# Gene Therapy: Introduction, Methods and Ethical and Social Issues

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## Abstract

Many diseases are genetically determined; for example, Huntington's disease and cystic fibrosis (CF). Others are influenced by genes, but involve additional factors as well; for example, cancer and diabetes mellitus. Recent scientific developments make it possible for medicine to target such genetically related diseases at the molecular level, and thus offer the prospects of effective new therapies. The genes of somatic cells can be manipulated to modify a disease in an individual. If genes in germ cells are modified, a genetic disease may be prevented in progeny as well. In this review, we will consider some of the scientific, social, and ethical issues associated with such genetic therapies. A related but separate controversy, manipulating genes to modify normal traits, or genetic enhancement, will be examined in accompanying papers.

## Introduction

Genes comprise deoxyribonucleic acid (DNA), and they are replicated during cell division, passing on the information they encode to subsequent generations of cells and of organisms. Genes become functional through a chain of biochemical events: DNA in the cell nucleus is transcribed, by base matching, into messenger ribonucleic acid (mRNA), which then leaves the cell nucleus, attaches to cytosomal ribosomes, and is translated into proteins by pairing of its bases with amino acids. Regulation of the amount of protein produced is achieved through a number of mechanisms, among which is the production of repressor and activator proteins, which prevent the appearance of too much or too little protein, respectively. Modification of genetic DNA leads to changes in both the structure and amounts of protein it ultimately produces. In recent years, a variety of techniques have been developed to identify genes associated with specific diseases. Since 1990, when the first protocols for gene therapy were approved, over 100 new research protocols have been initiated for a variety of diseases, including cancers, HIV infection, cystic fibrosis (CF), Gaucher disease, severe combined immune deficiency (SCID) due to adenine deaminase (ADA) deficiency, familial hypercholesterolemia, and rheumatoid arthritis, among many others**(Walters and Palmer, 1997)**. Proposed for future treatment are such diseases as the muscular dystrophies, particularly Duchenne, and hemoglobin diseases like sickle cell anemia and beta-thalassemia.

## Gene Therapy

With the recognition that thousands of diseases are caused by changes in single genes, so-called monogenic diseases, and the advent of recombinant DNA technology, the idea that one could manipulate the nucleic acid content of diseased cells to cure disease, “gene therapy,” was born (**Porteus *et al*., 2006**).

There are several approaches for correcting faulty genes; the most common being theinsertion of

a normal gene into a specific location within the genome to replace a non-functional gene. Gene therapy is classified into the following two types:

**1. Somatic Gene Therapy**

In somatic gene therapy, the somatic cells of a patient are targeted for foreign genetransfer. In this case the effects caused by the foreign gene is restricted to the individualpatient only, and not inherited by the patient's offspring or later generations.

**2. Germ Line Gene Therapy**

Here, the functional genes, which are to be integrated into the genomes, are inserted inthe germ cells, i.e., sperm or eggs. Targeting of germ cells makes the therapy heritable.

In the case of somatic cell therapies, the nature of a particular disease and other factors determine the specific cells targeted for genetic manipulation. Target cells have included lung, liver, white blood, endothelial, and cancer cells. All research to date has involved somatic cells, and the techniques used make improbable the spread of altered genes to germ cells. However, it seems likely that we will ultimately be able to alter the genes of germ cells, so that whatever changes are made are passed on to the subjects' progeny. In somatic cell gene therapy, target cells can be altered either in vitro (about two-thirds of existing protocols) and then infused or implanted in the host, or in vivo (the remaining one-third of protocols).

Three types of gene manipulation are possible. ***Gene addition***, in which the genetic material is added to the target cells with no attempt to incorporate it into chromosomes, is the only method used in human experiments up to this time. Techniques of G***ene repair*** can replace abnormal segments of DNA in defective genes in their normal chromosomal site. ***Gene replacement*** techniques permit excision of the abnormal gene from its chromosome and replacement with a normal gene. These methods have not been developed sufficiently to use in human trials, but will be critical to the eventual deployment of germ-line therapy.

**Methods of gene therapy**

There are mainly two approaches for the transfer of genes in gene therapy:

1. Transfer of genes into patient cells outside the body (*ex vivo gene therapy*)
2. Transfer of genes directly to cells inside the body (*in vivo*).

