

C_i^I = indirect costs

E_i = quality adjusted life years (QALYs)

k = threshold cost per QALY at which an intervention is considered cost-effective.

C and E are defined as discounted present values, with any future costs and benefits discounted at a socially optimal rate. If k is optimally chosen, (i.e. reflects the marginal social opportunity cost of additional investment in health care), eq. 1 defines the condition for socially optimal reimbursement.

Eq. 1 can also be used to define the maximum price at which the gene therapy is cost effective:

$$P_g^{max} \leq k\Delta E + (P_0 + \Delta C^d + \Delta C^I) \qquad (2)$$

where $\Delta C^d = C^d_0 - C^d_g$

$\Delta C^I = C^I_0 - C^I_g$

$\Delta E = E_g - E_0$

Simplifying:

$$P_g^{max} \leq k\Delta E + S^* \qquad (3)$$

where $B^* = P_g^{max}$

where $S = (P_0 + \Delta C^d + \Delta C^I)$, and B^* represents the social benefits (which may be positive or negative) arising from the use of treatment g as compared to treatment 0[3].

Assume that payers typically set the actual price at some fraction α of the maximum price, where α reflects the share of the social value that accrues to the innovator firm and $(1 - \alpha)$ is the share captured by the payer, so $P_g = \alpha P_g^{max}$. Eq. (3) implies that P_g^{max}, the maximum price at which the gene therapy is considered

[3] Strictly the net social gain would be calculated by subtracting the marginal social cost of producing the medicine.

cost-effective by payers, is positively related to: the gain in quality of life, ΔE; the threshold for cost-effectiveness, k; and the savings in other direct medical costs ΔC^d and in indirect costs, such as foregone productivity, ΔC^I. The actual price to the producer also depends on the innovator firm's share of the social gain, α.

Consider now the perspective of the firm that is considering investing in developing a gene therapy. Using a net present value investment valuation approach (ignoring option values), the producer's breakeven profit constraint can be written:

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

where

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

P_g = price of gene therapy treatment, assumed invariant over time

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

N = number of patients treated in year t and Q = the number of treatments per patient per year, such that NQ is the number of treatments sold in year t.

F = discounted present value of R&D cost, with F_r, $F_L > 0$, $F_p < 0$, where

r = cost of capital

L = expected years from discovery to launch

p = probability of success, per drug candidate entering clinical trials

We assume other fixed costs are zero

From eq. (4), expected profit is increasing in number of patients treated and treatments per patient ($\Pi_Q, \Pi_N > 0$); expected profit is decreasing in variable production cost per unit and in fixed R&D cost ($\Pi_M, \Pi_F < 0$).

To see the implications of the payer's cost-effectiveness requirement on the producer's breakeven constraint, substitute in the price from eq. (3) into the firm's breakeven constraint in eq. (4):

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

$$= \Sigma\{[\alpha (k\Delta E + S) - M Q^t N^t\} (1+r)^{-t}] - F(r,L,p) \quad (4)''$$

Equation (4)'' provides a framework to consider how the characteristics of gene therapy may affect its commercial viability compared to other pharmaceuticals.

The cost of R&D F(r,L,p) may be atypically high for gene therapies compared to conventional therapies, despite relatively small required trial size. The extremely novel mode of action means that the probability of success p is very low and expected duration of the R&D process L is relatively long. Several hundred clinical trials have been initiated but none have been successfully completed so far. Recent deaths of two trial participants[2] have no doubt made expectations even more pessimistic. Anecdotal evidence suggests that biotech's high risk of failure combined with the long period of delay before the uncertainty is resolved has been a major factor leading the shift of venture capital funds from biotech to e-commerce. These uncertainties

are even more extreme for gene therapy[3]. Similarly, an options model of R&D implies a higher cost of capital for early stage projects for which significant additional investment is required. Gene therapy may be considered very early R&D[4].

The expression in square brackets is the operating margin per treatment, which is positively related to the producer's share, α, and to the cost savings and gain in quality of life. To the extent that payers focus on current budget impact, ignoring future cost savings, the value of B actually used may be less than the true social value, B^*. Operating margin is negatively related to the variable cost of producing and delivering the treatment, M, which is likely to be significantly higher for gene therapies compared to other drugs due to the novel delivery systems required and the small patient base over which to gain experience in production.

The total operating net revenue is the per-treatment margin multiplied by treatment volume, which is the product of the number of patients treated per year N and number of treatments per patient, Q. Expected profit is positively related to N and Q. For all monogenic diseases, N is small relative to the population base for most current drug therapies. This small patient base problem is exacerbated by the long-lived nature of gene therapies, which means that each patient may require treatment only once or twice a year, rather than the once or twice a day norm for many chronic medications.

The problem of insufficient commercial incentives for investment in drugs for small populations is not unique to gene therapies. Orphan drug legislation enacted in the US in 1983 provides special incentives for drugs to treat diseases that affect fewer than 200,000 patients. Ten to twenty million Americans are estimated to suffer from about 5,000 orphan diseases for which there is no effective cure or treatment.[4] Comparable numbers are not available for the EU, although the EU is currently debating proposals to establish an orphan drug regime in Europe. The US Orphan Drug Act provides a 50 percent R&D tax credit[5] and a seven year period of market exclusivity following approval of an orphan drug by the FDA. In the decade following enactment of this legislation, 99 orphan drugs were approved, compared to 10 in the prior decade. However, long-lived gene therapies are disadvantaged relative to conventional therapies by the current form of this legislation. 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 $1/5^{th}$ of the population with the disease would obtain treatment per year. Thus to provide neutral incentives, the orphan drug threshold for long lasting therapies should be n x 200,000, where n is the average duration of benefits.

