This annotated bibliography with an introductory essay was first published as “Human Gene Therapy” in the Kennedy Institute of Ethics Journal, Vol. 4, No. 1, pp. 63-83, March 1994. It has been updated by Bioethics Research Library at Georgetown staff on a periodic basis through July 2011. These citations provide a representative sample of the literature on Human Gene Transfer Research as an aid for students and researchers who are beginning to explore the topic. Search strategies for numerous databases are supplied at the end of this bibliography to support comprehensive research.

I. Background  

Gene transfer research is a form of experimental treatment that involves transferring genetic material into the cells of a patient with a disease caused by a missing or mutated gene. The goal is to cure the disease by modifying the genetic information of the patient’s cells, thereby inducing normal protein expression to replace the mutated or lost gene. For this to work, genetic material must be inserted into the target cells. One way to do this is to take advantage of the fact
that some viruses can insert genetic material into host cells as part of their replication cycle; the virus inserts its genes into a host cell, induces the host cell to make more copies of the virus, then kills the host cell once the new viruses have been released from the host cell. A virus can be modified in the laboratory to delete the genes that the virus uses to make the host cell sick and those that kill the target cell after it has replicated the virus. In gene transfer research, those disease-causing virus genes are replaced with the “good” gene of interest which is missing or mutated in the patient. A viral vector, therefore, is a molecular biological tool in which the virus has been manipulated to allow insertion of the gene of interest into patient cells without the deleterious effects of viral infection.

Over the years, different expressions have been used to describe this procedure. The term “gene therapy” began to be used in the late 1960s. Other expressions include: genetic surgery, genetic engineering, and gene transfer research (V. Walters 2000). The preferred term at this time is gene transfer research.

In studying the ethics of gene transfer research, a distinction should be made between research on the somatic (non-reproductive) cells and the germ (reproductive) cells of an individual. Only the germ cells carry genes that will be passed on to the next generation. Therefore, somatic gene transfer only affects the treated individual, while in germ cell transfer the modified gene is incorporated in the genome of the individual and can be transmitted to subsequent generations.

On September 14, 1990 researchers at the U.S. National Institutes of Health performed the first (approved) gene transfer research procedure on four-year old Ashanti DeSilva. Born with a rare genetic disease called severe combined immune deficiency (SCID), she lacked a healthy immune system and was vulnerable to any passing germ. Children with this illness usually develop overwhelming infections and rarely survive to adulthood; a common childhood illness like chickenpox is life-threatening. DeSilva led a cloistered existence—avoiding contact with people outside her family, remaining in the sterile environment of her home, and battling frequent illnesses with massive amounts of antibiotics.

In DeSilva’s gene transfer procedure, doctors removed white blood cells from the child’s body, let the cells grow in the lab, inserted the missing gene into the cells, and then infused the genetically modified blood cells back into the patient’s bloodstream. Laboratory tests showed that the treatment strengthened DeSilva’s immune system, and she was immunized against whooping cough. This procedure was not a cure; the white blood cells treated genetically only work for a few months, and the process has to be repeated (V. Thompson 1994).

While optimism was strong in the early days of gene transfer research, it has been increasingly acknowledged as both a scientifically and ethically challenging procedure. The biology of human gene transfer is very complex, and there are many techniques that still need to be developed and diseases that need to be understood more fully before gene transfer can be used appropriately. The public policy debate surrounding the possible use of genetically engineered material in human subjects has been equally complex. Major participants in the debate have come from the fields of biology, government, law, medicine, philosophy, politics, and religion, each bringing different views to the discussion.
Some commentators on gene transfer research have objected to any form of genetic manipulation, no matter how well-intentioned (V. Rifkin 1983). Many others approve of the use of somatic cell gene transfer, but hesitate to allow the use of germ-line gene transfer that could have an unforeseeable effect on future generations. Still others have argued that with proper regulation and safeguards, germ-line gene transfer is a logical extension of the progress made to date, and an ethically acceptable procedure. Currently, germ-line gene transfer is considered by most to be ethically unacceptable and research has been prohibited around the world due to its unknown risks (II. David and Peebles 2008). On the other hand, the consensus on somatic cell gene transfer is that it is “…ethical to insert genetic material into a human being for the sole purpose of medically correcting a severe genetic defect in that patient” (II. Anderson 1984). Some argue that technology developed to treat disease in somatic gene transfer could be used to transfer genes for non-therapeutic reasons, namely to artificially enhance some members of society to become superior in one way or another, essentially causing a resurgence of the eugenics movement (VIII. Smith, et al. 2010). Others argue that the possibility that this technology could be misused should not delay research and clinical application of therapy that could ameliorate human suffering (VI. Munson 1992).

Techniques

The first somatic cell gene transfer procedure inserted a normal gene into the DNA of cells in order to compensate for the nonfunctioning defective gene (VII. Kessler et al. 1993). This technique involves obtaining blood cells from a person affected with a genetic disease and then introducing a normal gene into the defective cell. This can be done by directly introducing the new DNA into the cells or by using domesticated viruses. It is important that the DNA be inserted in the correct cell and at the correct place in the genome of the cell. Various types of viral vectors (see description above) could be used to deliver the gene of interest, with each having its own advantages and disadvantages (II. Njeim 2010). Current research is trying to determine the most effective candidate. Effective vectors should have the following characteristics: (1) the vector should be easy to produce, (2) once introduced the vector should express the gene(s) it carries for a certain amount of time or expression should be able to be regulated depending on the disorder being treated, (3) the vector itself should not illicit an immune response, (4) introduction of the gene should be restricted to the target tissue, (5) the vector should be large enough to carry the gene of interest, (6) the vector should be able to be introduced specifically into a target site in the genome, and (7) the vector should be able to infect non-dividing as well as dividing cells (II. Somia 2000). Recently, researchers have tested such vectors as adenoviruses derived from viruses that commonly cause respiratory infections. Some examples are: adeno-associated virus (AAV), small DNA viral vectors, and lentiviruses derived from the HIV retrovirus.

Germ-line gene transfer is technically more difficult, and as noted, raises more ethical challenges and is not allowed. The two main methods of performing germ-line gene transfer would be: 1) to treat a pre-embryo that carries a serious genetic defect before implantation in the mother (this necessitates the use of in vitro fertilization techniques); or 2) to treat the germ cells (sperm or egg cells) of affected adults so that their genetic defects would not be passed on to their offspring. This approach requires the technical expertise to delete the defective gene and insert a properly functioning replacement.
**Candidate Diseases for Gene Transfer Research**

Gene transfer research is likely to have the greatest success with diseases that are caused by single gene defects. By the end of 1993, somatic cell gene transfer research had been approved for use on such diseases as severe combined immune deficiency, familial hypercholesterolemia, cystic fibrosis, and Gaucher's disease. Most protocols to date are aimed toward the treatment of cancer; a few are also targeted toward AIDS. Numerous disorders are discussed as candidates for gene transfer research: Parkinson's and Alzheimer's diseases, arthritis, and heart disease.

Eve Nichols describes the criteria for selection of disease candidates for human gene transfer research: 1) the disease is an incurable, life-threatening disease; 2) organ, tissue and cell types affected by the disease have been identified; 3) the normal counterpart of the defective gene has been isolated and cloned; 4) the normal gene can be introduced into a substantial subfraction of the cells from the affected tissue; or that introduction of the gene into the available target tissue, such as bone marrow, will somehow alter the disease process in the tissue affected by the disease; 5) the gene can be expressed adequately (it will direct the production of enough normal protein to make a difference); and 6) techniques are available to verify the safety of the procedure (V. Nichols 1988).

Cystic Fibrosis (CF) has long been thought to be an ideal genetic disorder for gene transfer research. First, because the disease is caused by a loss of expression of a single gene product, cystic fibrosis transmembrane conductance regulator (CFTR), re-expression of this one gene should be feasible. Second, CFTR is a membrane channel that functions to regulate the composition of lung secretions, and even though CF patients have various phenotypes in multiple organs, the main cause of death is due to chronic lung infections and inflammation. The lung is a tissue that is easily accessible for gene transfer treatments delivered by aerosol inhalation or direct injection of liquid. The development of new vectors, technologies, and animal models will help the possibility of treatment of CF with gene transfer come to fruition. New clinical trials are currently being planned to determine if CFTR gene transfer can improve CF lung disease (II. Sinn 2011).

The eye is another organ that has characteristics that make it an ideal candidate for gene transfer research. The eye, especially the retina and vitreous of the eye, is easily accessible to treatment, and since it is transparent, it is easy to monitor efficacy of treatment. Its unique structure of interconnected well-organized cells aids in delivering therapy to the appropriate cell types. In addition, the blood-retina border prevents unintentional side effects and immunological responses that could compromise the therapy, because movement of therapy to other organs is limited. Leber congenital amaurosis (LCA) is a disorder that causes the progressive degeneration of the retina, eventually leading to loss of vision. LCA is caused by mutations in many genes, one of which is the retinoid isomerase enzyme, RPE65, which is essential for production of a pigment in the rods and cones of photoreceptors in the retina. Gene replacement or augmentation therapy for LCA would be expected: 1) in young patients with little impairment, to improve vision by restoring photoreceptor function lost when RPE65 was mutated, or 2) in older patients with advanced disease, to prevent further photoreceptor loss. In 2007, three different gene transfer research clinical trials treated three patients each, and have shown some early success in gaining and preserving visual function in patients with LCA by replacing
RPE65. These trials were able to support the safety of subretinal gene transfer, since no serious adverse effects, toxicity, or immune responses were detected. They were also able to show an improvement in visual function and retinal sensitivity, namely a gain in perception of stationary targets, within a few weeks after the gene transfer. Long term improvement was shown to persist for over two years, indicating that the gene was produced at physiologically relevant levels and was stable. Further studies started in 2009 included patients as young as 8 years of age. Again, the treatment’s safety and efficacy was supported even over a 2.5 year interval. Children showed the greatest improvement, being able to move about independently and participate in normal classroom and athletic activities (II. Cideciyan 2011; II. Den Hollander 2010; II. Smith 2009).