**Vectors for gene therapy**

**Vectors for gene therapy can be classified into two types:**

**1. Viral vectors**

**2. Non-viral**

**Ethical and Social Concerns in Somatic Cell Gene Therapy**

Public debate over the ethics of using gene technology to treat human beings raged when

recombinant DNA research began in the 1960s. Long before the technology became available for a gene therapy protocol, the emergent discipline of bioethics focused on genetic engineering. The reason for intense interest in a potential but non-existent technology was straightforward: genetics embodied both the immense promise and the worst fears associated with modern biomedicine. The prospect of altering what many viewed as the blueprint of human life raised questions about "playing God." While some had hopes of eliminating virtually all disease, others saw the specter of eugenics and catastrophic unintended consequences. All believed that there was something unique, something ground breaking about this new science and technology. Gradually, the debate moved from general philosophical and theological reflection to attempts to develop a practical review process for research protocols. It was at this time that the distinction between somatic and germ-line genetic engineering was put forward as a way of distinguishing appropriate from inappropriate types of genetic interventions. Many felt that somatic cell gene therapy was merely an extension of conventional therapies, posing few if any new ethical problems. This view is still generally accepted. Some gene therapies represent novel ways to produce the same medications that are already available at high cost. For example, SCID due to ADA deficiency can be treated by administration of ADA, but the enzyme is very expensive and must be taken frequently. The same enzyme could be produced by the genetic addition of the ADA gene at the cost of a one-time procedure **(Kohn *et al.,* 1995).** Other gene therapies have similarities to transplantation. For example, CF may be treated by providing the patient with normally functioning pulmonary cells. Such cells can be introduced in two ways: by doing a lung transplant, or by genetically altering the patient's own lung cells so they are not subject to damage by CF genes. The former is an expensive halfway technology that requires ongoing immunosuppression to prevent rejection, and constant alertness to infection that may result from immunosuppression **(Zabner *et al.,* 1996).**Gene therapy, on the other hand, would require one treatment to achieve permanent reversal of the CF pathophysiology, with none of the continuing risks of immunosuppression. In producing normal pulmonary cell function, genetic alteration of the patient's own lung cells seems far less invasive, and is potentially far less costly, than transplantation. One of the early concerns about gene therapy was that genetic material used to treat somatic cells would find its way into sperm and ova, thus affecting offspring of the patient. By careful selection of vectors and target cells, however, spread of genetic material to germ cells has not occurred. Beyond safety and efficacy issues, ethical concerns in somatic gene therapy research are familiar in many other clinical settings: weighing potential harms and benefits, establishment of procedural fairness in selection of patients for research, assurance that consent to experimental treatments is informed and voluntary, and protection of privacy and confidentiality of medical information.

**Ethical and Social Concerns in Germ-line Gene Therapy**

Ethical concerns about germ-line therapy have been widely discussed, particularly since the beginning of the Human Genome Project **(Juengst *et al*., 1993, Zimmerman, 1997)**. Underlying some of those concerns are technical issues. Germ-line gene therapy is far more technically difficult than somatic cell therapy. Interactions between genes and their genetic repressors and activators are complex, depending in part on their precise location within a particular chromosome. Stable intergenerational transfer of genetic information and accurate gene expression, therefore, will require replacement or repair of a defective gene in situ. The only method of therapy currently available for humans, however, is gene addition. Technical breakthroughs are thus needed before gene replacement or repair becomes practical. Although many other technical hurdles face germ-line gene therapy, like minimizing risks of insertional mutations and inadvertent production of chimeras, the highest by far is the unavailability of replacement or repair technologies. Germ-line gene therapy is carried out in gametes or pre-embryos. This presupposes a reproductive process that involves in vitro fertilization (IVF) for identification of a defective gamete or pre-embryo. Only at-risk couples willing to use such procedures will benefit from germ-line gene therapy. Even if IVF is used, however, there are questions about why gene therapy would be pursued. If a potential disease is identified in a gamete, then one can avoid the disease by simply discarding that gamete. Any medical procedure involves risks of harm, and there seems to be little warrant for such risk, if the disease can be avoided altogether by choosing not to proceed with a particular gamete. If a disease is identified in a preembryo, which possesses the full complement of 26 chromosomes, the issue is more complex. Those involved in the research related to germ-line gene therapy regularly create and destroy embryos as a part of their research. For those who do not find such destruction of the pre-embryo problematic, the same question raised about gametes is relevant: why would a defective pre-embryo ever be implanted? Those who consider it wrong to destroy a preembryo have a stronger reason to pursue gene therapy. However, such individuals would strongly criticize a research process that perfects the techniques of germ-line gene therapy by the use of extensive nontherapeutic research on embryos. Moreover, those who object to destruction of pre-embryos usually also reject the IVF procedures used to create and test embryos. They would thus be unlikely to avail themselves of the technology for gene therapy. Such concerns raise questions about why research in germ-line gene therapy should be pursued at all. If not for the sake of treating diseases in particular individuals and their progeny, then it may be for the sake of developing the science needed for enhancing genetically determined characteristics; that is, for pursuing genetic enhancement. The technology needed forenhancement is the same as that needed for therapy. If enhancement is illicit, an issue which we consider in the following essay,