The duration of benefits and hence frequency of administration (low Q per patient for long-lasting therapies) would be irrelevant if payers were willing to pay prices for new therapies in proportion to the full social benefits: $P = \alpha P^{max}$. In this case, the price for gene therapy treatment would increase in proportion to duration of its effects, that is, an infrequent but long-lived treatment (low Q) would be associated with a

[4] Myers S. Measuring Pharmaceutical Risk and the Cost of Capital – Chapter 5 in Risk and Return in the Pharmaceutical Industry. OHE 1999.

[5] Such tax credits should be made transferable to future years, in order to set neutral incentives for both established companies that have current tax liabilities and start-ups that do not, who currently cannot take advantage of the tax

relatively high benefit ($\Delta E + S$) per treatment compared to a once-a-day alternative therapy, thereby preserving incentives for efficient investment in R&D that are neutral with respect to duration of benefits. This may, however, be undermined in practice for several reasons.

First, payers tend to scrutinize and perhaps regulate or bargain aggressively over the prices of products that are seen as relatively high priced. 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, as for example in the US, 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. The fact that HMOs in the US reimburse for preventive services, for which this argument would also be true, at least as much as indemnity plans does not refute this concern, because offering prevention services may be in part a positive selection strategy, intended to attract health conscious patients who have lower medical costs. By contrast, patients in need of gene therapies are likely to have relatively high other medical costs. 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 no choice of health plan, such as the UK. However, in these systems managers and doctors face annual budget constraints which limit ability to invest in treatments that have high immediate costs but longer term benefits.

Thus, the characteristics of gene therapy – long and uncertain R&D, small patient base and infrequent treatment – may lead to suboptimal commercial investment in these therapies. Although society has signaled a willingness to pay additional subsidies to encourage treatments for orphan diseases, current legislation is not neutral between once-a-day vs. long-lived treatments, and reimbursement systems may reinforce this bias, if payers focus on short term drug budget costs without due weight to long term health benefits and societal savings.

An examination of clinical trials in gene therapy tends to support our concern, that low patient numbers and investor perception of payer resistance to long-lived therapies may be influencing the allocation of R&D effort. One review noted that most gene therapy trials are in cancer, with AIDS running second [3]. Many trials are currently focussing on variants of treatment that would require repeat administration rather than providing a one-off cure. Only one monogenetic disorder, cystic fibrosis, is the subject of significant clinical development activity, reflecting in part the early discovery of the gene for this disease. Another study found that[5], unlike all other areas of drug development, most clinical trials in gene therapy are undertaken with at least partial public funding. Our own search of trial activity was not able to identify funding sources but does confirm the importance of cancer and other major disease areas in company research. We reproduce in the Appendix our analysis together with a summary of the earlier analysis by Martin and Thomas[5]. These findings and this analysis suggests that the initial promise of gene therapy – that of delivering cures for

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credits offered under current US orphan drug law. This is particularly important in gene therapy where many of the companies are start ups.

monogenetic diseases - is unlikely to be realised without changes in incentives or with significant public investment. We consider the public policy implications in the final section of the paper.

Pharmacogenetics

Pharmacogenetic testing is designed to identify patients genotypes in order to target drugs to the subgroup that is like to benefit, thereby avoiding the waste and cost of treating patients whose genetic make-up makes them either unlikely to benefit or suffer harm. For example, new tests developed from work on the ApoE gene may be able to identify those patients who will benefit from drugs designed to slow the symptomatic degeneration associated with Alzheimer's disease.

Payers are likely to adopt pharmacogenetic testing prior to treatment if the savings from treating fewer patients and avoiding complications exceed the costs of testing. For drug companies, pharmacogenetic testing means lower patient volume and hence lower revenues per drug, other things 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 for the drug. Thus pharmacogenetic testing could be socially beneficial but could nevertheless reduce firms' incentives to develop new drugs, due to fragmentation of the patient population and to the costs of testing, unless there are offsetting cost reductions – for example, in cost of R&D per drug – or price increases reflecting the greater specificity of use and hence great health gain per patient treated.

To analyse the problem, assume that the innovator 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 receive no benefit and may be harmed.[6] Adapting eq (4), 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, and assume that Q=1 for simplicity. The innovator 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 produced at constant marginal cost C_T. Let Π_1 be the producer's profit with no testing, Π_2 the profit with testing:

$$\Pi_1^T = \Sigma[(P_{d1} - M)(N_1^t + N_2^t)(1+r)^{-t}] - F_1(r, L, p_1) \qquad (5)$$

$$\Pi_2^T = \Sigma[(P_{d2} - M)\, N_1^t\, (1+r)^{-t}] - F_2(r, L, p_2) + (N_1^t + N_2^t)(P_T - C_T)(1+r)^{-t} \qquad (6)$$

where P_d = price of the drug

P_T = price of the test

C_T = cost of the test

[6] In practice, with chronic therapies it may well be that doctors are able to identify at least a proportion of non-responders without testing, and so are able to take them off the therapy after a short period of treatment.

The maximum price that the payer is willing to pay with testing could be higher or lower than without testing, depending on whether the cost of testing is less or greater than the perceived increase in value of the drug, due to more certain efficacy and lower probability of side effects. We therefore let $P_{d2} = P_{d1} + \Delta P_d$, where ΔP_d could be positive or negative. The producer's profit is greater with the test than without only if:

$\Pi_2^T - \Pi_1^T > 0$, or

$$\Sigma (P_{d1} + \Delta P_d - M) N_1^t (1+r)^{-t} + (F_1 - F_2) + \Sigma(N_1^t + N_2^t)(P_T - C_T) (1+r)^{-t} > \Sigma[(P_{d1} - M) N_2^t] (1+r)^{-t} \quad (7)$$

Eq. (7) shows that if the test is competitively supplied, such that $P_t = C$, and final drug price is unchanged, i.e. $\Delta P_d = 0$, the innovator firm has no incentive to invest in pharmacogenetic testing in development that will result in a narrower indication, unless there are significant savings in R&D cost ($F_1 - F_2$), particularly if the number of patients that do not benefit, N_2, is large. 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. 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 shrink the average size of the target population per drug would be mitigated. Moreover, if the proportion of patients who fail to benefit N_2/N is expected to be relatively large, the untargeted drug might fail to qualify for reimbursement.