Brief History of Gene Transfer Research and Its Regulation in the United States

John Fletcher cites 1967 as the threshold of the gene transfer research debate, when Nobel Prize winner Marshall Nirenberg wrote of programming cells with synthetic messages, and recognized the promise and danger of this scientific procedure (VI. Fletcher 1990).

A seminal event in the history of gene transfer research occurred when an American doctor, Stanfield Rogers, collaborated with a German physician to treat two sisters suffering from an inborn error of metabolism, hyperargininemia, with Shope papilloma virus (SPV) between 1970 and 1973 (III. Terheggen 1975). It was erroneously believed that the virus would cause expression of the gene defective in the children. The gene normally regulates the production of arginine and it was thought that treatment could alleviate some of the symptoms of the disorder such as slowed mental and physical processes and spasticity of the muscles.

In 1974 the National Institutes of Health (NIH) took the lead in regulating research with recombinant DNA (rDNA)—one of the building blocks of gene transfer research. According to the NIH Guidelines, recombinant DNA molecules are defined as molecules constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell (VII. NIH 2011). The Recombinant DNA Advisory Committee (RAC) to the NIH Director was originally created in response to concerns of the general public about the safety and ethics of rDNA research. The RAC was at first responsible for approving all research projects involving recombinant DNA in laboratories in the United States, and then handled gene marking research. Gene marking allows researchers to mark a gene in some way as to be able to follow that gene once introduced into target cells. Gene marking is different from gene transfer research because there is no intended benefit to the host of inserting this marked gene—it is simply a way to follow what the gene does and where it goes once inserted, for the sole purpose of information gathering in a research setting. This is different from the goal of gene transfer research, which is to give some clinical benefit to the host cell into which the gene is inserted. As of 2011, the RAC reviews rDNA issues and recommends a course of action or policy to the NIH Director. These recommendations are disseminated through the NIH Office of Biotechnology Activities (OBA), which is responsible for oversight of rDNA research at NIH.

In addition, the RAC reviews all gene transfer protocols in conjunction with the Food and Drug Administration (FDA). The FDA focuses on the safety and efficacy of genetically altered products, on the safety of the manufacturing process, and on control of the final product. Current information about the RAC can be found on NIH's Office of Biotechnology Activities' Web site.
The document "Points to Consider" continues to be updated, and can be found as Appendix M of NIH's Guidelines for Research Involving Recombinant DNA Molecules. RAC scrutiny of gene transfer clinical trials does not duplicate FDA oversight or IRB review, but rather focuses on the scientific integrity of the research (VII. Ertl 2009). RAC meetings are open to the public, and video recordings of the meetings can be downloaded from the RAC website.

Oversight by the RAC and the FDA requires preliminary approval by the home institution's institutional biosafety committee (IBC) and institutional review board (IRB); final approval is then required by the RAC. These regulations apply to all federally funded institutions performing rDNA research, regardless of the funding for the specific project, and regardless of whether or not the research took place in the United States.

The first attempt at human gene transfer research was performed under questionable circumstances by University of California at Los Angeles (UCLA) researcher, Dr. Martin Cline. Without the approval of his UCLA IRB, Cline performed a recombinant DNA transfer into cells of the bone marrow of two patients with hereditary blood disorders in Italy and Israel. At the time, Italy did not have IRBs, and Dr. Cline did not disclose fully to the Israeli IRB the exact nature of the gene transfers he proposed. In October 1980, the Los Angeles Times published details of Dr. Cline's activities (III. Jacobs 1980). Subsequently, he was forced to resign his department chairmanship at UCLA, he lost grant funding, and for a period of three years, all of his applications for grant support were accompanied by a report of the investigations into his activities in 1979-1980.

In light of Dr. Cline's experiment, and at the prompting of the National Council of Churches, the Synagogue Council of America, and the United States Catholic Conference, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research became involved with the issue of gene transfer research and released a landmark study called Splicing Life in 1982 (IV. United States President’s Commission 1982). The President's Commission vigorously defended the continuation of gene transfer research. Splicing Life responded to the concern that scientists were playing God, concluding that we can distinguish between acceptable and unacceptable consequences of gene transfer research. The Commission suggested that the RAC broaden the scope of its review to include the ethical and social implications of gene transfer research.

In 1984 the RAC created a new group, called the Human Gene Therapy Working Group (later called the Human Gene Therapy Subcommittee (HGTS)), specifically to review gene therapy protocols (VI. Walters 1991). The first task of the Working Group was to produce the "Points to Consider for Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects" document as a guide for those applying for RAC approval of gene transfer protocols (VII. United States National Institutes of Health 1990).

Another outcome of the hearing was the 1984 U.S. Office of Technology Assessment (OTA) background paper Human Gene Therapy, which stressed the difference between somatic and germ-line gene therapy (VII. United States Congress Office of Technology Assessment 1984). OTA also issued an important survey on public opinion regarding genetic technologies, New
Other attempts by Congress to participate in the public debate on gene transfer research were less effective. Emanating from the hearings chaired by then Congressman Al Gore, was legislation to create a federal commission to study the ethical, legal and social issues of genetic engineering (VII. United States Congress 1982), but the bill never passed. The Biomedical Ethics Advisory Committee briefly studied the issue of gene transfer research, but its mandates to study issues relating to death and fetal tissue research led it to become embroiled in abortion politics, and the Committee collapsed before taking action (VII. Cook-Deegan 1990).

By late 1985 the RAC Subcommittee had its "Points to Consider" document ready and waited for gene transfer protocols to be presented. The first protocol it received, in 1988, was actually for gene marking. Steven Rosenberg proposed using gene marking techniques to track the movements of tumor-infiltrating blood cells in cancer patients; no actual therapy was proposed. After several months of discussion among the HGTS members, and the gathering of additional information, the protocol was approved by a mail ballot in December 1988. The experiment was briefly stalled by a lawsuit filed by the Foundation on Economic Trends questioning the validity of the review process (VII. Foundation on Economic Trends 1991). Eventually Rosenberg and colleagues did perform the experiment, and found that they were successfully able to follow the distribution and survival of the tumor-infiltrating lymphocytes that had been induced to express a gene for antibiotic resistance by retroviral gene transduction (III. Rosenberg 1990).

In 1990 the HGTS received two protocols to review. One was from Michael Blaese and French Anderson for gene transfer research on children like Ashanti DeSilva who suffered from SCID; the other was from Steven Rosenberg and colleagues who wanted to use the same tumor-infiltrating blood cells, now genetically altered, to deliver a tumor necrosis factor designed to kill tumor cells. Both protocols were approved. The SCID clinical trial found that after two years of gene transfer of the adenosine deaminase (ADA) gene in two SCID children, certain aspects of the immune system remained normalized even four years after the initial treatment. The conclusion was that gene transfer was safe and effective (III. Blaese 1995). In initial studies by Rosenberg and colleagues using the tumor-infiltrating cells secreting tumor necrosis factor, five patients were treated. When the injection site was incised three weeks after gene transfer, no viable tumor could be found (III. Rosenberg 1993).

In December 1992 Dr. Bernadine Healy, then Director of the NIH, approved a compassionate use exemption from the regular review process to allow a critically ill patient to receive gene transfer. This circumvention of the regular approval process proved very controversial and set off a series of meetings aimed at creating procedures for dealing with expedited review of single patient protocols in the future (VII. United States National Institutes of Health 1993).

In October 1999, the death of Jesse Gelsinger, the first fatality in a gene transfer experiment, was reported in Nature (III. Lehrman 1999). Gelsinger carried the diagnosis of partial deficiency of ornithine transcarbamylase (OTC), an enzyme in the pathway to break down ammonia. Patients with a total lack of this enzyme die shortly after birth due to the build-up of ammonia, whereas patients like Gelsinger can be treated with drugs and diet. He was in a Phase I trial of escalating
doses of adenoviral vectors with the OTC gene when he died. He was the first patient whose death could be directly attributed to administration of the adenoviral vector. Subsequent investigations revealed that deaths in animal trials did not receive the usual public disclosure (III. Nelson November 3, 1999). Gelsinger's death also raised questions about researcher entrepreneurial activities and conflict-of-interest, and about government oversight procedures (III. Nelson November 21, 1999). The United States Senate held hearings on this topic on February 2, 2000 (VII. United States Congress 2000), and the heightened scrutiny has resulted in increased reporting of adverse effects and renewed oversight by both NIH and FDA (VII. Smith and Byers 2002). Gelsinger's death also resulted in federal charges being brought against the clinical trial researchers and their institutions, who reached a settlement with the U.S. Office of the Attorney General in February, 2005 (VII. United States, Department of Justice, Office of the Attorney General 2005).

The success of a multi-center trial for treating children with SCID held from 2000 and 2002 was questioned when two of the ten children treated at the trial's Paris center developed a leukemia-like condition. Clinical trials were halted temporarily, but resumed after regulatory review of the protocol in the United States, the United Kingdom, France, Italy, and Germany (VII. Cavazzana-Calvo 2004).

In 2007, a death in a gene transfer trial for arthritis was found to be from factors not related to the trial. This case prompted discussion of including procedures for investigating illness occurring during a study in the trial’s protocol (III. Zaia and Federoff 2009).

