Playing With Fire: The Ethics of Germ Line Genetic Therapy

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ABSTRACT

Due to several recent, highly publicized advances in genetic engineering, public interest in potential human genetic therapy applications is currently very high. Some forms of genetic therapy, such as somatic cell therapy, have generally been accepted. Germ line genetic therapy, has not been as openly endorsed. In fact, currently existing restrictions ban the use of any human germ line genetic therapy. Despite these restrictions the future role of germ line therapy is far from being resolved. Research is still being conducted using animal models and knowledge is being acquired from human somatic cell research. This paper reviews the major issues that should be ad-dressed in order to properly deal with the ethical dilemmas that may arise from the use of germ line genetic therapy.

The rapid development of new medical technology over the last century has had a profound effect on the practice of health care. Perceptions of what constitutes life, death and self-identity are constantly being reevaluated and redefined medically. The accelerated rate at which new treatments and therapies are being discovered has led to the emergence of several new ethical dilemmas. One recent example of public concern over the ethical implications of medical research was raised with the well publicized cloning of the sheep, "Dolly". The uneasiness with which the majority of the public viewed this development suggests need for discussion and debate, on the acceptability of all forms of genetic related medical research.

Another area of genetic research that has garnered much public and scientific attention is that of genetic therapy. Much of the interest in this area stems from the growing realization of the importance of genes in influencing the course of many illnesses. Although the potential of permanently curing many currently untreatable diseases makes genetic therapy very attractive, strong concerns have been raised over the biological, social, and evolutionary implications of altering a person's inherent genetic make-up.

WHAT IS GERM LINE GENETIC THERAPY?

One main problem in trying to deal with the issue of germ line genetic therapy stems from the highly speculative nature of what will and will not be possible in the future. The premise behind gene therapy is that many human diseases are carried by abnormal alleles. The most effective way to correct these genetic deficiencies is to use techniques that replace, correct, or supplement the malfunctioning gene (1). Somatic cell therapy aims at correcting genetic defects in the patient's non-germ line or non-reproductive cells (2). Any changes made are thus limited to the individual treated. Germ line genetic therapy aims at correcting or preventing genetic deficiencies through the transfer of properly functioning genes into reproductive cells (3). In germ line genetic therapy any changes made carry the consequence of manifesting themselves in the following generations.

Currently, somatic cell genetic therapy is generally accepted as a form of treatment, while human germ line genetic therapy is banned (4). Since both therapies involve the use of genetic manipulation, future research and development in somatic cell therapy will hold relevance to any potential long term germ line genetic therapy. While human germ line therapy may still be considered unacceptable, research nevertheless continues using animal models. The current practical application of germ line genetic therapy in animals involves genetic modification of early stage embryos. In this process, the genome of early stage embryos is altered by inserting genes, repairing defective genes, or deleting genes. The early stage embryos are fertilized in vitro, genetically altered and then inserted into the uterus (5). Presently, most experimental work involves DNA transfer into one of the pro-nuclei of the zygote, the delivery of DNA into a four or eight cell embryo by a vector, or the use of embryonic stem cells (3).

Currently, there is growing literature that indicates that the transfer of genes into the mouse germ line can result in the correction of specific genetic defects. Some successes in mice include the restoration of growth hormone production (3), prevention of insulin dependent

diabetes (3), and restoration of reproductive capacity (3). Research has even been able to link gene addition to the possible treatment of cancer (6).

It should be apparent that as cures for various human related diseases are discovered in animals and somatic cell genetic therapy becomes more efficient, increasing pressure will mount to re-evaluate the restrictions currently placed on germ line genetic therapy. Regardless of whether the arguments for germ line therapy are persuasive enough to merit further investigation, research will continue indirectly in the form of these animal and somatic cell models.

Ultimately, the decision on whether germ line genetic therapy will ever become an acceptable form of treatment rests on the public's interpretation of the arguments for and against its use.