More realistically, if there is free entry to the business of developing genetic tests to determine which population subgroups will benefit from a specific drug, then pre-treatment tests are likely to be developed where such testing is likely to yield a net saving to the payer, that is, the cost of testing the entire patient population $(N_1^t + N_2^t) P_t$ is less than the savings from avoiding treatment of non-responders $P_d N_2$. Testing is even more likely to achieve benefits if the N_2 non-responders would actually suffer harm. 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 which case the producer suffers the loss of sales but gets none of the possible benefits of smaller trials or a better designed drug. 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 costs of R&D.

The analysis so far assumes that the price of the drug is the same, whether or not testing occurs, i.e. $\Delta P = 0$. However, this implies that the price of the drug is invariant to the expected benefits per patient who takes the drug. More appropriately, if prices reflect expected social benefits, the price of the drug will increase in proportion to the expected benefits, as specificity increases and the risk of zero benefit or positive harm declines as a consequence of genetic testing.

The payer perspective

To explore the possible price changes under pharmacogenetic testing, let us consider the choices from the payer perspective. Let B_1 denote the potential payer benefit per period with no test, and B_2 denote the potential payer benefit with testing. Assume further that the patient group N_2 suffers an adverse reaction with monetary equivalent cost of a if they take the drug. Adapting equation (3) above yields:

$$B_1 = N_1 b - N_2 a - (N_1 + N_2)\, P_{d1} \qquad (8)$$

$$B_2 = N_1 b - N_1\, P_{d2} - (N_1 + N_2) P_T \qquad (9)$$

where

$b = k\Delta E_{N1} + S_{N1}$, i.e. the health gain plus cost savings per patient in group N_1, relative to current treatment

$a = k\Delta E_{N2} + S_{N2}$, i.e. the adverse health effect ($\Delta E_{N2} < 0$) plus costs for each patient in group N_2.

In assessing the cost-effectiveness to the payer, the net benefit ($N_1 b - N_2 a$) in the absence of a test has to be offset against the cost of giving the drug treatment to all ($N_1 + N_2$) patients. The protocol with testing offers greater benefit to the payer than indiscriminate treatment of all patients if:

$B_2 - B_1 > 0$, or

$$N_2 (a + P_{d1}) > N_1 \Delta P_d + (N_1 + N_2) P_t \qquad (10)$$

Thus testing is socially beneficial if the savings from avoiding treatment and side effects for the N_2 non-responders exceeds the cost of testing all patients plus any increase in price of the drug given to the company to reflect the benefits of greater specificity. If a is zero (no side effects) and the price of the drug is unchanged, this can be rewritten:

$$N_2 / (N_1 + N_2) > P_t / P_d$$

Thus in the simplest case, testing is worthwhile from the payer perspective if the ratio of nonresponders to the total population exceeds the ratio of the cost of the test to the cost of the drug.

More generally, we can solve eq. 10 for the increase in the price of the drug ΔP_d that leaves the payer as well off with the test as without:

$$B_2 \geq B_1 = 0 \quad \text{as} \quad \Delta P_d \leq \{N_2(a + P_{d1}) - (N_1 + N_2) P_t\} / N_1$$

Thus the testing regime still leaves the payer better off as long as the increase in the price of the drug does not exceed the savings from avoiding treatment of the N_2 non-responders, weighted by the ratio of non-responders to responders N_2 / N_1, minus the costs of testing the entire population, amortized over the N_1 responders.

Alternatively, we can solve equations (8) and (9) for the maximum prices the payer will be willing to pay, P_{d1}^{max} and P_{d2}^{max} respectively in the case of no testing and testing, such that the benefits to the payer fall to zero, i.e. $B_1 = 0$, $B_2 = 0$. Let $N = (N_1 + N_2)$. Prior to the introduction of testing the payer's maximum offer price for the drug is:

$$P_{d1}^{max} = (b N_1 - a N_2)/N \qquad (11)$$

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

$$P_{d2}^{max} = b - P_T N / N_1 \qquad (12)$$

The increase in the maximum price a payer would offer is therefore:

$$\Delta P_d^{max} = P_{d2}^{max} - P_{d1}^{max}$$

$$= b(1 - N_1/N) - P_t N/N_1 + a N_2/N = (b + a)(N_2/N) - P_t N/N_1 \qquad (13)$$

The increase in the maximum unit value of the drug to the payer is made up of three factors:

- the increment in expected health benefit per patient treated, which is equal to b (the benefit per responder) times the proportion of non-responders N_2/N
- a cost of testing the whole patient population, $P_t N$, amortized over the N_1 responders
- the averted costs of treating the adverse effects of the drug on non-responders, a.

In the absence of adverse reactions and test costs (i.e., if a = 0, $P_T = 0$), price could rise in proportion to the increase in proportion of patients expected to benefit and still leave the payer equally well off:

$$P_{d2}^{max} / P_{d1}^{max} = N/N_1$$

Note that this ratio remains unchanged if we assume that in practice companies will only get a proportion of the maximum price the payer is willing to pay and that this ratio is unchanged, i.e.

$$P_{d2} / P_{d2}^{max} = P_{d1} / P_{d1}^{max} = \alpha \qquad (14)$$

In this case only a share of the cost of the test is borne by the company, with the payer accepting a share (1 - α).