Arguments in Favor of and Against Gene Transfer Research

The central argument in favor of gene transfer research is the hope that it can be used to treat desperately ill patients, or to prevent the onset of horrible illnesses. Conventional treatment for the candidate diseases for gene transfer research is limited; for patients with those diseases, gene transfer may offer the only hope. Many commentators liken somatic cell gene transfer research to other new medical technologies, and argue that we have an obligation to treat patients if we can.

Eric Juengst summarized the arguments for and against human germ-line gene transfer in 1991: 1) germ-line gene transfer offers a true cure, and not simply palliative or symptomatic treatment; 2) germ-line gene transfer may be the only effective way of addressing some genetic diseases; 3) by preventing the transmission of disease genes, the expense and risk of somatic cell transfer for multiple generations is avoided; 4) medicine should respond to the reproductive health needs of prospective parents at risk for transmitting serious genetic diseases; and 5) the scientific community has a right to free inquiry, within the bounds of acceptable human research.

Arguments specifically against the development of germ-line gene transfer techniques include: 1) germ-line gene transfer research would involve too much scientific uncertainty and clinical risks, and the long term effects of such research are unknown; 2) such gene transfer research would open the door to attempts at altering human traits not associated with disease, which could exacerbate problems of social discrimination; 3) as germ-line gene transfer involves research on early embryos and effects their offspring, such research essentially creates generations of unconsenting research subjects; 4) gene transfer is very expensive, and would never be cost...
effective enough to merit high social priority; and 5) germ-line gene transfer would violate the rights of subsequent generations to inherit a genetic endowment that has not been intentionally modified (VI. Juengst 1991).

Many people who voice concerns about somatic cell gene transfer use a "slippery slope" argument against it. They wonder whether it is possible to distinguish between "good" and "bad" uses of the gene modification techniques, and whether the potential for harmful abuse of the technology should keep us from developing more techniques (V. Hubbard and Wald 1993). Other commentators have pointed to the difficulty of following up with patients in long-term clinical research (III. Ledley 1993). Some are troubled that many gene transfer candidates are children too young to understand the ramifications of gene transfer research.

Others have pointed to potential conflict of interest problems—pitting an individual's reproductive liberties and privacy interests, on the one hand, against the interests of insurance companies, or society on the other—not to bear the financial burden of caring for a child with serious genetic defect. Issues of justice and resource allocation have also been raised: in a time of strain on our health care system, can we afford such expensive research? Who should receive gene transfer? If it is made available only to those who can afford it, concerns have been raised that "...the distribution of desirable biological traits among different socioeconomic and ethnic groups would become badly skewed" (VI. Juengst et al. 1991).

The ethical issues posed by both somatic and germ-line gene transfer research are international in scope. The documents listed below serve to demonstrate the variety of reactions to gene transfer research, and to illuminate the complexity of this continuing public debate.

II. The Science


Anderson argues for three requirements for the clinical trial of somatic gene transfer in humans. These are based on animal experiments. Animal studies must show that:
1) the gene can be put into the target cells and be effective
2) the gene can be expressed at an appropriate level
3) the gene will not harm the cell or the animal.

Anderson also discusses germline cell transfer research, enhancement and eugenics.


This early article from the chief of the Laboratory of Molecular Hematology, National Heart, Lung and Blood Institute, National Institutes of Health discusses candidate diseases for gene transfer research. These diseases include Lesch-Nyhan Disease and...
Severe Combined Immunodeficiency Disease, which are diseases caused by defective or missing enzymes or proteins that do not need to be exactly regulated. Anderson states that “all observers” believe that it is ethical to insert genetic material into a human being in order only to correct a severe genetic defect.


This is a review of the clinical trials of gene transfer research in Leber Congenital Amaurosis, including a discussion of animal models and prospects for the future.


The authors, members of the Obstetrics and Gynaecology faculty at University College London Medical School, discuss the possibility of gene transfer for the fetus. As of publication, fetal gene transfer research is an experimental procedure done in animal models. There may be advantages for the treatment or prevention of early-onset disorders such as cystic fibrosis and Duchenne muscular dystrophy. Stem cell populations that are not accessible after birth may be available in the fetus.

Den Hollander, Anneke I.; Black, Aaron; Bennett, Jean; and Cremers, Frans P. M. *Lighting a Candle in the Dark: Advances in Genetics and Gene Therapy of Recessive Retinal Dystrophies*. The Journal of Clinical Investigation 120(9): 3042-3053, September 2010. doi:10.1172/JCI42258

Leber Congenital Amaurosis is an early-onset recessive retinal dystrophy caused by retinal pigment epithelium-specific protein (RPE65) mutation. Eighteen patients have been treated in three different studies (Children’s Hospital of Pennsylvania, University of Florida, and University College, London). Each patient was injected unilaterally with recombinant adeno-associated virus (rAAV2) containing human RPE65 complimentary DNA; the treatment was found to be safe and efficacious.


The authors discuss advances in somatic cell gene transfer technologies, and summarize the advances made in constructing different vectors and methods of delivery.

This paper from the Program in Gene Therapy at the University of Iowa is a discussion of the state of gene transfer research for cystic fibrosis in 2011. Because airway epithelium is accessible by aerosol and is determined by the transmembrane conductance regulator (CFTR) gene, cystic fibrosis is potentially a good candidate disease for gene transfer research. There has been difficulty in developing a good animal model for cystic fibrosis.


This paper discusses the potential for treating other forms of retinal degeneration by using gene transfer subsequent to clinical trials to treat Leber congenital amaurosis.


Written in the wake of the death of Jesse Gelsinger, this article reviews the state of the art of commonly used viral vectors. The properties of an ideal vector are delineated. A glossary of terms is provided.


This detailed report on the status of viral vectors for gene delivery in gene transfer research reviews clinical trials to date. Retroviruses, lentiviruses, adenoviruses and adeno-associated viruses have been used for this purpose. Geneticists, virologists, cell biologists, bioengineers and clinicians will need to work together to accomplish successful treatment of disease with gene transfer research.

**III. Clinical Trial Experience**


Two patients with severe combined immunodeficiency were treated with retroviral vector transfer of the adenosine deaminase (ADA) gene. The treatment ended after two years, but ADA expression persisted at four years.


This case report from the University of Chicago, Departments of Pathology and Medicine; the Division of Rheumatology Research, University of Washington; the Gene
Therapy Center, University of North Carolina at Chapel Hill; and St. John’s Hospital, Springfield, Illinois, describes the clinical course of a patient who in 2007 received systemic anti-tumor necrosis factor α (anti-TNF α), methotrexate and prednisone at the time of a gene transfer study of anti-TNF α delivered into the right knee joint by means of an adeno-associated virus (AAV) type 2 delivery system. The patient subsequently developed a febrile illness with abdominal bleeding and multiple organ failure. The cause of death was determined to be a widespread fungal disease, Histoplasmosis, which occurs in immunocompromised persons and which is found primarily in the geographic region in which the patient lived. The authors conclude that subjects of gene transfer trials require close follow-up especially when they become ill.


In response to the Gelsinger case, Friedmann ranks informed consent as the most important mechanism for patient protection in human gene transfer research. He states that improvements are needed in review and regulation.


After noting that gene transfer research is "...a field in which hype has far outstripped payoffs," Gura provides a history of genetic research in hemophilia, and describes the current climate of clinical trials using human subjects after the field's first death [Jesse Gelsinger].


This authors recommend that unusual infectious agents be considered carefully as a cause of fever in gene transfer trial subjects. Subjects should be educated about possible infection.


Hohmann writes that the “inclusion and exclusion criteria for this study [see Frank et al. above], as posted at ClinicalTrials.gov, were reasonable.” The rapid reporting of adverse effects and a solid plan for the follow-up of unexpected events for trial subjects is recommended.

This news article reports the first clinical trial of human gene transfer conducted by Martin Cline in 1980. While his research protocol was under review at the University of California, Los Angeles, Dr. Cline undertook gene transfer trials for Beta Thalassemia on two patients: one in Israel and the other in Italy. The Institutional Review Board at UCLA subsequently rejected Cline’s protocol pending further experimentation on laboratory animals.


Biologist Ledley raises the question of whether current clinical trials gained approval prematurely. He suggests that gene transfer research can be performed in select clinical trials safely and with public acceptance, and while there is still much to be learned, existing methods may be employed fairly in clinical trials.


This is a news item from *Nature* concerning the death of Jesse Gelsinger.


This news report concerns the death of Jesse Gelsinger.


This news report concerns the death of animal models in the wake of the death of Jesse Gelsinger.


This is a report of studies to develop treatments for cancer based on “genetic modification of lymphocytes and tumor cells.” The hope is to increase host immunity to cancer growth. Three patients were treated and none experienced tumor growth at the injection site.

Rosenberg and colleagues describe retroviral gene transduction for gene transfer in a group of five patients with melanoma. The patients received genetically modified tumor-infiltrating leukocytes. No side effects were noted.


This summary reports data submitted to the Recombinant DNA Advisory Committee through June, 1995 by the principal investigators of existing gene therapy studies. It provides an overview of gene transfer clinical trials in the United States. In addition to describing individual projects, the article contains charts on number of protocols/patients by disease and protocol type, and the number of vectors used and their advantages/disadvantages.


This volume contains the proceedings of the Ernst Schering Research Foundation Workshop No. 43 on human gene therapy held in Berkeley, California on October 2-4, 2002. Discussions focus on four themes: 1) cardiovascular diseases; 2) cancer; 3) CNS diseases; and 4) novel technologies.


In this editorial, Savulescu argues that in the Gelsinger case the risk of harm proved to be more important than the ability to give consent.


