investor confidence may increase the dangers to patients through secrecy and poor supervision. Placing too much emphasis on genes as the determining factor in health and disease may lead to prolongation of the illness is experienced (such as the lungs with cystic fibrosis) so the genetic alteration should not be passed on to the patient’s children. Somatic cell gene therapy is the only form that is permitted in this country.

**Germ line gene therapy** involves genetically modifying a fertilised egg and therefore will affect not only the individual that develops from it, but also their offspring and successive generations. Because no actual therapy of an individual is involved, it is more accurately called germ line gene transfer. Although germ line genetic modification of plants and animals is now commonplace, germ line genetic modification of humans is currently banned in this country. This is in line with an existing world-wide consensus that such techniques should not be allowed because of the serious ethical and health implications of modifying the human germ line.

A variation of somatic cell gene therapy is ‘in utero’, where a foetus is modified within the womb or, in the case of embryos, in a test tube (in vitro). However, gene therapy on the somatic cells of a foetus or embryo carries a significant danger of inadvertently affecting the reproductive cells of the baby and hence becoming germ line gene therapy ‘by default’. For this reason, *in utero* gene transfer is not allowed in this country.

**Different Approaches to Gene Therapy**

There are five ways in which gene therapy has so far been approached:

- **Gene augmentation or addition** – in situations where a gene is faulty, a normal working version can be introduced to take over its functions.
- **Gene inhibition** – in situations where a faulty gene is producing a harmful product, it can be switched off by an introduced gene.
- **Targeted gene mutation** – a faulty gene is repaired by using genetic techniques to correct the defect.
- **Killing of disease cells** – genes which cause the production of a toxin can be targeted into diseased cells such as cancer cells or cells infected with a virus. Once inside the cell, the toxin produced by the gene kills the diseased cell.
- **Targeting the immune system to kill disease cells** – a gene which causes the production of a protein recognised as foreign by the patient’s immune system is targeted into diseased cells such as cancer cells. The patient’s immune system then attacks and kills the cells.

Public opposition to genetically modified (GM) crops in the UK and Europe has propelled the issue to the top of the political agenda. At the same time, there is growing public interest in the potential costs and benefits of applying the techniques of genetic modification to treating human illness and disease. This briefing examines the case for gene therapy and considers the safety, social and ethical concerns.

**What is Gene Therapy?**

Gene therapy is defined as ‘the treatment or prevention of disease by gene transfer’ and involves the genetic modification of human cells by introducing one or more new genes. There are two types of gene therapy - somatic and germ line:

- **Somatic cell gene therapy** involves the genetic modification of any cells in a patient’s body apart from the reproductive cells (egg and sperm). The intention is to confine changes to the individual being treated and the parts of the body where the illness is experienced (such as the lungs with cystic fibrosis) so the genetic alteration should not be passed on to the patient’s children. Somatic cell gene therapy is the only form that is permitted in this country.

**References**

Only the first three approaches are aimed at correcting genetic (inherited) disorders. The last two are part of targeting systems to treat, not prevent or correct, a disease and are sometimes referred to as ‘gene-based’ immunotherapy or cancer therapy.

### The Regulation of Gene Therapy in the UK

In the UK, permission to conduct gene therapy research has to be obtained from a Department of Health advisory body known as the Gene Therapy Advisory Committee (GTAC) in conjunction with the appropriate Local Research Ethics Committee and the Medicines Control Agency (MCA). Researchers are required to notify any adverse effects from their trials to all three of these bodies. GTAC operates six key principles when licensing gene therapy trials:

1. Gene therapy is research and not an innovative treatment because it has not yet been sufficiently developed.
2. Only somatic cell therapy should be considered.
3. In view of safety and ethical difficulties, germ line interventions are not allowed.
4. Gene therapy should be restricted to life threatening disorders where no alternative effective treatments are available.
5. Patients should take part in gene therapy research trials only after a full explanation of the procedures, risks and benefits and after they have given their informed consent.
6. For those not able to give consent, including young children, the research must not put them at disproportionate risk.

GTAC also considers that in utero gene therapy is not permissible.

### Gene Therapy Trials

Attempts are currently being made to apply gene therapy research to a whole range of diseases including inherited disorders such as muscular dystrophy and cystic fibrosis as well as cancers and heart diseases. In North America and Europe, approximately two thirds of clinical trials of gene therapy in humans have been cancer treatments. The majority of the rest have focused on inherited ‘single gene’ diseases (i.e. where one faulty gene is responsible) and particularly cystic fibrosis, which is one of the most common inherited diseases (see Table 1). Studies have also been conducting using gene therapy to treat infectious diseases (such as HIV), cardiovascular diseases and rheumatoid arthritis. In the UK, of 41 gene therapy trials approved between 1993 and 2000, 30 have been for different forms of cancer, 8 for single gene disorders and 1 for HIV. However, there have been no applications for trials on single gene disorders since 1996.