In practice, payers may be unlikely to permit the price of the drug to increase in proportion to its expected benefit per patient (adjusted for cost of testing and side effects averted). We suggest above that payers scrutinize most stringently products that are relatively highly priced; if so, actual price is a decreasing proportion of the maximum price: $d\alpha / dP^{max} < 0$, in which case P_{d2} would be lower than that suggested by eq (14). The cost of the test, P_T, the ratio of non-responders to responders N_2 / N_1, the size of adverse reactions, a, and the value of α are all crucial to the ability of a company to obtain a price premium for a more targeted product and hence to face, ex ante, neutral incentives as between developing targeted products with testing vs. more indiscriminate products for mass markets that have lower expected benefits per patient treated. Of course if the company expects tests to be re developed anyway, then the willingness of payers to award higher prices for targetted benefits (i.e. maintaining a constant value of α) will be essential to retaining neutrality.

Examples

The potential impact of testing for manufacturers and payers can be illustrated by looking at two examples of drug launches. In one case, Centoxin, no test was available. In the other case, Herceptin, competitively supplied tests are available.

Centoxin

Centoxin 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 caused by gram negative bacteremia – which is approximately one third of all sepsis cases. With a $4,000 per patient cost, doctors found themselves under pressure to use the drug on all cases of sepsis, despite knowing that every 1,000 patients treated involved spending $2.67 million on drugs for patients who could not benefit. In the event it became clear that Centoxin was harmful to patients without gram negative bacteremia. In a trial of 538 sepsis patients, whilst 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 of 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 identify patients promptly 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 as compared to not testing is:

$B_2 - B_1 > 0$, or

$$N_2(a + P_{d1}) > (N_1 + N_2)P_T + N_1 \Delta P_d \qquad (10)$$

Thus for the payer, testing is beneficial if the costs of treatment plus adverse reactions for the N_2 patients who do not benefit, $N_2(a + P_{d1})$ exceed the cost of testing all patients $(N_1 + N_2)P_T$, plus any price increase for responders $N_1 \Delta P_d$. If $\Delta P_d = 0$, then:

$$N_2 / (N_1 + N_2) > P_T / (a + P_{d1}). \qquad (15)$$

In these circumstances testing is worthwhile from a payer perspective if the ratio of non-responders 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 non-responders[8]. The maximum price at which a test is worthwhile to a payer is therefore:

$$P_T < [N_2 / (N_1 + N_2)] (a + P_{d1}) \qquad (16)$$

In the Centoxin case, using the data above we obtain the following rough values:

$N_2 / (N_1 + N_2) = 0.67$

$a = [\ 0.11\ (20 \times \$10{,}000)] = \$22{,}000$ i.e. we assume that each death costs 20 QALYs, $\Delta E = 20$, and k is $10,000. We ignore extra treatment costs.

[7] The information for this example is taken from Centoxin: A lesson on patient selection? Pharma Pricing Review, 1999, 4(2):

[8] We can note that the social benefit will be as in equation (22) but replacing on the right hand side the prices P_T and P_{d1} with the costs M and C_T, and adding to the left hand side any savings in the research and development process, $(F_1 - F_2)$, i.e.

$$[N_2 / (N_1 + N_2)] + [(F_1 - F_2) / (N_1 + N_2)] > C_T / (a + M).$$

Thus testing is more likely to be socially beneficial the higher is the ratio of non responders, the greater are any savings in R&D cost, the higher the health and treatment cost of adverse reactions, the higher the marginal cost of the treatment and the lower the cost of the test.

P_{d1} = \$4,000

Thus P_T < 0.67 x \$26,000, or

P_T < \$17,420

However, this assumes that at a drug price of \$4,000, Centoxin was cost-effective and that the benefit to the payer, B_2, as set out in eq (9), is positive. If we assume that the health gains per patient and marginal cost per QALY threshold are as in the case of the adverse reactions, then

b = [0.19 (20 x \$10,000)] = \$38,000

From eq. 8, the payer benefit per patient treated with no testing is:

B_1 = 0.33 x \$38,000 - 0.67 x \$22,000 - \$4,000 = \$12,540 – \$14,740 – \$4,000 < 0

Thus at the price of \$4,000 the drug is not cost-effective without testing. For the drug to be cost –effective with testing and with treatment confined to gram negative patients, from eq (9):

B_2 = \$38,000 - \$4000 – N/N_1 $P_t \geq 0$, or $P_T \leq$ 0.33 x \$34,000 = \$11,333.

Thus, using these assumptions, with a bedside diagnostic test costing up to \$11,000 per test to buy and use, Centoxin would have been cost-effective to payers at a price of \$4000. Without the test the product was not cost-effective at any price.

Herceptin

Herceptin is a new product from Genentech for the treatment of breast cancer. It benefits only those patients with lesions that express increased quantities of the HER-2 protein, around 25% of patients[6]. Three diagnostic tests have been approved by the FDA[7]. Each costs less than \$100 per test. There are no adverse reactions in the patient group that does not respond. Thus, eq (15) shows that, conditional on the decision to use the product, using the test is of benefit to payers if

$P_d > P_t / [N_2 / (N_1 + N_2)]$ (17)

$P_d >$ 100/0.75

$P_d >$ \$133

The US Herceptin price is \$1,382 for a 440mg injection and patients need to take therapy throughout the period in which the disease is being treated. T hus 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. We also do not know if the product will provide positive returns to the company. We can note, however, the quoted views of one of the senior managers involved in the development of the product

‘“Genentech’s changed a lot, and I would tell you that in ninety one, people’s concept of drug development was much less developed than it is today,” Curd says. Based on simple business principles, he believed that Her-2/neu’s potential would never justify the crushing cost – ultimately more than \$150 million – of getting

the drug to market. Because a minority of breast-cancer patients – 25 to 30 percent – suffer from the type of disease positively affected by the treatment, "today if Her-2 came forward, you couldn't get it into development, " he says. If the decision had been his, Genentech would never have taken Her-2/neu to advanced development. But when he arrived, the company was already committed to developing Her-2/neu.'[8]