This paper reports a trial of Shope papilloma induced virus-coded arginase. The researchers were testing the hypothesis that the virus would cause expression of the defective gene. Intravenous injection of the virus in three hyperargininemic patients did not affect the underlying disease in this report.


The panel, chaired by geneticist Arno Motulsky and hematologist Stuart Orkin, reviews the status of gene therapy after 5 years of experimentation and notes that, despite positive
anecdotal reports, "...significant problems remain in all basic aspects of gene therapy", and "[e]xpectations of current gene therapy have been oversold." The panel's recommendations focus on funding limitations, project coordination, basic science/clinical research combinations, and study evaluations.


Zaia and Federoff discuss the concept of therapeutic misconception' for the researcher as well as for the trial subject. They recommend that the “protocol should clearly state how to proceed in the event of any unforeseen illness.”

IV. Organizational Statements/Policies


The American Medical Association approves of the use of somatic and germ-line gene transfer research provided: 1) that the research conforms to its Council on Ethical and Judicial Affairs' guidelines on clinical investigations; 2) that it adheres to stringent safety considerations; and 3) that gene therapy only be utilized for therapeutic purposes in the treatment of human disorders, and not for enhancement or eugenic purposes.


The American Medical Association recommends that gene transfer research be limited to somatic cells. It should be used to provide treatment rather than enhancement. Complete written informed consent must be obtained.


The Committee concluded that certain forms of somatic cell gene transfer research are ethically acceptable, but recommended that researchers in Australia not undertake germ-line gene transfer either in the laboratory or in human subjects.

This document is the general statement for Australia on conduct in human research. The chapter on Human Genetics (Chapter 3.5, pp. 41-45) does not use the term ‘gene transfer’ or ‘gene therapy.’


The Councils state that alteration involving stem cells or embryos is not acceptable. Alteration which involves human somatic cells or for specific therapeutic purposes may be considered by the Councils.


The Council approved the use of somatic cell gene transfer research for single-gene diseases with no other successful therapies. For the foreseeable future, germ-line gene therapy on only animal models may proceed.


Intended to be of use to the general public as well as to professionals in law, medicine, and pastoral counseling, this report on the moral problems raised by gene transfer is a product of a four-year collaboration by Roman Catholic clergy, physicians, lawyers, and philosophers in the United Kingdom. Chapters include a general review of the scientific aspects of gene transfer, a discussion of "genetic responsibility" and the value of human life, and recommendations on permissible forms of genetic intervention. Excerpts from papal documents relating to gene transfer research are included as an appendix.


The CHA supports gene transfer as a therapeutic intervention. However, transfer research that modifies genetic inheritance is immoral.


The CHA focuses on germ-line gene transfer research and research on gametes and pre-embryos. It sees the development of "gonadal cell” therapy as an "especially important
good to be sought insofar as therapies will provide a positive solution to a negative diagnosis." Because such therapy helps to avoid selective abortion for genetic defects, the CHA supports it.


At a 1990 conference held in Tokyo and Inuyama, Japan, the Council adopted a policy statement on human genetics. Somatic cell gene transfer should be evaluated like other innovative therapies. It requires independent review and interventions should only be limited to conditions that cause significant disability, and not enhance or suppress cosmetic, behavioral or cognitive defects unrelated to a disease. Before germ-line gene transfer is undertaken, its safety must be very well established.


The Council unconditionally opposes germ-line gene transfer research. Problems of obligations to future generations and social discrimination against those who do not submit to genetic engineering make such research intolerable.


The Council prefers the terms “gene modification” or “gene manipulation” to “gene therapy.” In the Council’s view the word ‘therapy’ denotes medical benefit. This Position Paper discusses eugenics and the possible elimination of diseases such as cystic fibrosis by coercive means. A permanent ban on germline cell gene modification is recommended.


The European Health Committee of the Council of Europe notes the promise of gene transfer research for the treatment of monogenic disorders. Among these disorders are Duchenne muscular dystrophy, hemophilia and Leber’s amaurosis congenital.

Based on its support of the right to life and to human dignity, the Council rejects germ-line genetic engineering because it would violate the implied right to inherit a genetic pattern which has not been artificially changed. Somatic cell transfer research is acceptable provided researchers follow standard guidelines for informed consent and for oversight by research ethics committees.


The Medical Research Councils of Austria, Denmark, Finland, France, The Netherlands, Norway, Spain, Sweden, Switzerland, the United Kingdom and West Germany agreed not to allow germ-line gene transfer research.


Article 16.4 states that no germline cell transfer research is to be done per this extract of French Civil Code.


While approving research on gene transfer research in France, the Committee placed some stringent constraints on such research. First, only somatic cell research is permitted; germ-line gene transfer research is banned. The use of viral vectors to transfer genes is prohibited out of fear of damaging germ cells. Only monogenic (single gene) defects are candidates for gene transfer research in France.


The German Society of Human Genetics recommends promotion of somatic cell gene transfer research. The Society rejects the development and use of germline gene transfer.


This document contains national policies for countries such as China, India, Israel, Japan, Mexico, South Africa and South Korea. Resources and webpage links, where available, are provided along with a descriptive synopsis for each country.

Germline cell transfer research is prohibited in the Netherlands. The gene transfer vector is regarded as a drug, whose use is regulated by the guidelines for Good Clinical Practice (GCP).


This web document includes background and prospects, legislation comments, and recommendations.


The Dutch Health Council approved of somatic cell gene transfer research and urged a voluntary moratorium on germ-line gene transfer.


Research and experiments aimed at performing gene transfer research on human somatic cells are ethically acceptable. When doing gene transfer experiments on such cells, steps must be taken to prevent the simultaneous occurrence of undesirable effects on gametes. Gene transfer on human gametes (sperm and ova) presents concerns over "human upgrading," which is deemed unethical and thus, prohibited.

doi:10.1089/hum.1992.3.5-519

The Clothier Committee recommended that germ-line gene transfer research should not yet be undertaken; given the success with preimplantation genetic diagnosis, the Committee advised against further research due to its unknown risks. It approved continued study of somatic cell gene transfer. The Committee further recommended the establishment of a government supervisory body to provide scientific and medical advice on the safety and efficacy of human gene modification, and its use.

United Kingdom. United Kingdom Research Ethics Committee. Gene Therapy Advisory Committee. *Operational Procedures for the Gene Therapy Advisory Committee in Its Role as*
Germline gene transfer research is unlawful. Inadvertent modification of germ cells in a clinical subject is to be avoided by contraception.


In this first report by a U.S. government body, the Commission proposed new agencies to continue oversight of human gene transfer research, and defended research on gene transfer in the United States. The Commission concluded that somatic cell transfer research was similar to other standard medical treatment, and is ethically acceptable. Germ-line gene transfer was not rejected, but indefinitely delayed due to technical and ethical barriers.


This English translation of the crucial section on germ-line gene transfer research from the Report of the Enquête Commission raises specific questions relating to germ-line gene transfer within the context of human embryo research. The Commission recommended that germ-line gene transfer be made a criminal offense. A previous section of the Report deals with somatic gene transfer which is ethically acceptable. Published with a critique by Hans-Martin Sass.


The Council calls for a ban on germ-line gene transfer research and recommends strict control over somatic cell gene transfer, bearing in mind the potential misuse of the technology to discriminate against those held to be defective.


“Human Gene Transfer Research” is not used as a term in this document. Genetic engineering is used with regard to plants and animals. Again, concern is expressed about those persons deemed “disabled.”
The Association makes general recommendations regarding gene transfer research. It suggests that such research on human subjects adhere to guidelines posed in the Declaration of Helsinki, and that full informed consent be obtained. No hazardous or unwanted virus can be inserted into patients. Evaluation of the effectiveness of the therapy should be made. Human gene transfer research should not be performed if simpler or safer treatment exists for a disease.

The WMA calls for gene transfer research to conform to the Declaration of Helsinki; gene transfer conducted in a clinical context is to adhere to standards of medical practice. Informed consent is essential. Risk-benefit analyses should govern the use of this technology.


Hematologist and gene therapist Anderson describes the first 11 clinical protocols dealing with gene transfer or gene marking. He briefly surveys ethical and social considerations of gene transfer research.

The authors describe three different types of somatic cell gene transfer - *ex vivo*, *in situ*, and *in vivo* - and the methods by which genes are transferred to an individual. They detail the criteria necessary for the development of germ-line (reproductive cell) transfer and explain the potential impact of such procedures on society and future generations.


This textbook chapter reviews the pros and cons of gene transfer research and describes the biological basis for concerns raised about the potential effects of germ-line interventions on future generations.

Henderson et al. evaluate therapeutic misconception in early phase gene transfer research using three parameters: 1) reason for joining, 2) expectation of benefit, and 3) study purpose. Sixty-eight subjects responded. Seventy-four percent of them scored high on the therapeutic misconception scale (10 or greater on a scale of 1 to 15).


Howell surveys the recent history of eugenics including the Immigration Restriction Act of 1924, the sterilization of Carrie Buck, and Nazi eugenics. Pointing to history's relevance for those contemplating germ-line gene transfer research, he believes that scientists, physicians, and the public ought to be aware of the slippery slope on which we as a society have embarked.


Hubbard, a professor emerita of biology at Harvard, and Wald, a freelance writer, prefer the term genetic manipulation to gene therapy. They express concerns about unintended consequences of such treatment as well as consent issues for minor children. They are also concerned about the significant cost required to treat a relatively small number of patients. In their view, the money would be better spent on major public health issues.


Kim discusses informed consent in this article. Because the risks and benefits in gene transfer clinical trials are so unpredictable, it is difficult to communicate this uncertainty to individuals in a standardized fashion. Subjects of such trials continue to believe that the research is primarily intended as individualized treatment for them rather than as creating research knowledge to benefit society.