then reservations about enhancement may extend back to germ-line gene therapy, thus making the somatic vs. germ-line distinction a basis for distinguishing admissible from inadmissible types of research. Other arguments against permitting germ-line genetic research are related to the possibilities of genetic enhancement the new technology makes possible. Totalitarian governments, for example, may produce superior humans who will reduce the non-enhanced to menial servitude. Gene therapy is expensive, and its association with IVF makes it unlikely, in the near term, that costs will be covered by insurance schemes that are moving in the direction of more sparse types of coverage. People of means may thus have better access. This problem is not unique to genetics. It is found in other economic sectors, and technology that is initially expensive usually becomes increasingly available to all people; computer technology is an example. Much of the cost of gene therapy, however, is associated with the labour-intensive character of the highly skilled procedures, making rapid lowering of costs unlikely in the near future. Automation may reduce costs dramatically over longer time periods. Nevertheless, short-term differential access has raised legitimate concerns about the use of public funds to advance such research. Potential unintended consequences are part of the price of virtually all advances in medicine, but gene technology introduces the prospect of seemingly new kinds of harms. The human genome underlies species design, so the incidental elimination of important but unappreciated function may lead to decreased species fitness. All medical interventions affect human evolution by extending lives that would otherwise end, but germ-line modifications may affect evolution to a greater degree and in a shorter time frame than other interventions. Moreover, conventional medical interventions risk harm to individual subjects, while germ-line modifications pose risks to future generations, as well. Some deleterious consequences may not become manifest in the first generation. This makes germ-line gene therapy in some ways more akin to a public health intervention, rather than a traditional medical one. Other considerations favourpursuing germ-line gene therapy research. A persuasive medical reason is that this kind of therapy may be the only way to treat certain problems. For example, to prevent the expression of certain genetically determined tumours, like retinoblastoma, it may be necessary to reach every individual cell that could initiate growth of a tumor **(Wivel and Walters 1993).** The only way to be certain that appropriate genetic changes are made in every such cell is to correct the genetic problem in gametes, zygotes, or multi-cell pre-embryos. Diseases like cystic fibrosis or diabetes could potentially be treated with somatic cell gene therapy, but parents may, for good reason, want to relieve their children of the necessity of undergoing such treatment or of the responsibility of transmitting unwanted harmful genes to their own children. Moreover, it seems far more efficient to cure a genetic disease with a single treatment that will prevent its appearance in future generations, than to treat the disease each time it appears, generation after generation. From a

public health perspective, efficient prevention of disease is an important social value, as is conservation of future health care resources. Germ-line gene therapy may lead to both of these outcomes.

Somatic cell gene therapy research is relatively uncontroversial, but the debate about germ-line genetic research has not been resolved. Perhaps the strongest argument against an extensive ban on research is that this technology cannot be eliminated. If research is banned in the United States, it will be done elsewhere, with fewer resources to responsibly address the consequences. The science is here, and we must anticipate its development. The key question is whether and how to regulate it so that basic ethical norms are not violated and harms are minimized. Legitimate concerns regarding the harms that may be associated with gene therapy must be identified and publicly discussed, even as the beneficial uses of gene technology are sought. Gene technologies embody the paradigm of the potential benefits and dangers of modern science. They provide humanity with unprecedented power over its own nature. We can only hope that, as the body of genetic knowledge grows, we will have the wisdom to use it constructively.

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***Reference***

1. *Kohn, D.B., Weinberg, K.I., Nolta, J.A., Heiss, L.N., et al.: Engraftment of gene-modified umbilical cord blood cells in neonates with adenosine deaminase deficiency.* ***Nature Medicine*** *1(10):1017-1023, 1995.*
2. *Matthew H. Porteus, Jon P. Connelly, Shondra M. Pruett. A Look to Future Directions in Gene Therapy Research for Monogenic Diseases.* ***PLOS genetics*** *online publication. Vol. 2, Issue. 9. 2009*
3. *Walters, L., Palmer, J.G. Germ-line gene therapy in The Ethics of Human Gene Therapy. Oxford University Press, New York, 80-89. 1997.*
4. *Wivel, N.A., Walters, L. Germ-line gene modification and disease prevention: some medical and ethical perspectives.* ***Science.*** *262:533-538, 1993.*
5. *Zabner, J., Wadsworth, S.C., Smith, A.E. Welsh, M.J. Adenovirus-mediated generation of cAMP-stimulated Cl- transport in cystic fibrosis airway epithelia in vitro: effect of promoter and administration method.* ***Gene Therapy*** *3(5):458-65, 1996.*