The Centoxin example clearly illustrates the potential gains to payers and manufacturers from diagnostic tests that can identify potential responders from non-responders in order to target treatment solely to the latter. 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 identify 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 still been cost-effective for payers. Of course we do not know if Centoxin would have earned a commercial return for its developers even in these circumstances. The Herceptin example again indicates the value to payers of a test when responders are a small fraction of potential patients. We do not know whether the product is cost-effective at this price and even if it is whether the company will earn a return that covers R&D costs. It does suggest that manufacturers benefit from having such tests at the time of drug development, if 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 may ultimately not cover their development costs. Of course, the implication is that, with testing becoming feasible and probably competitively supplied 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 forego treatment, unless R&D costs can be significantly reduced for targeted drugs. 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:

- 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 benefits would fall to other insurers, or a fear of attracting high cost patients;
- orphan drug legislation to encourage development of treatments for diseases with low patient numbers is not designed to be neutral as between once-a-day and long-lived therapies.
- the novel nature of the treatment implies atypically high risk of failure and 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. There is also an issue as to whether payer cost-effectiveness thresholds for monogenic diseases should be higher than for other diseases – in addition to the benefits offered by orphan drug status and public funding of trials to establish proof of concept. If, ex post, this is the case then it is important that the full social benefit of such an adjustment is obtained by signalling to companies that this is the case.

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

- 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 who are genetically appropriate candidates for treatment. This requires companies and payers to use economic evaluation to identify the higher value associated with such targeting;
- 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 do not adjust, then an increasing number of potential treatments may be shelved for lack of commercial viability at normal payer thresholds. Even where prices do adjust patient populations may be too small to make commercial development viable. This small numbers problem is analogous to that associated with gene therapy for monogenic diseases, and may require similar remedies if society wishes these diseases to be treated.

TABLE IA. LEADING GENE THERAPY PRODUCTS OF U.S. GENE AND CELL THERAPY COMPANIES Nov. 19

Company	*Disease*	*Leading product*	*Clinical trial*	*Vector*
Applied Immune Sciences (RPR Gencell)	Breast cancer	*Ex vivo* cancer immunotherapy expressing IL-2	Phase I	Lipid/ synth vector
Cell Genesys	HIV	*Ex vivo* modification of T-lymphocytes to express HIV antigen specific receptor	Phase II	Retroviral vector (RV)
GeneMedicine	Lung disease	*In vivo* administration of alpha-1-antitrypsin	Phase I/II	Synthetic ve
Genetic Therapy Inc.	Glioma	*In vivo* HSTK/Glancyclovir pro-drug activation system	Phase II/III	RV
(Sandoz)	CF	*In vivo* administration of CFTR gene to lung	Phase I/II	Adenoviral vector (AV)
	Gaucher's	*Ex vivo* insertion of GC gene into haemopoetic progenitor cells	Phase I/II	RV
	Breast cancer	*Ex vivo* insertion of MDR-1 gene into haemopoetic progenitor cells for chemoprotection	Phase I	RV
Genetix	Cancer	*Ex vivo* insertion of MDR-1 gene into haemopoetic progenitor cells for chemoprotection	Phase I	RV
GenVec	CF	*In vivo* administration of CFTR gene to lung	Phase I	AV
	Colon cancer	*In vivo* cytoside daminase pro-drug activation	Phase I	AV
Genzyme	CF	*In vivo* administration of CFTR gene to lung	Phase I/II	AV
Ingenex	Cancer	*Ex vivo* insertion of MDR-1 gene into haemopoetic progenitor cells for chemoprotection	Phase I	RV
Introgen	Lung cancer	*In vivo* administration of p53 gene to residual solid tumour-two trials	Phase I	RV
	Head and neck cancer	*In vivo* administration of p53 to tumour	Phase I	AV
Somatix	Melanoma and kidney cancer	*Ex vivo* cancer immunotherapy expressing GM-CSF	Phase II	RV
	CGD	*Ex vivo* insertion of p47 phox gene into HSC's	Phase I	RV
Targeted Genetics	HIV	*Ex vivo* modification of HIV-specific CTL's	Phase I	RV
	Gaucher's	*Ex vivo* insertion of GC gene into HSC's	Phase I	RV
	CF	*In vivo* administration of CFTR gene to lung	Phase I	AAV
(Rgene Therapeutics)	Ovarian and breast cancer	*In vivo* administration of E1A to inhibit oncogene	Phase I	Lipid
TransKaryotic Therapies	Kidney cancer	*Ex vivo* modification of autologous fibroblasts to secrete IL-2	Phase I	Electroporat
Viagene	HIV	*In vivo* administration of immunotherapeutic expressing HIV specific antigens	Phase II	RV
	Melanoma Neuroblastoma	*In vivo* cancer immunotherapy expressing gamma interferon	Phase I	RV
Vical	Melanoma and other cancers	*In vivo* cancer immunotherapy expressing HLA-B7	Phase II	Lipid
	Lymphoma and solid tumours	*In vivo* cancer immunotherapy expressing IL-2	Phase I/II	Lipid