Noting that "[s]ince the early 1990s, investigators have toiled to establish the transfer of genes to human somatic cells as a valid therapy", Kimmelman describes the difference between using regular drugs and gene transfer agents in a clinical trial, summarizes the unusual ethical issues raised by these differences, and details the risk factors unique to gene transfer trials.

University professor Krimsky criticizes the common distinctions used for gene transfer research: somatic versus germ cells, and therapeutic use versus enhancement, because the distinctions are too easy to blur. He argues that we should only allow somatic cell gene transfer for life-threatening or severely debilitating disease until we can find better moral rules.


These Chicago Tribune writers covered the developments in genetic research for over a decade and expanded their articles into a journalistic history of gene transfer. They report on the initial gene transfer experiments, the scientists involved in the research, the patients selected for treatment, and the oversight activities of the federal government. Various opinions on whether the potential benefits of gene transfer research have been "oversold" are presented along with differing views of appropriate government regulation.


The author reviews basic terminology for genetic clinical protocols, outcomes of clinical trials to date, and oversight of human gene transfer research (HGTR). Lysaught also discusses using economic incentives for "orphan disease" drug development as it applies to HGTR.


When the Recombinant DNA Advisory Committee's (RAC) duties were revised and it was no longer reviewing each gene transfer protocol, the RAC's "Appendix M" listing the particulars of all existing trials ceased to exist. A European consulting firm, TMC Development, took on the task of compiling a similar list of data provided to them on a voluntary basis. Their chart includes information on the number of participants in each trial and the disease from which they suffer, the gene and vector used, the type of procedure (in vivo/ex vivo) employed, and the country of origin.


A summary of the findings of NIH's Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy is followed by an elaboration on the panel's fear that "basic science [is] being neglected as enthusiasts race to join the gene
therapy club". This article also reports on responses to the recommendations by geneticists involved in gene transfer research.


Following a segment on the technical and clinical aspects of human gene transfer are sections on ethical and economics issues, federal oversight, and prospects for the future of human gene transfer research. The text of the "Points to Consider" document, and a glossary of genetics terms are included.


Social thinker Rifkin defines ‘algeny’ as the process by which a living thing is transformed from one state to another; he states that the final goal of algeny is to perfect the organism. He describes the terms ‘molecular electronics’ and ‘commercial eugenics.’ He is critical of the biotechnology industry.


The authors describe what they term "the first germ-line therapy protocol developed" – IVONT (in vitro ovum nuclear transplantation) - in vitro fertilization of an egg which has had its abnormal mitochondria replaced. This protocol is proposed to eliminate degenerative neuromuscular abnormalities in children born to those suffering from MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes). The authors address fears and ethical quandaries concerning germ-line gene transfer generally, such as whether "by removing certain diseases we destroy a flexibility in the genome that would be a benefit to future generations, just as sickle-cell anemia is thought to be a benefit in people faced with malaria." While they recommend caution in the use of germ-line gene transfer, the authors point out that "the skills developed in intervening in the germ line will stand us in good stead for further interventions down the line should problems later be revealed." They call for "a collective, world-wide effort of cooperation and discussion" on germ-line interventions since the issue lies "not just along an ethical or scientific axis, but also along the axis of the power of human healing."


A journalist for the Washington Post, Thompson traces the development of gene transfer research and reports on the establishment of federal guidelines and administrative procedures to protect those involved in the experiments. He concludes with an epilogue
on genetically altered stem cells and the hopes of researchers and patients for the perfection of this treatment.


While this brochure does not specifically address ethical questions pertaining to human gene therapy, it does provide a concise explanation of how one variety of gene transfer research works, highlights the regulatory process for such research, and provides an outline of the "Points to Consider" document.


This chapter discusses the various terms used for the concept of “gene therapy” as well as the history of the terms. “Genetic engineering” evolved into “gene therapy” and subsequently to “gene transfer research.”


In their preface, the authors note that this book is published "at an appropriate moment for appraising the first stage of gene therapy research with human patients." Even though more than 100 gene therapy protocols have been developed since the first approved study in 1990, "...many researchers in the field are pausing to catch their breath... [as] diseases that plague human beings have proven to be much more difficult to defeat than some researchers had anticipated." Chapters focus on the biology of gene function, somatic and germ-line therapies, enhancement genetic engineering, and public policy for gene therapy. The NIH Recombinant DNA Advisory Committee's "Points to Consider" are included as an appendix along with brief overviews of cell function, Mendelian inheritance, methods for transferring genes to cells, and homologous recombination.


When his brother Stephen was diagnosed with amyotrophic lateral sclerosis (also known as ALS, Lou Gehrig's disease, or Charcot's disease) at the age of 29, Jamie Heywood formed a biotech company to find a cure for ALS utilizing gene transfer research. In his chronicle, Weiner interweaves personal narratives and discussions of the emerging ethical issues with descriptions of the business and scientific milieux of the time.
The head of the Office of Recombinant DNA Activities at the NIH and the chair of the RAC summarize the technical obstacles that must be overcome before human germ-line gene transfer research can be considered for approval, and encourage public debate over the ethical considerations that will likely be faced by the RAC sometime in the future.

VI. Philosophical Aspects


Anderson believes we should draw a moral line at gene transfer research for enhancement purposes. The basis for our uneasiness over enhancement therapy lies with the fear that genetic engineering could lead to changes in "human nature."


Chan and Harris identify these ethical issues in gene therapy: 1) Is it ethical to modify the human genome, 2) Does such modification lead to eugenics, 3) What is considered disease (for example, if genes contribute to criminal tendencies, should these genes be “repaired”), and 4) Is the risk worth the benefit, particularly to children who cannot give informed consent.


The authors discuss the ease with which genetic research is misnamed "therapy", and provide an historical background for this misnomer. While noting that "...the persistent failure to distinguish clearly between research and therapy in medical science" is not limited to genetic protocols, the authors suggest that the term "gene transfer research" be used to highlight its experimental nature and deemphasize its therapeutic potential.


This paper, from researchers from the University of Sydney, Australia, contains outlines of risks to be considered in gene therapy. Included are questions to consider 1) in the analysis of preclinical data; 2) when analyzing the context of risk assessment (e.g.—what is the natural course of the disease); 3) in the analysis of study design and participant selection; and 4) when engaging participants in risk assessment and decision-making.

The author maintains that "absent a religious or culturally normative understanding of human nature and given the availability of germ-line genetic engineering, there is a plurality of possibilities for refashioning our nature." While elimination of deadly diseases is one aspect of genetic engineering's moral significance, another is "the possibility that numerous possible future alternatives may be chosen, fracturing mankind into numerous different species of humans." Given that there are no content-full norms for guidance, the author concludes that the decision to undergo germ-line gene transfer research would rest with the individual.


Bioethicist Fletcher traces the development of the acceptance of somatic cell gene transfer research in the United States, beginning with Nirenberg, Cline, Rogers, and culminating in gradual acceptance of genetic treatment.


Fletcher and Anderson present an ethical argument that supports the approval of pre-embryo experiments, and compares ethical and social priorities of research in germ-line gene transfer to other human subjects research.


Three sets of arguments against developing gene therapy are discussed, concentrating on the clinical risks, social dangers and better alternatives. Those arguments are evaluated from the perspective of the client-centered ethos that traditionally governs practice in medical genetics. This vantage point suggests useful new directions for the professional discussion of germ-line gene transfer and suggests that germ-line gene transfer in human pre-embryos may always be more problematic for medical genetics than adult germ-line interventions despite greater technical difficulties.


Although, Fuchs discusses the general debate on germ-line intervention and genetic enhancement, this article primarily concerns somatic gene transfer research. It remains to be seen “when trials should be commenced, interrupted, and restarted and with which
participants.” Fuchs argues against toxicity studies for somatic gene transfer and advocates the procedure only as curative in the absence of other therapeutic options.


Goering explores the "treatment vs. enhancement" distinction in genetic medicine, and suggests using a decision-making model based on Rawls' "veil of ignorance" as a first step in determining what would constitute a justifiable genetic improvement. Speculating that the designation of a trait as a "disability" may in fact devalue the lives of those currently living with that trait, the author points out that any discussion of what constitutes treatment or enhancement is based primarily on how society defines disease.


Grey examines the conundrum where..."the difficulty in identifying the individuals who might be adversely affected by [germ-line gene transfer research is that] the identity of the individuals is determined, at least in part, by the choices made." The author proposes that these future individuals be safeguarded by limiting germ-line research to those traits that would enrich but not change basic human characteristics.


Describing his journey from gentle Luddite to democratic post-humanist in regard to germ-line intervention, Hughes addresses critiques ("bio-luddisms") and concerns ("gene angst"), including the "geneticization" of life and the value of genetic diversity. He concludes that "...the relations between new genetic communities will hopefully be mediated by the same institutions, courts and legislatures, minority rights and majority rule. The real challenge faced by a post-human ethic is to define new parameters for which forms of life should be considered property."


This entire issue of the Journal is on germ-line gene therapy, and includes many oft-cited articles. In the introductory article, Germ-Line Gene Therapy: Back to the Basics, Juengst outlines the arguments in favor of and against human germ-line gene transfer research. Burke K. Zimmerman discusses risks and uncertainty in Human Germ-Line Gene Therapy: The Case for Its Development and Use. In How Do We Think about the Ethics of Human Germ-Line Genetic Therapy? Kathleen Nolan addresses the persistent questions as to who is the patient in germ-line gene transfer and how much discretion should be left to potential parents and/or researchers. Marc Lappé focuses on intergenerational equity and secondary germ-line effects in Ethical Issues in
Manipulating the Human Germ-Line. In Maintaining the Somatic/Germ-Line Distinction Ray Moseley challenges the conventional wisdom that while somatic gene transfer may be ethically acceptable, germ-line gene transfer is not. Swiss authors Alex Mauron and Jean-Marie Thévoz report on European reaction to human germ-line gene transfer research in Germ-Line Engineering: A Few European Voices. And finally, in Genetic Disorders and the Ethical Statues of Germ-Line Gene Therapy, Edward M. Berger and Bernard M. Gert discuss evolutionary concerns and iatrogenic dangers of gene transfer research, and express their reluctance to approve of germ-line gene research based on slippery slope arguments.