Most research work is being undertaken with experimental animals. For example, a gene to increase red blood cell production (the EPO gene) has been introduced into attempts are being made to apply gene therapy research to different forms of cancer and HIV.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>NUMBER</th>
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<tbody>
<tr>
<td>Cancer</td>
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<tr>
<td>Single gene disorders</td>
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<tr>
<td>(e.g. cystic fibrosis)</td>
<td>49</td>
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<tr>
<td>Inherited diseases</td>
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<tr>
<td>Cardiovascular diseases</td>
<td>8</td>
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<tr>
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<tr>
<td>Cerebral palsy</td>
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### Genetic Modification for Profit rather than Gene Therapy for Health

The way in which profitability influences attitudes to gene therapy was graphically demonstrated in an article in a scientific journal commenting on the success with the SCID gene therapy trial. The news was considered of ‘commercial insignificance’, because ‘the new data are barely relevant to gene therapy companies, most of which are hoping to treat the large patient populations suffering from cancer, HIV, and other complex diseases. Indeed, stocks of such companies as Introgen Therapeutics (Austin, TX) and Targeted Genetics (Seattle, WA) were not affected by the news’.

This focus on profitability has serious consequences. The number of people affected with serious single gene disorders (or so-called ‘minority diseases’) is relatively small, making research in this area commercially unattractive even though, on current evidence, this group could be the easiest to treat with gene therapy. The profit motive also means that the interests of the rich may drive the exploitation of the technology. There are already fears that gene therapy may be misused in sport. Desirable ‘improvements’ to people’s appearance, skills and personality could become the target of gene therapists and herald the prospect of designer babies.

A new social divide between the genetically advantaged and disadvantaged could arise. The creation of two distinct species built upon such a distinction is nearing reality rather than being science fiction. Chromos Molecular Systems Inc. in British Columbia is currently developing artificial human chromosomes. People who were given artificial chromosomes and who wanted to pass complete sets of these to their children intact would only be able to mate with others carrying the same artificial chromosomes. This condition, called ‘reproductive isolation’, is the primary criterion that biologists use to classify a population as a separate species.

### Conclusions

Gene therapy not only brings the prospect of treatments for previously untreatable illnesses, it may also enable the prevention of certain diseases through the correction of genetic disorders. However, it is clear from gene therapy under development that, in the short to medium term, most gene therapy will not be used for prevention but for developing more effective ‘gene-based’ treatments for cancer and AIDS.

Although gene therapy has been heralded as a major breakthrough in medical science, it also carries the potential for abuse and for commercial imperatives, not human need, to drive its progress. The demands of industry in maintaining the profit motive also means that the interests of the rich may drive the exploitation of the technology. There are already fears that gene therapy may be misused in sport. Desirable ‘improvements’ to people’s appearance, skills and personality could become the target of gene therapists and herald the prospect of designer babies.

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from tackling social problems such as poverty and environmental pollution which are more important in illness prevention.

- The false belief is likely to be increasingly promoted (even among scientists) that a whole range of aspects of human psychological health, performance and behaviour can be reduced to a one-to-one correspondence with particular genes or groups and families of genes. For example, researchers at the Salk Institute in La Jolla, California, claim to have found a ‘neurosis’ gene even though ‘neurosis’ is a label for a complex cluster of human behaviours, not a single disease\(^{27}\).

### The Commercialisation of Gene Therapy Research and its Implications

It is clearly in the interests of the genomics industry to argue that genes are the most important cause of disease given the commercial pressure to develop and retain investor confidence in a promise of drugs and treatments for the future. The multi-national pharmaceutical companies Aventis and Novartis in particular have made large investments in this research field.

Public and private research are also becoming inextricably intertwined and “company sponsorship is pervasive in gene therapy”\(^{14}\). For example, SmithKline Beecham has been working with the University of Cambridge and the Medical Research Council’s Dunn Nutrition Unit on the control of energy metabolism and the identification of a ‘lean gene’ in a search for treatments for obesity\(^{26}\). Oxford BioMedica, a UK gene therapy company, was set up by two Oxford University professors “armed with six patents from their work in the university lab”\(^{26}\).

Mixing private and public funding raises questions about the control of the trajectory of research and conflicts of interest may arise in gene therapy trials. In the Gelsinger case, the technique used was patented by the institute’s head, James Wilson, and both he and Pennsylvania University have a financial stake in a company developing the technology\(^4\).

Against a backdrop of genetic ‘hype’, secrecy, the privatisation of basic knowledge and profit driven motives, the benefits of gene therapy may not only be more elusive than predicted, they may also be restricted to the few who can afford them. In the meantime, corner’s are likely to be cut in safety testing. Evidence of such trends are already emerging.

### Secrecy in Safety Testing

Gene therapy is big business but, as with the so called ‘dot.com’ companies, genomics companies are trading on a promise of what might be in the future. They rely heavily on gaining investor confidence in this promise and news of deaths in gene therapy trials is extremely damaging. Since the death of Jessie Gelsinger in a gene therapy research trial, there have been a number of accusations of cover-ups of adverse effects in the USA\(^{25}\).