Source: Martin, P.A. and Thomas, S.M. Human Gene Therapy 9:87-114, 1998

TABLE IB. UPDATED GENE THERAPY PRODUCTS OF CANADIAN AND U.S. GENE AND CELL THERAPY COMPANIES (1) Jan. 1999

Company	*Technology Product*	*Disease/Application*	*Clinical Trial*
Aastrom Biosciences, Inc.	Cell therapy application for bone marrow and umbilical cord blood cells	Cancer and blood disease	Phase I/II
Apoptogen Inc.	Unknown	Unknown	
Activated Cell Therapy, Inc.	Dendrite Cell Immunotherapy	Prostate cancer	Phase I/II
Alexion Pharmaceutical	Cell therapy application using fetal pig brain cells	Parkinson's disease	Phase II
Apollon, Inc.	DNA plasmid-based vaccine	HIV	Phase I/I
ARIAD Pharmaceuticals, Inc.	*Ex vivo* modification of blood T cells by AP 1903 gene	Graft-versus-host disease	Phase I
(with Genovo, Inc.)	*In vivo* administration of EPO gene with oral pill activation system	Anemia	pre-clinical
Atlantic Pharmaceuticals	*In vivo* antisense DNA therapy	Viral infection	Pre-clinical
Avigen	*In vivo* administration of factor IX gene into muscle	Hemophilia B	Pre-clinical / Phase I
	In vivo administration of EPO gene into muscle	Anemia	Pre-clinical
Baxter International Biotech (with Genentech)	*In vivo* administration of factor VIII	Hemophilia A	
BioChem Pharma	*In vivo* immunotherapy using inactivated influenza antigens	Influenza	Phase I
Biogen Inc.	Unknown.	Unknown	
Calydon	*In vivo* administration of gene for prostate tissue specific enhancer (PSE)	Prostate cancer	Phase I
Canji	*In vivo* administration of p53	Cancer	
CardioGene Therapeutics	*In vivo* administration of smooth muscle cell specific promoter	Cardiovascular disease	
Cell Genesys	*In vivo* administration of factor IX gene into liver	Hemophilia B	pre-clinical
	In vivo administration of EPO gene into muscle	Anemia	pre-clinical
	In vivo administration of L-dopa into brain tissue	Parkinson's disease	pre-clinical
	Ex vivo modification of T-lymphocytes to express HIV antigen against specific receptor	HIV	Phase II
(with Japan Tobacco)	*Ex vivo* immunotherapy of tumor cells with GM-CSF (GVAX(TM) technology)	Melanoma, prostate and lung cancer	Phase I/II
Cell Therapeutics	Cell therapy application for bone marrow transplantation	Graft-versus-host disease	Phase III
Chiron Corp. (with Baxter Int. Biotech.)	*Ex vivo* modification of lymphocytes with herpes simplex thymidine kinase gene in leukemia patients.	Graft-versus-host disease	Phase I/II
Codon Pharmaceuticals (with Kimeragen Inc.)	Undisclosed.	Undisclosed.	
Collateral Therapeutics	*In vivo* administration of adenylate cyclase gene into heart	Congestive heart failure	Pre-clinical
	In vivo administration of growth factor gene (FGF-4) into heart	Coronary artery disease	Phase I/II
Copernicus Gene Systems	*In vivo* administration of CFTR gene	Cystic fibrosis	Pre-clinical
	In vivo administration of factor IX gene	Hemophilia B	Pre-clinical
	In vivo administration of LDL receptor	Familial hypercholestrolemia	Pre-clinical
CytoTherapeutics	Engraft neural stem/progenitor cells into damaged regions of brain and nervous tissue	Brain/nervous tissue damage	Pre-clinical
	Cell Therapy application using bioartificial organs.	Nervous tissue repair	

Diacrin (with Genzyme)	Implantation technology of porcine neural cell products	Parkinson's and Huntington's diseases	Phase I
DeveloGen	*Ex vivo* modification of pancreatic duct cells	Diabetes	

TABLE IB. UPDATED GENE THERAPY PRODUCTS OF CANADIAN AND U.S. GENE AND CELL THERAPY COMPANIES (2) Jan. 1999

Company	***Technology Product***	***Disease/Application***	***Clinical Trial***
Enzo BioChem	*In vivo* antisense gene therapy	HIV	Phase I
Epoch Pharmaceuticals Inc.	*In vivo* gene modifying technology applied to HIV co-receptor CCR5	HIV	
	In vivo gene therapy using undisclosed gene	Arthritis	
Gene Therapy	*In vivo* administration of histocompatibility locus antigen-7 (HLA-7) into tumor	Head and neck cancer	Phase II
GeneMedicine	*In vivo* administration of Alpha-antitrypsin	Lung disease	Phase I/II
(with Merck & Co.)	*In vivo* GeneSwitch technology	Undisclosed	Undisclosed
(with Roche Holdings Ltd.)	*In vivo* administration of IL-2, IFN-a, and IL-12	Cancer	
Genetix	*Ex vivo* insertion of MDR-1 gene into haomopoetic progenitor cells for chemoprotection	Cancer	Phase I
GenVec	*In vivo* administration of VEGF121	Peripheral vascular disease	Phase I/II
(with Varian Biosynergy)	Combined gene therapy and radiation application using TNF-alpha gene	Cancer	
Genzyme	Cell therapy/tissue repair application	Tissue damage	
	In vivo administration of anticlotting agent antithrombin	Bypass surgery	Phase III
Hybridon, Inc.	*In vivo* antisense oligonucleotide therapy	HIV	Phase II
Immune Response	*In vivo* administration of interleukin-2	Colon cancer	Phase Ib
Immusol Inc.	*In vivo* administration of ribozyme therapy	HIV, hepatitus B & C	Phase I
InKine	*In vivo* administration of the Fc receptor gene	Infectious diseases	Pre-clinical
Introgen Therapeutics, Inc.	*In vivo* administration of PTEN tumor suppressor into cancer tissue.	Prostate and brain cancer	
	In vivo administration of p53	Cancer	Phase I/II
R.W. Johnson (with Gene Shears)	*In vivo* administration of ribyzyme gene	HIV	Phase I
LXR Biotechnology Inc. (with RPR Gencell)	*In vivo* administration of SARP-1 gene into heart	Myocardial ischemia, heart failure	Pre-clinical
Megabios (with Glaxo Wellcome)	*In vivo* administration of CFTR gene	Cystic fibrosis	
(with Eli Lilly & Co.)	*In vivo* administration of BRCA1 gene	Breast, ovarian cancer	
Neocrin	Cell therapy application involving transplantation of pancreatic cells	Diabetes mellitus	Phase I
NeuroVir	Gene therapy technology using herpes simplex virus as vector	Brain cancer, neurological diseases	
Nexell Therapeutics Inc.	Genetically modified stem cell therapy	Granulomatous disease	Phase I/II
Osiris Therapeutics	Cell therapy application using mesenchymal stem cells	Myasthenia gravis	
Pangaea Pharmaceuticals Inc.	Unknown	Unknown	
Rhone-Poulenc Rorer Gencell	*In vivo* administration of hypoxia response element	Cardiovascular disease	Pre-clinical
	In vivo administration of the gene for the Fv-Ras antibody.	Pancreatic cancer	Pre-clinical
Ribozyme Pharmaceuticals Inc.	*In vivo* ribozyme based therapy	HIV	Phase I/IIa