This 2007 update of Juengst and Walters’ 1999 chapter Ethical Issues in Human Gene Transfer Research in The Development of Human Gene Therapy describes the attempt to alter the regulation of gene transfer work from the "gatekeeping of research" mode to that of an accepted form of therapy. Current ethical concerns include: 1) "scientific uncertainties, 2) the need to use resources efficiently, 3) social risks and 4) conflicting human rights concerns."


Reviewing early commentaries on the social implications of genetic intervention by such authors as Hermann J. Muller, Paul Ramsey, and Karl Rahner, Juengst and Walters chronicle the responses of both professional organizations and governments to the advent of genetic research. They note that the intense public debate about the potential abuses of genetic technologies has resulted in a high level of public confidence about the ability of the parties involved to work for the good of all, and that previous biomedical developments could have benefited for such a comprehensive dialogue.


Theologian Keenan argues that an act-oriented ethics is inadequate and that only a virtue-oriented ethics enables us to recognize and resolve problems caused by genetic manipulation. He expresses concerns that through genetics we will be in danger of objectifying the human subject.

In this brief article, Lowenstein discusses the encouraging early results of gene transfer research of Leber’s Congenital Amaurosis (LCA), a disease of photoreceptor degeneration which begins at birth and results in blindness by the mid to late teens. Awaiting treatment until the age of consent is reached reduces the effectiveness of gene transfer. In order for this treatment to be most effective, parents will need to consent to the treatment on behalf of their children [Accessed May 6, 2011.]


Beginning her chapter with the statement "[t]he cultural face of gene therapy is that of a child", Lysaught argues that this iconic status functions to "...forestall critique, to displace argument, to garner public support - and public monies - for human gene transfer research." Drawing from her experience as a reviewer of a gene transfer protocol for HIV-positive children, the author examines the ways in which uncertainty about what constitutes "minimal risks" and "prospects for benefit" in research with children generally are intensified when gene transfer research is considered to be "gene therapy."


The author suggests that the distinction between gene transfer research as cure versus genetic intervention for enhancement is a false one. McGee reminds us that the desire for self-improvement predates genetic experimentation, and notes that "our current cultural focus on the moral issues associated with 'enhancement' depends on a cultural faith in a particular and deceptively clear description of the limits of human nature and the territory of clinical medicine... When new interventions are proposed, the correct question is not 'Is this medicine or enhancement?' but rather 'Will this approach to this issue work better than others?" The author critiques Norman Daniels' notion of "species-typical functioning" (as it pertains to the cure versus enhancement debate) as an inappropriate exercise in specifying norms.


After discussing the distinction between logical and rhetorical slippery slope arguments, the author reviews the application of both types to gene therapy. McGleenan points out that the clear conceptual and biological differences between somatic cell and germ-line transfer research seriously undermine the use of slippery slope arguments when evaluating these procedures (i.e. if somatic cell transfer is permitted, germ-line transfer research doesn't necessarily follow because it is distinctly different). The author goes on to note that the "rhetorical force [of slippery slope arguments] can obscure the arguments' obvious philosophical flaws. Detailed analysis of the weakness of slippery slope claims should help to displace such claims from their prominent position in ethical debates and
allow attention to be focused on the demanding and important aspects of moral line-
drawing in the new genetic technologies."


Munson and Davis argue that medicine has a prima facie moral obligation to continue developing gene transfer research techniques, and that germ-line gene transfer is not morally unacceptable.


The author ponders "what might be lost if, to an unprecedented extent, we could reduce our vulnerability to change and chance" through gene transfer research. He contrasts the work of philosopher Francis Bacon "...[who] thinks that nature is ours to use in whatever ways conduce to our desires..." with that of theologian Hans Jonas "...[who] thinks that because nature is in an important sense not ours - 'being [is] strictly on loan' - we ought not to use it." While he asserts that gene transfer research should be used to heal the sick and that attempts to control genetic enhancement would be foolish, Parens calls for us to "think more deeply about how attempts at control and alteration that truly enhance life are different from those that impoverish it" for "it would be profoundly tragic if the virtue that is our capacity for self-transformation became a vice."


The editors of this work, all from the University of Sydney, Australia, represent the fields of medicine, public health, and bioethics. The viewpoints of the contributors include law, ethics, and social and biological science. “Their purpose is to consider how society might deal with the ethical concerns raised by inheritable genetic modification and to re-examine...whether these kinds of interventions will ever be ethically and socially justifiable.”


Philosopher Resnik argues that genetic enhancement can be governed by regulations and need not become unjust or unethical.

Richter and Bacchetta place the ethical debate of gene transfer into a three dimensional framework:
1) target cell (somatic versus germ-line)
2) purpose (therapeutic versus enhancement)
3) genomic type (nuclear genome – nDNA versus mitochondrial genome – mtDNA)


Attorney Rosenkranz argues that we have a duty of "genetic rescue," and that human germ-line gene transfer research is morally acceptable so long as: 1) the redesigned person is "still the same;" and 2) the intervention is beneficial.


Shickle discusses genetic enhancements in the context of cosmetic and pharmacological ones, and notes that the high percentage of side effects in the latter calls into question the "progressive" nature of enhancements. Noting that all decisions about biotechnology are based on some concept of the "good," the author describes "enhancement" as a normative concept rather than as a cost-benefit ratio to be analyzed.


An enthusiastic supporter of germinal choice technology (GCT), the author rebuts the stock arguments against modifying our biology. Claiming that genetic enhancement is "...more like a slippery sidewalk than a slippery slope", Stock suggests that we "...concentrate on the specific choices parents can make about their children's genes and try to discourage those practices that seem damaging" rather than follow our current approach "...to worry about the technicalities of the procedure itself “which hinge ”...on philosophical abstractions far removed from dangers to present or future humans."


Devoted to ethical and social issues in biotechnology, the issue includes articles by Robertson Parkman on "Gene Therapy in the 1990s;" Alexander Capron on "Biomedical Technology and Health Care;" Michael Shapiro on "The Technology of Perfection;" and Daniel Kevles on "Vital Essences and Human Wholeness."

Tauer concludes that most of the ethical concerns expressed about gene therapy have appeared in the bioethical literature already in other contexts. She revisits concerns about tampering with "human nature," our obligations to future generations and the status of early human embryos. Tauer sees subtle changes in our attitudes to risk and human experimentation, in publicity and public perceptions of biotechnology, and in our attitudes toward "defective" individuals.


Dutch philosopher Van Tongeren argues that we need to be careful that science and politics not lead the discussion of the morality of genetic engineering. The crucial question is: When and how are we allowed to manipulate?


Bioethicist Walters begins by tracking the early history of gene therapy from the unauthorized experiments of Martin Cline, through the creation of the RAC's Human Gene Therapy Working Group/Subcommittee, and ending with details on the review process for the first gene transfer experiment in 1989 and the first gene therapy protocol in 1990. The second half on the article delineates some ethical arguments relating to germ-line gene transfer research.


Zohar argues that persistence of the human genotype is necessary to maintain the personal identity, and the essence of the individual, including preembryos. We must not use prenatal genetic intervention unless an embryo is at risk for some deadly illness.

**VII. Regulation and Public Policy** top


Adams, a professor of philosophy, devises a Human Germline Modification Scale with four categories: Category 1, germline modification which should be prohibited, Category 2, germline modification which should be available to all, Category 3, germline modification which is available to those who can afford it, and Category 4, germline modification that is mandatory for all.

In a brief essay, law professor Areen outlines the reasons for ethics review panels and emphasizes the necessity of carrying out RAC deliberations in public. Ethics review panels can: 1) educate the public; 2) lead to protocols that are more scientifically rigorous; and 3) are the requisite safeguards imposed by democratic government.


Noting that public opinion concerning human germline genetic modification (HGGM) "...has come from Hollywood in the form of disquieting, sometimes horrific portrayals of the results of irresponsible scientific tampering or accidental mishaps", the authors conducted focus groups across the country to collect data regarding what Americans really think about HGGM. This report provides a summary of their research, a review of current regulatory oversight, and suggestions for future government policies that could foster innovation within an ethical environment.


After reviewing the guidelines of various countries for genetic screening and transfer research, the author critiques the goal of "transnational harmonization" for genetic intervention as reflecting "...the assumption that genes are public resources, like the sea and air, and that deliberations must represent all humans." She concludes that international normative codes should develop from empirical evidence gathered in diverse communities rather than from abstract principles imposed in a hierarchical fashion.


Carmen argues that political science offers the best methodology with which to evaluate decisions regarding the future of human gene transfer research. He focuses on the track record of the RAC in directing the procedures by which human gene therapy protocols are approved.


After providing the history of a multi-center clinical trial for treating SCID in which two patients developed leukemia, the authors discuss the ethical dilemma posed by technological advances that both improve treatment success rates and increase the risk for adverse effects.

Cook-Deegan traces the developments of the 1980s with regard to the regulation and politics of human gene transfer research. As a staff member of the Office of Technology Assessment, and the Director of the abortive Biomedical Ethics Advisory Committee, he provides an insider's overview of the political complexities surrounding human gene therapy.