MAJOR ARGUMENTS FOR GERM LINE GENETIC THERAPY

The tremendous potential of germ line therapy in the permanent correction of serious illness and disease ensures that it will never be completely dismissed as a future form of treatment. Recent findings have shown that certain forms of cancer (retinoblastoma, acute myelogenic leukemia), muscular dystrophy (Duchenne type), arthritis (juvenile), ADA deficiency, Tay-Sachs disease, sickle cell anaemia, cystic fibrosis, hemophilia, emphysema, and Lesch-Nyhan Syndrome all have genetic components (7, 8). All these painful, chronic, potentially fatal ailments have a simple pattern of inheritance involving recessive mutations at a single gene that leads to the formation of a non-functional allele (7). This property makes them ideal candidates for correction via germ line genetic therapy. Given medicine's current limited ability to cure these ailments, germ line genetic therapy provides an attractive future potential solution. Germ line genetic therapy may be the only effective way of treating some genetic diseases. The concept of medical beneficence dictates that the physician is morally obligated to provide the best available treatment for the patient, which in many cases may be germ line genetic therapy. In turn, providing the best treatment for the patient can also be broadly extended to include the health of the patient's child. A good example of such situation would be treatment for Huntington's Chorea. Huntington's Chorea is a dominant, autosomal disorder that has a 50% chance of being passed on to each offspring by a parent with the gene (9). Severely debilitating and ultimately fatal, Huntington's Chorea is almost completely untreatable. When faced with the option of death or possible alleviation of an illness, the physician has a duty to consider the option of therapy. Germ line genetic therapy, theoretically, is more effective and cost efficient than repeated use of somatic cell therapy in correcting a disorder. In essence, it is more practical, in terms of suffering, discomfort, risk, and technical requirements to correct such disorders at the beginning of life via germ line then to try correcting them later (10). The prevailing ethic of science and medicine is that knowledge is of intrinsic value and that its pursuit should not be impeded except under extraordinary circumstances (11). An argument can be made that knowledge is not inherently dangerous, but that it is how the knowledge is interpreted or used by society that makes it dangerous. There is an equal possibility that knowledge obtained can be used safely or dangerously. In summary, the motivation to possibly pursue germ line genetic therapy research is strong when the major advantages and current research developments are considered. In the future, as techniques are improved and more is discovered about the genetic basis for disease, the temptation to consider human germ line genetic therapy will grow. Ultimately efforts to try to settle this issue on a strictly permissible/non-permissible level may be futile. Instead, concentra-tion should perhaps be focused on ensuring that the major concerns with regard to germ line genetic therapy are not overlooked, but are being constantly evaluated.

MAJOR ARGUMENTS AGAINST GERM LINE GENETIC THERAPY

The following four major arguments against germ line genetic therapy provide a good counterpoint from which to judge the major advantages. The greatest public concern over germ line therapy stems from the potential misuse of this therapy for genetic enhancement and eugenic purposes. While germ line genetic therapy may offer a vast new potential to treat severely debilitating conditions, the acquired knowledge may also lead to the potential to alter traits that are not related to serious medical conditions. The traits that would be the most popular to alter, such as intelligence, are polygenic and would be the hardest to modify (12). This does not change, however, the possibility that someday altering these 'desirable' traits may be possible. The immediate problem with this possibility is that what constitutes 'desirable' reflects the dominating stereotypes in society, which may be extremely detrimental (e.g. waif like thinness in women). Germ line therapy may also be more of a quick fix then a true answer. The solution to being overweight should not be solely germ line therapy, but rather, a change in how society views and treats obesity. Pure genetic determinism belies the richness in which social and environmental factors also indelibly shape perception.

The suggested solution to the problem of what should and should not be deemed acceptable

has been to designate genetic interventions as either therapeutic or enhancement (13). The problem with this distinction is that a large grey area exists in between. Height is an example. Increasing someone's height could be justified medically as alleviating severe psychological stress suffered by an individual with short stature but it is unclear what stress constitutes a medical rather than social concern.