Sandoz Pharmaceuticals	*In vivo* administration of thymidine kinase to glioblastoma tumor cells.	Brain cancer	
Sertoli Technologies Inc.	Cell therapy application using sertoli cells	Diabetes	
Shering-Plough Pharmaceuticals	*In vivo* administration of the p53 gene	Cancer	Phase I
(with Immune Response)	*In vivo* administration of the interferon alpha-2b gene	Hepatitus B	
StressGen Biotechnologies Corp.	*In vivo* administration of stress protein (hsp) gene 65	Cancer	

TABLE IB. UPDATED GENE THERAPY PRODUCTS OF CANADIAN AND U.S. GENE AND CELL THERAPY COMPANIES (3) Jan. 1999

Company	***Technology Product***	***Disease/Application***	***Clinical Trial***
Targeted Genetics	*In vivo* administration of CFTR gene	Cystic fibrosis	Phase I
	Ex vivo insertion of GC gene into HSC's	Gaucher's	Development terminated
Theratechnologies Inc.	*In vivo* administration of modified Vpr gene	HIV	Pre-clinical
Therion Biologics	*In vivo* Immunotherapy application utilizing NY-ESO-1 antigen	Cancer	
	In vivo Immunotherapy application utilizing HIV-1 IIIB antigen	HIV	Phase I
	In vivo Immunotherapy application utilizing MART-1 antigen	Melanoma	Phase I
Titan Pharmaceuticals Inc.	*In vivo* administration of small RNA molecules	HIV	Phase II
	Cell therapy application using sertoli cells	Parkinson’s disease	Pre-clinical
Transkaryotic Therapies Inc.	Alpha-galactosidase A enzyme replacement therapy	Fabry disease	Phase II
	Ex vivo administration of factor VIII into skin cells	Hemophilia A	Phase I
	In vivo administration of EPO gene	Anemia	Phase III
Vascular Genetics Inc.	*In vivo* administration of VEGF-2 gene	Coronary artery disease	Phase I/II
Vical Inc.	*In vivo* cancer immunotherapy expressing IL-2	Prostate cancer	Phase I/II
VivoRx	Cell therapy using porcine islets	Diabetes	Phase I/II

Sources: Prompt Library Database, InfoTrac Inc., University of Pennsylvania, 1999.
*Drug & Market Development **9:**334-338, 1998.*

TABLE IIA. SUMMARY OF LEADING U.S. GENE THERAPY COMPANY PRODUCTS Nov. 1996

Disease targets and therapeutic strategies of leading products		*Mode of application*	*Number of firms*
Cancer	*Ex vivo* immunotherapy	*Ex vivo*	3
	In vivo immunotherapy	*In vivo*	2
	Pro-drug activation	*In vivo*	2
	Chemoprotection (MDR)	*Ex vivo*	3
	Application of tumor suppresser (p53)	*In vivo*	2
HIV	Adoptive immunotherapy	*Ex vivo*	2
	Immunotherapy using HIV antigens	*In vivo*	1
CF	Direct application of CFTR gene	*In vivo*	4
Gaucher's	Insertion of gene into HSCs	*Ex vivo*	2
CGD	Insertion of gene into HSCs	*Ex vivo*	1
Lung disease	Administration of AAT	*In vivo*	1

Source: Martin, P.A. and Thomas, S.M. Human Gene Therapy 9:87-114, 1998

TABLE IIB. SUMMARY OF U.S. AND CANADIAN GENE AND CELL THERAPY COMPANY PRODUCTS Jan. 1999

Disease targets, medical applications and their therapeutic strategies of leading products		*Mode of application*	*Number of firms*
Anemia	Protein based gene therapy	*In vivo*	4
Arthritis	Protein based gene therapy	*In vivo*	1
Brain/Nervous Tissue Damage	Cell Therapy	*In vivo*	1
Cancer	Cell therapy	*In vivo*	2
	Chemoprotection	*Ex vivo*	1
	Ex vivo immunotherapy	*Ex vivo*	1
	In vivo immunotherapy	*In vivo*	2
	Protein based gene therapy	*In vivo*	13
Cardiovascular/Heart disease	Protein based gene therapy	*In vivo*	7
Cystic Fibrosis	Direct application of CFTR gene	*In vivo*	3
Diabetes	Cell Therapy	*In vivo*	3
	Cell modification	*Ex vivo*	1
Fabry disease	Enzyme replacement therapy	*In vivo*	1
Gaucher's	Insertion of gene into HSCs	*Ex vivo*	1
Graft-versus-host disease	Protein based gene therapy	*Ex vivo*	2
	Cell Therapy	*In vivo*	1
Granulomatous disease	Cell Therapy	*In vivo*	1
Hypercholestrolemia	Protein based gene therapy	*In vivo*	1
Hemophilia	Protein based gene therapy	*In vivo*	4
	Cell modification gene therapy	*Ex vivo*	1
HIV	Adoptive Immunotherapy	*Ex vivo*	1
	Antisense gene therapy	*In vivo*	2
	Immunotherapy using HIV antigens	*In vivo*	2
	Gene modification therapy	*In vivo*	1
	Protein based gene therapy	*In vivo*	1
	Ribozyme therapy	*In vivo*	3
	RNA based gene therapy	*In vivo*	1
Lung disease	Protein based gene therapy	*In vivo*	1
Myasthenia gravis	Cell therapy	*In vivo*	1
Parkinson's disease	Cell therapy	*In vivo*	3
	Protein based gene therapy	*In vivo*	1
Tissue damage	Cell therapy	*In vivo*	1
Viral Infection	Antisense Gene Therapy	*In vivo*	1
	Protein based gene therapy	*In vivo*	2
	In vivo immunotherapy	*In vivo*	1
	Ribozyme therapy	*In vivo*	1