DeWachter highlights the stands taken by various government commissions and independent organizations in Europe on human gene transfer research.


Epstein explains the regulatory responsibilities of the United States Food and Drug Agency (FDA) and its interaction with the RAC in evaluating protocols for human gene transfer research. The RAC focuses on basic sciences, clinical medicine, law, ethics, theology and preclinical testing in regularly scheduled, public meetings. The FDA studies basic science, clinical medicine, regulatory issues, manufacturing processes, quality control and preclinical testing in confidential meetings scheduled on an as-needed basis. The scientific and regulatory basis for the requests for data in the FDA "Points to Consider" document are also discussed.


As a Recombinant DNA Advisory Committee (RAC) member, Ertl describes in detail the RAC’s responsibilities: revising the *NIH Guidelines for Research Involving Recombinant DNA Molecules*; reviewing any rDNA research that may pose a threat to public health; recommending in-depth review and public discussion of specific human gene transfer research protocols when deemed necessary; and monitoring adverse events. The author differentiates these tasks from those required of the Food and Drug Administration (FDA), institutional review boards (IRB), and institutional biosafety committees (IBC) which also review aspects of gene therapy protocols. Instead of duplicating efforts, Ertl posits that the RAC review is important because it scrutinizes a clinical trial’s scientific value.

Foundation on Economic Trends. *Petition to Amend the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules to Establish a Public Policy Advisory Committee*, 18 September 1990 [and] *Proposed Amendment to the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules to*

The Foundation proposes to establish a Public Policy Advisory Committee, parallel to the RAC to advise the NIH on matters relating to public policy and genetic research. Foundation President Jeremy Rifkin seeks to give more voice to public policy concerns in the approval process for such genetic research. Citing the SCID protocol approved by the NIH in 1990, the Foundation opposes gene therapy on the basis that "the therapy violates the general ethical rule that the benefits to an individual from an experimental therapy should equal or exceed the potential harm."


The author maintains that banning gene therapies that enhance human capabilities not only would be unenforceable but also could lead to "DNA audits" that "would violate other principles prized in liberal societies, including the privacy of reproductive decision-making and the autonomy of families in choices about the development and rearing of children."


Juengst examines the basis for the "Points to Consider" document: the ethical discussion of research with human subjects and the recombinant DNA debate. Such precedents provided six criteria by which to evaluate human gene therapy proposals. Juengst writes that the criteria have not provided a principled basis for our banning the development of these forms of genetic intervention. "Points to Consider" will facilitate the discussion of gene therapy in terms its moral limits and the professional policy question about the goals of medicine, instead of seeing the gene therapy debate as a social policy question about the public good.


While gene therapy trials for X-linked severe combined immunodeficiency (X-SCID) had resumed following a review of two trial participants who had developed leukemia, an additional case of a different form of leukemia occurring in another child prompted a recommendation that only patients for whom conventional treatment has failed should be enrolled in X-SCID trials.

The authors provide definitions for the various somatic-cell and gene therapy protocols that they had reviewed, and discuss safety issues involved when the cells are directly removed from humans for the procedure.


King and Cohen-Haguenauer present a model for planning first-in-human gene transfer trials. They discuss the question of the timing of gene transfer and whether it should be tried early or used only if other treatment options have not been successful.


In an entire issue devoted to the Genetics and the Law Symposium, law professor Larson provides a highly readable survey of the varied literature on gene therapy. Additional articles germane to gene transfer research include: Alexander Capron on *Which Ills to Bear?*; John Robertson on *Procreative Liberty and Human Genetics*; and John Fletcher and Dorothy Wertz on *Ethics, Law, and Medical Genetics*.


Using a hypothetical case of a human gene therapy experiment gone awry, attorney Palmer discusses legal liability associated with gene transfer research. Basic negligence principles are applied to the case, including its prior governmental review and its potential effect on future generations. Palmer expresses concerns about the limits of liability and the effects of gene transfer research on future generations.


Suzanne Pattee, J.D., Vice President of Regulatory and Patient Affairs for the Cystic Fibrosis Foundation, comments on the July 24, 2007 death of Jolee Mohr, a 36 year old woman who participated in a phase I gene transfer clinical trial for rheumatoid arthritis. She recommends providing greater public education about clinical trials, including more people who have participated in clinical trials in the development of such trials and the informed consent forms, establishing centralized IRBs with disease-specific experts, and establishing central data and safety monitoring boards for phase I trials.

Although the authors assert that "therapeutic" genetic enhancement (that which enables one to live a full and healthy life) is desirable, they caution that regulating such therapies should not be left solely to either the government or to individuals. Rather, "...the genetic endowment of children should be in the same hands it has always been in - the hands of parents. But parents who wish to use genetic engineering to bring about a characteristic that had not previously been sanctioned by society through its government should have to apply for permission...[a] broadly based government body could be set up to approve or reject particular parents' proposals...." For those who are skeptical of any plan where the state can interfere with individual choice, the authors refer to immigration law and the right of society to choose its members based on certain criteria.


After reviewing the history of gene transfer research in the United States, the authors discuss the effects on the field brought about by the death of volunteer research subject Jesse Gelsinger.


Thomson, an attorney in litigation in Canada, examines the legal framework for liability as gene transfer research becomes gene therapy. Although she mentions negligence and causation, Thomson’s focus is on informed consent; under standards for informed consent, she also discusses conflict of interest. Her explanation of these principles is clear and concise, and overall very good for someone without legal education. Her references seem fairly balanced between Canadian cases, laws, and regulations and U.S. ones. For instance, the 1999 case of Jesse Gelsinger in the U.S. has a Canadian counterpart—the 1997 case of James Dent—a case which did not come to light until 2000.


This report gives information on gene therapy research in the United Kingdom, including the number of approved clinical trials by disease, the status of those trials, exemptions and guidance issues, and a list of committee members and their addresses.


These regulations were first promulgated in 1978; this is the most recent revision. They apply to all research with human subjects in the United States.

This Bill established the President’s Commission on the Human Applications of Genetic Engineering.


The Office of Technical Assessment (OTA) convened a workshop for an advisory panel on human gene therapy in September, 1984 “to discuss the technical feasibility and diverse implications of human gene therapy.” This Background Paper was written by the seventeen members of that panel. The draft report was reviewed by more than seventy scientist, ethicists, and religious and community leaders.

Contents include: Why is Congress Interested in Human Gene Therapy Now; Types of Gene Therapy; Techniques of Gene Therapy; Background on Genetic Diseases; Medical Aspects of Gene Therapy; Issues That May Arise from Clinical Application; Social Implications of Gene Therapy; and The Federal Role in Gene Therapy.

Chaired by Senator Bill Frist (R Tenn.), this hearing features testimony from Paul Gelsinger, the father of Jesse Gelsinger, a research subject who died while taking part in a gene therapy experiment at the University of Pennsylvania; Eric Kast, a frequent participant in gene therapy trials for cystic fibrosis; Amy Patterson, M.D., Director of the Office of Biotechnology Activities at the U.S. National Institutes of Health; Jay Siegel, M.D., Director, Office of Therapeutics Research and Review, U.S. Food and Drug Administration; Inder Verma, Ph.D., Professor of Molecular Biology, Laboratory of Genetics, Salk Institute; LeRoy Walters, Ph.D., Director, Kennedy Institute of Ethics, Georgetown University; and H. Stewart Parker, representing the Biotechnology Industry Organization.


When the FDA issued its first set of guidelines for gene therapy in 1991 (Points to Consider in Human Somatic Cell Therapy and Gene Therapy, Recombinant DNA Technical Bulletin 15(1): 43-56, March 1992), the majority of gene transfer protocols involved ex vivo procedures (where the patient's cells are removed and a normal gene added before reinsertion). With the addition of new methods for gene transfer (vectors) and increasing utilization of in vivo procedures (where the therapeutic gene is injected directly into the bloodstream), the FDA needed to evaluate safety concerns for recombinant vectors and cord blood stem cells. This document reviews preclinical issues for in vivo safety, guidance for cell banking systems, and the use of different types of viruses as vectors in gene therapy.


Gene transfer products may be biological products (if they contain viral vectors) or drugs (if they contain chemically synthesized materials). Additionally, there are products which act on cells rather than independently on the patient and are termed medical devices.


This document was intended to provide information to manufacturers of products related to somatic cell therapy and gene therapy. Preclinical testing and manufacturing control are addressed.
The minutes of this important meeting of the RAC relate the story of Bernadine Healy's compassionate use exemption, and the subsequent turmoil caused within the RAC.

This document provides researchers with a framework against which to evaluate their proposals for human gene transfer research. It includes technical questions as well as ethical ones.

This document contains the findings of the Ad Hoc Committee created to review the activities of the Recombinant DNA Advisory Committee (RAC). RAC is no longer to conduct a case by case review of gene therapy trials; this function will be carried out by the Food and Drug Administration (FDA). RAC is to continue to review novel protocols and provide advice on policy matters.

Revised in May 2011, these guidelines specify the terms and conditions for the funding of gene transfer research projects by any United States federal agency. See particularly, Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants.
After the death of Jesse Gelsinger in a gene transfer clinical trial, the U.S. Department of Justice brought charges against both the researchers involved (James Wilson, Mark Batshaw, and Steven Raper) and their institutions (University of Pennsylvania and Children's National Medical Center) for misrepresenting the findings of research supported with federal funds. These misrepresentations resulted in the failure to obtain properly informed consent from Gelsinger. The press release discusses the terms of the settlements and contains links to the agreement documents.


Walters provides an insider's review of the early discussion of the ethics of gene therapy, the actions of the RAC, and the approval of the first gene therapy protocols. He summarizes public opinion and international policy statements on gene therapy, and promotes a formal public process for the ethical assessment of germ-line gene therapy.