The safest way to monitor potential germ line therapy, therefore, is not to try and designate therapy into categories, but instead to judge the acceptability of the suggested therapy case by case. Treatment should be limited only to clear medical situations where the condition is fatal or leads to a chronic, painful existence. This strict criterion would limit potential research. Given the present large societal concerns, it may be the safest procedure to follow at present.

The possibility of germ line therapy being the only potential way of correcting an illness or disease must not cloud the potential damage that may arise medically from altering genes. At present, dangers such as disruption of normal gene function or induction of cancer makes gene therapy a risky procedure(14). The amazing potential of germ line therapy should not exclude future treatments from satisfying strict safety standards.

Care must also be taken not to infringe upon patient autonomy. If germ line therapy becomes available and is widely used, increased pressure will be placed on those in position to receive treatment. Societal pressure may exist to conform to traits deemed as "normal". Governmental pressure may exist to undergo therapy to reduce future cost. Medical pressure may exist to submit to the treatment deemed most beneficial. Legal pressure may even exist to ensure the welfare of the child. If children have sued for the right not to be born, is it implausible to envision the possibility of children suing for the right not to be born with defects (15)? Again, limiting germ line genetic research to those afflictions which are life threatening or which lead to a chronic painful existence may help minimize these problems.

While germ line therapy may eventually become more economical than repeated somatic cell therapy, initial costs per patient, as well as future research costs will be expensive (16). Some form of cost/benefit analysis must be done before large amounts of money are allocated to future research.

While a strong case can be made for scientific freedom, past history suggests that concern over uncontrolled experimentation is not unwarranted. Certainly the improvements that science has made to health and well-being have been impressive. At the same time, humankind's utilization of scientific knowledge has not always been used wisely. Ideally, the knowledge acquired by germ line genetic therapy research would be utilized in an ethically responsible manner. Realistically, however, the possibility that someone may use such therapy for more questionable purposes is a potential and relevant danger. Society's inability to predict accurately future consequences indicates clearly that caution is merited.

Imposing strict guidelines at this stage of germ line genetic research is not necessarily a harmful idea. Given the uncertainty of the safety of germ line genetic therapy, limitations should prevent possible premature misuse. Also, limiting research to fatal/severe conditions prevents experimentation in the more ethically problematic areas of germ line therapy.

In conclusion, the arguments in favour of germ line genetic therapy present a powerful incentive to continue research. Regardless of any current ban, research will continue in the closely associated areas of somatic cell therapy and germ line animal models. While public sentiment may view genetic therapy with unease at the moment, this opinion may change as gene manipulation techniques become safer and more refined. Germ line therapy will most likely then continue to resurface as a medical option.

Therefore, to focus discussion solely on the overall acceptability or unacceptability of germ line genetic therapy may show a lack of foresight. Future ethical debate on germ line genetic therapy should focus on how to ensure that proper rules and guidelines are in place to monitor long term research. Given the wide range of conditions to which germ line genetic therapy may be applied, the safest alternative is to establish guidelines that examine the ethical justification for each condition separately. The five major arguments against germ line therapy act as a counterpoint against which to judge the merit of each of the major arguments for it's use. For example, when judging the merit of a future germ line therapy on it's ability to cure a medical condition, the therapeutic enhancement repercussions must be considered.

Given the large number of ethical problems to which germ line therapy may lead, only afflictions which are life threatening or which lead to a chronic painful existence appear to merit justification for further research. While this may seem like a temporary solution, this

may be the safest procedure to follow given the present ethical concerns. The establishment of criteria by which to judge the value of germ line genetic therapy will ensure that any further research will be done in a responsible and ethical manner. The tremendous potential of germ line genetic therapy combined with the possibility for its misuse presents a challenging test for humanity.

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