Sources: Prompt Library Database, InfoTrac Inc., University of Pennsylvania, 1999.
*Drug & Market Development **9:**334-338, 1998.*

TABLE IIIA. STRATEGIES OF EUROPEAN GENE THERAPY FIRMS Nov. 1996

Name	Vector technology	Disease targets	Product	Staff
Bavarian Nordic Research Institute S/A	Retrovirus	Breast cancer	Cell implant devices	11
		HIV	*Ex vivo* cell therapy	
		Vaccines	Gene drugs	
CellGenix	N/A	N/A	*Ex vivo* cell processing service	20
			Ex vivo cell therapies	
Genopoietic	Retrovirus	Melanoma, gliboblastoma	Gene drugs	N/A
HepaVec	Viral and non-viral	Liver cancer	Gene drugs	5
		Familial hypercholestrolemia	Gene drugs	
IntroGene	Retrovirus	Chemoprotection	*Ex vivo* cell processing	17
	Adenovirus	Gaucher's, thalassemia	*Ex vivo* cell processing	
	Adeno-associated virus	Cancers	Gene drugs	
MediGene	Adeno-associated virus	Hodgkin's lymphoma	Gene drugs	25
		Cervical cancer	Gene drugs	
Orthogen	Retrovirus	Arthritis	*Ex vivo* cell therapy	7
		Musculoskeletal disorders		
Oxford BioMedica	Retrovirus	Cancers, HIV	Not disclosed	>5
		CF, Parkinson's disease		
Therexsys	Synthetic DNA complexes	HIV	Gene drugs/ *ex vivo* cell therapy	30
		Gaucher's	Gene drugs	
Transgene	Adenovirus	Lung, breast and cervical cancer	Gene drugs/ *ex vivo* cell therapy	180
		CF	Gene drugs	
	Retrovirus	HIV	*Ex vivo* cell therapy	

Source: Martin, P.A. and Thomas, S.M. Human Gene Therapy 9:87-114, 1998

TABLE IIIB. UPDATED GENE THERAPY PRODUCTS OF EUROPEAN GENE AND CELL THERAPY COMPANIES Jan. 1999

Company	***Technology Product***	***Disease/Application***	***Clinical Trial***
Bavarian Nordic Research	Cell therapy implants of gentically altered cells expressing cytochrome p450	Pancreatic cancer	Phase I
	Ex vivo immunotherapy of virally infected cells	HIV	Pre-clinical
	Ex vivo immunotherapy of tumor cells	Melanoma	Phase I/II
Cantab Pharmaceuticals	*In vivo* immunotherapy of papillomavirus infected cells	Genital warts	Phase IIa
Eurogene	*In vivo* gene therapy using undisclosed gene		
Introgene	*In vivo* administration of Interleukin-3	Cancer	Phase I/II
	In vivo administration of nitric oxide synthase gene	Angioplasty and pulmonary hypertension	
	In vivo administration of β−globin gene.	β-thalassaemia	pre-clinical
MediGene (with Hoechst Marion Roussel)	*Ex vivo* immunotherapy of tumor cells	Melanoma	Phase I/II
NeuroTech	Drug delivery system produced by cell-based gene therapy	Nervous and opthalmic disorders	Phase I/II
Novartis	Bilayered skin cell therapy	Venous leg ulcer	FDA approved
	Ex vivo immunotherapy of genetically altered cells expressing RevM10 mutant protein	HIV	
	In vivo administration of thymidine kinase gene	Glioblastoma	Phase III
(with Osiris Therapeutics)	Mesenchymal stem cell therapy	Tissue regeneration	
Oxford BioMedica	*In vivo* administration of an undisclosed gene derivative	Breast cancer	Phase I/II
Schering-Plough	*In vivo* administration of p53 gene	Cancer	Phase I
Therexsys	Gene therapy application using Locus Control Region technology	Cancer	
Transgene	Cell therapy immunotherapy using IL-2 gene	Melanoma	Phase II
	Cell therapy immunotherapy using MUC-1 gene	Cancer	Phase II
	In vivo administration of angiogenic gene	Myocardial ischemia	pre-clinical
	In vivo administration of interferon-gamma	Melanoma	Phase I
	In vivo administration of an undisclosed suicide gene and immunotherapeutic agent	Cancer	

Sources: Prompt Library Database, InfoTrac Inc., University of Pennsylvania, 1999.
*Drug & Market Development **9:**334-338, 1998.*

TABLE IV. SUMMARY OF LEADING EUROPEAN GENE AND CELL THERAPY COMPANY PRODUCTS Jan. 1999

Disease targets, medical applications and their therapeutic strategies of leading products		***Mode of application***	***Number of firms***
Angioplasty	Protein based gene therapy	*In vivo*	4
Cancer	Cell therapy	*In vivo*	2
	Ex vivo immunotherapy	*Ex vivo*	2
	Protein based gene therapy	*In vivo*	2
Genital warts	*In vivo* immunotherapy	*In vivo*	1
HIV	*Ex vivo* immunotherapy	*Ex vivo*	2
Myocardial ischemia	Protein based gene therapy	*In vivo*	1
Opthalmic disorders	Cell-based gene therapy	*Ex vivo*	1
β-Thalassaemia	Protein based gene therapy	*In vivo*	1
Tissue regeneration	Cell therapy	*In vivo*	1
Venous leg ulcer	Cell therapy	*In vivo*	1

Sources: Prompt Library Database, InfoTrac Inc., University of Pennsylvania, 1999.
*Drug & Market Development **9:**334-338, 1998.*

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