For example, the US Food and Drug Administration (FDA) sent a warning letter to a cardiac specialist at St. Elizabeth’s Medical Center in Boston saying that “a death was not properly reported”\(^{14}\). In another case, Ronald Crystal of the New York Hospital reported a gene therapy death to the US authority but
A much larger number of diseases can be directly linked to the negative impact of environmental abuses such as malnutrition, chemical pollution or smoking and, in practice, the majority of diseases, including cancers and heart diseases, are produced through a complex interaction between environmental and genetic factors. (In the case of breast cancer, for example, only 5-10% of all cases are thought to be related to the presence of a defective gene and having one of these ‘breast cancer genes’ does not, in itself, guarantee that a woman will develop the disease.) Therefore, an important challenge for scientists is to understand how gene-environment interaction works.

2. Delivering the new genetic material into the patient’s cells and keeping it working

Gene therapy research continues to be hampered by the difficulty of inserting genes into cells. Cells can be modified while they are still in the patient (in vivo) or removed – as in the successful SCID trial - treating them in a test tube and then returning them to the patient (ex vivo). Ex vivo gene therapy is more efficient in terms of gene transfer but it is patient specific and more costly than in vivo. In vivo approaches, as are being attempted with cystic fibrosis, have problems modifying enough cells to have an effect.

At present, viruses (including adenoviruses, adeno-associated viruses, retroviruses and lentiviruses) are the most common means or ‘vectors’ used to introduce the new genetic material into cells because viruses are naturally well equipped to infect cells. Other ways of delivering genetic material using other non-viral vectors (such as packaging genes into fatty droplets called liposomes which are taken up by cells) or physical methods (such as directly injecting genes – so-called ‘naked’ DNA) are also being developed. All have pros and cons. Viruses may trigger an immune reaction rendering the newly inserted genetic material ineffective and some (e.g. retroviruses) are relatively poor at invading non-dividing cells. Physical methods tend to be short lived and gene expression only lasting a matter of days or weeks. The search for a reliable vector remains one of the biggest challenges for gene therapy.

3. Side-effects

In theory, the viral vectors used in gene therapy are ‘disabled’ so they should not be able to replicate and spread. However, there is a risk that this safeguard could break down and endanger the patients and others. Even if harmless, an immune response may be triggered to ‘fight off’ a virus vector. In September 1999, 18 year old Jessie Gelsinger, who suffered from a rare genetic liver ailment (although his life was not threatened by it), died while taking part in a gene therapy trial at the University of Pennsylvania. The trial used an adenovirus vector and it seems Gelsinger died from a massive immune response to the vector. In animal experiments, lentiviruses (a group of viruses including HIV) also appear to have caused liver damage.

As it is not possible to control where the new genes are inserted, they could be introduced into the patient’s genes and result in mutations which could cause illness in the future. This potential problem is greatest for those virus vectors (retroviruses, adeno-associated viruses and lentiviruses) which result in the new gene being integrated in the patient’s DNA. There is also thought to be a remote but real chance that if a retrovirus was wrongly inserted, it might promote cancer. In animal experiments, genetic modification has resulted in disruptions in adjacent genes.

This scenario may be more likely with in utero gene therapy where, as a professor of Cell Biology and Anatomy at New York Medical College has pointed out, “The biology of the developing individual will ... be profoundly altered by the manipulation on his/her genes at an early stage. Laboratory experience shows that miscalculations in where genes are incorporated into the chromosomes can lead to extensive perturbation of development. The disruption of a normal gene by insertion of foreign DNA in a mouse caused lack of eye development, lack of development of the semicircular canals of the inner ear, and anomalies of the olfactory epithelium, the tissue that mediates the sense of smell.”

4. The push towards germ line gene transfer

One of the outcomes of these technical difficulties in getting gene therapy to work has been the emergence of pressure in the scientific community to allow germ line gene transfer because they consider it may be technically easier to do. For example, by altering genes in the fertilised egg, the genes should be included in all cells as the embryo divides and forms a baby, removing the problem of only a limited number of cells being altered as is the case with somatic cell therapy. Other developments in genetic technologies, such as embryonic stem cell cloning, also make germ line gene transfer more feasible.

However, germ line gene therapy brings risks to the individual involved as interfering with genes in this way could have very damaging consequences if other genes are disrupted. Furthermore, because the changes will also be passed on to any offspring, the human gene pool will be altered irrevocably. It also raises the disturbing prospect of ‘designer babies’ and even eugenics (‘the study and practice of methods designed to improve the quality of the race, especially by selective breeding’).

The Problem of Genetic Determinism

The genome of an organism is all the genetic (hereditary) information it contains. In June 2000, it was announced that a draft ‘map’ of 95% of the human genome had been completed. The news was hailed by politicians, scientists and media columnists alike as a historic breakthrough, with US President Clinton calling the announcement “more than just a triumph of science and reason. Today we are learning the language in which God created life”. It is now commonplace to see the genome described in quasi religious terms such as ‘the book of life’ and it would appear that genes are being given a God-like status in determining our future.

To place genes on a pedestal in this way takes attention away from the complex interaction between biological and environmental, social and cultural factors responsible for most disease. This is unhelpful and dangerous in relation to gene therapy for several reasons:

- It raises highly unrealistic expectations concerning the potential of gene therapy. This is likely to lead to considerable disappointment for individual patients.
- Political attention (and therefore funding) is likely to shift further and further...