VIII. Religious Aspects


This collection of eight essays ends with Cole-Turner’s discussion of concerns which limit religious approval of human germline modification: 1) avoiding unacceptable levels of risk, 2) avoiding harm to human embryos, 3) avoiding injustice, and 4) avoiding enhancement. In the majority of the essays presented, germline modification is not ruled out on religious grounds, providing that “strict conditions are observed.”


The editors divide the work into three parts: "Genetic Engineering and Society" with eight essays concerned with gene therapy and its relation to religion, justice, and human rights; "Genetic Engineering the Family" containing six essays including discussions of genetic testing and counseling, neonatal intensive care, and reproductive issues; and "Genetic Engineering and the Individual" with six essays, among them two on cloning. The introduction notes that the essays point out the need for responsibility and opportunity applied to genetics in the "light of the Christian faith.”

Moral theologian Dunstan asks whether gene transfer research affects human nature, whether we have a right to inherit a non-manipulated genome, and whether churches should have a definite position on gene transfer. He concludes that truly therapeutic gene therapy could not change human nature, a product of the distinctively human cerebral cortex. Dunstan rejects the legalistic approach to the second question, though he does agree that parents have a duty to safeguard and to serve the interests of their potential child. The role of churches is to be faithful to their theological principles.


Although finding support for somatic cell gene therapy in the *halachah*, Golinkin calls for a rabbinic enactment to forbid genetic enhancement as it is not in keeping with Jewish theological teachings.


Observing that, for scientists, "...the naturally normal in a biological sense is the basis for a moral norm," theologian Gustafson stresses that "God, the ultimate power, is ordering life in the world through the patterns and processes of interdependence of life." He does not see his theocentric perspective as necessarily contradicting that of scientists, and calls for "communities of moral discourse' in which the scientific medical, ethical and political issues are engaged by informed and intelligent persons who represent both different interests and different perspectives on the nature of humanness and human well-being."


Professor Gustafson critiques the writings of French Anderson and poses some questions of his own on humanness, and what is distinctly human, and what ought we to value in the human? He studies the implications of the biblical teaching that man is made in the image of God and the moral status of the natural human life.


Gene transfer research directed at the correction or amelioration of a disorder is acceptable to the Catholic Church, provided it promotes the personal wellbeing of the individual being treated. Germ-line interventions are of dubious moral probity, but are not totally rejected. To be morally acceptable germ-line intervention should include due respect for the psychological nature of each individual human being. In addition, no harm should be inflicted on the process of human generation, and its fundamental design should not be altered, nor should any new species be created.

Though this document states explicitly that it is not a policy statement on genetics for the Council, it raises some religious questions, and encourages further discussion.


Theologian Nelson outlines the participation of religious scholars in the gene transfer research debate, and the notable impact theology has had on public policy formation.


Perlin places questions of genetic intervention within the broader context of Jewish medical ethics. While somatic cell gene therapy is permissible because it may cure someone(*pikuach nefesh*), germline intervention possibly would be discouraged because "Judaism prohibits mating between diverse kinds of animals, different kinds of seeds, as well as the blending of linen and wool in a garment."


The author discusses germ-line gene therapy in light of the Christian concept of *Imago Die* (that man is created in the image and likeness of God). Peters refers to the work of Philip Hefner when describing human beings as "created co-creators", and suggests that as such, we "play human" by seeking a better future, "as God intends us to." Emphasizing God's ongoing creative work, the author asserts that "...realism about technological limits and risks is insufficient warrant for prematurely shutting the door against possibilities for an improved human future."


Written to meet the need of thinking through the "ethical challenges of human genetic intervention," the work is presented from the perspective of the Christian tradition and provides a framework for a semester course. The author moves from genetic research to "genetic testing, genetically created pharmaceuticals, and finally genetic surgery that directly alters a person's genes." Peterson describes the need in genetic engineering for clarity, especially in terminology, the need for careful reflection, and the need to think and plan ahead.

This letter, signed by over 50 religious leaders from a vast array of religious traditions, and a few scientists concludes that efforts to engineer specific genetic traits into the germ-line of the human species should not be attempted. The body of an accompanying paper discusses gene transfer research in the context of Nazi eugenics and public policy making.


The authors discuss gene transfer research as it relates to *Dignitas personae*, the 2008 Instruction of the Congregation for the Doctrine of the Faith of the Catholic Church. There is support for gene therapy for diseases such as cystic fibrosis and cancer, so long as germline cell gene transfer is not practiced. The authors discuss ‘non-medical’ gene therapy as a new form of eugenics. This is the treatment of non-diseases with gene transfer to produce genetic enhancements.


In discussing the Roman Catholic position that a complete human being is present at fertilization, the author examines the misconception (citing twinning) that this position has a scientific basis in genetics. He notes that spirituality "evolve[s] in concert with...biological development" and goes on to suggest that "[s]ince human consciousness already intervenes in an indirect and uncontrolled way in the evolutionary process, it may be time to consider a more rational and designed intervention in the evolution of Homo sapiens." Stig Hansen calls for a thorough discussion of gene transfer research by both scientists and moral theologians, a dialogue that should include consideration of "...the goal of evolution and what blueprint of the human serves this purpose best."


Sutton finds somatic cell gene transfer research to raise the same moral issues as conventional medicine - i.e. questions of risks/benefits to individual patients. However, she finds that germ-line intervention is "...an offense to human dignity, because [it] means treating children as commodities ...ignor[ing] the inherent dignity and worth of each..."
IX. Surveys


Bioethicist Macer compares attitudes and general public acceptance of the use of gene therapy in humans. Macer details reactions in Japan to gene therapy experiments, which are basically favorable, and compares Japanese reactions to European and American public opinion.


The authors describe a survey conducted in Asia and Australasia that gathered data on public attitudes toward gene therapy. They discovered that the "diversity of comments was generally found to be the same in different countries, suggesting that reasoning about these issues goes deeper than cultures, or religions..." The authors discuss the implications of their findings for the development of international guidelines for gene therapy.


This article presents the results of a survey of members of the American Society of Human Genetics. Ninety-three percent of the respondents used potential for a cure as a criterion for choosing target diseases. In addition, the respondents saw a distinction between gene therapy to treat disease and gene transfer research to provide enhancement. The survey instrument is included.


This study compares the moral evaluations of somatic gene transfer research made by patients and providers. Medical providers did not view gene transfer as “ethically different from other medical interventions.” Consumers (possible patients) viewed “genetic interventions as changing a person’s identity.”


The report contains the result of a nationwide survey of public knowledge and attitudes about genetics and the future of technology, including a section on gene therapy
X. Search Strategies for Human Gene Transfer Research

These search strategies reflect the status of the respective databases as of April 2011.

Database: Academic Search Premier (Private Database: EBSCO Industries, Inc.)
Search Strategy:
1\textsuperscript{st} query box: gene therapy [select \textit{Subject Terms} from the right drop-down menu]
2\textsuperscript{nd} query box: AND legislation or privacy or confidentiality or discrimination or policy or religion or bioethics or ethics or ethical or bioethical [select \textit{Subject Terms} from the right drop-down menu]

Database: ETHX (Public Database: Bioethics Research Library at Georgetown University)
Search Strategy: (15.4[pc] or (“*gene therapy”))

Database: Google Scholar (Public Database: Google)
Search Strategy: exact phrase gene transfer research
at least one legislation or privacy or confidentiality or discrimination or policy or religion or ethics or ethical or bioethics or bioethical

Database: JSTOR (Private Database: ITHAKA)
Search Strategy:
1\textsuperscript{st} query box: “gene therapy” or “gene transfer research” [retain full-text]
2\textsuperscript{nd} query box: AND (legislation or privacy or confidentiality or discrimination or policy or religion or bioethics or bioethical or ethical or ethics) [retain full-text]
Database: LexisNexis Academic (Private Database: Reed Elsevier, Inc.)

Search Strategy:
Combined Search “gene therapy” or “gene transfer research” [check Law Reviews]

Database: NLM Book Catalog (Public Database: U.S. National Library of Medicine)

Search Strategy: (gene transfer techniques/ethics OR gene therapy/ethics)

Database: ProQuest (Private Database: Cambridge Information Group)

Search Strategy:
1st query box: (“gene therapy” or “gene transfer techniques”) [select Subject from the right drop-down menu]
2nd query box: AND (legislat* or privacy or confident* or policy or religion) [select Subject from the drop-down menu]
3rd query box: OR (bioethic* or ethic*) [retain Citation and abstract]


Search Strategy: (gene transfer techniques/ethics OR gene therapy/ethics)

Database: WorldCat (Public Database: OCLC Online Computer Library Center)

Search Strategy:
1st query box: “gene transfer techniques” [select Subject from the left drop-down menu]
2nd query box: ethic* [select Keyword from the left drop-down menu]
**Human Gene Transfer Research** was originally entitled **Human Gene Therapy** authored in 1994 by Mary Carrington Coutts, a Reference Librarian at the Bioethics Research Library (BRL) and published in the *Kennedy Institute of Ethics Journal*, Vol. 4, No. 1, pp. 63-83, March, 1994. This publication has been updated periodically by BRL staff members Martina Darragh, Harriet Gray, and Kathleen Schroeder. Maddalena Tilli Shiffert, Assistant Professor, Department of Biology, Georgetown University, was a scientific advisor on this project in 2011, when this bibliography was last updated. Also in 2011, Katherine L. Record and Melissa K. Bourne of the Georgetown University Law Center, developed search strategies to access the legal literature; these are incorporated into each Scope Note on genetics, along with strategies for other disciplines designed by BRL staff.

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