

Human Gene Therapy: Must We Know Where to Stop Before We Start?

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ABSTRACT

Human genetic modification has begun without a clear consensus on where the moral boundary lines should be placed to insure that the technology of human genetic engineering is not abused. Two principal recommendations have been made for setting the boundaries. The first is between somatic cell *versus* germ-line correction; the second is between the amelioration of disease and the enhancement of traits. Each proposal involves a distinction and a rule. There is a dilemma in that the first case involves a well-grounded distinction but a dubious rule, while the second offers a more favored rule, but a fuzzy distinction.

OVERVIEW SUMMARY

Since a human gene transfer clinical protocol is now underway, it is important for society to determine where the boundary lines should be drawn in the human uses of genetic engineering. Krimsky has long been active in considering the socially responsible uses of genetic technologies. Here he points out the areas that still remain unresolved in the moral debate on human gene therapy.

RECENT DEVELOPMENTS IN HUMAN GENETICS are paving the way for what some people believe is a revolution in the treatment of inherited diseases through the direct modification of genes. Public discussions about human gene therapy have centered mainly around protecting the rights of experimental subjects and preventing the eugenic uses of genetic technology. Individual cases involving life-threatening diseases are setting the context for the ethical discussions. Those individuals closest to these cases, particularly primary care physicians, are understandably frustrated by the lack of suitable treatments for many inherited disorders. The possibility of a new form of intervention provides hope that modern medicine will not be a helpless bystander in the face of a disease process that is locked into the genetic code. Abstract ethical discussions often seem irrelevant under such circumstances.

The modification of human genes, whether we call it human gene therapy or human genetic engineering offers more than a hope for the treatment of dread disease. The exclusive attention to specific cases involving human suffering can obscure the fact that genetic modification may also have applications for altering certain traits either in the whole organism or in the fertilized egg. It is difficult to think about the potentially positive applications of human genetic engineering without also thinking about its controversial uses.

There are those who believe that we have all the safeguards in place that we need for preventing the misuses of HGE. They might have a convincing case if there were a broad consensus on the scope and limits of its use. But it is precisely the consensus that we are lacking.

What are we to do? Should we proceed on a case-by-case basis blazing a trail of ethical common law? Or should we seek generalized ethical principles that address many types of potential human genetic modifications, even those that are far off into the future? These two approaches—moral incrementalism *versus* moral rulemaking—raise unique problems. In the former case the central question is: Should we begin and if so under what conditions? In the latter case the moral problem of beginnings is eclipsed by the question: Where do we stop?

Some have argued that the conditions of beginning and stopping are interrelated. These individuals have asked that large classes of human gene experiments be proscribed on the grounds that any form of human genetic engineering will eventually and inexorably lead to the most objectionable cases. This thesis accepts a form of technological determinism that places humans at the mercy of their inventions.

A somewhat weaker form of the argument rejects the necessity of the outcome but ascribes to it a nontrivial probability. Both forms of technological determinism (fatalistic or probabilistic) either fail to distinguish among the many possible objectives and methods of human genetic modification or view them as mutually reinforcing.

With an experiment in human genetic modification already underway, the call for a general prohibition seems irrelevant. The force of the argument that society should forego treating those with serious illnesses on the grounds that once we start we cannot stop has not been very persuasive, unless of course we never discuss where to stop. The pragmatic approach to this problem evaluates each case on its own merits balancing risks and benefits and taking into consideration the current moral climate.

An alternative is to seek guiding principles and moral boundaries at the outset. The search for ethical principles is a search for order amidst the cacophony of human moral experience. We seek general moral rules to protect us against the abuse of power and to promote equity and fairness in the treatment of individuals.

Human genetic modification has begun without a clear consensus on where the moral boundary line should be placed. Two principal recommendations have been made for setting that boundary. Each proposal involves a distinction and a rule.

The first proposal distinguishes somatic from germ-line gene alteration and adopts as a moral rule that no genetic engineering should be permitted on human germ cells. The distinction between heritable change and change that is limited exclusively to the individual is well within the purview of public understanding.

It is reasonably clear when a genetic modification is designed to alter the organism itself. Inevitably, there are grey areas. Chemotherapy or radiation therapy for the treatment of cancer may inadvertently cause a mutation in the germ cells. But that is not what is intended. Moreover, efforts can be taken to minimize the likelihood of such effects.

The distinction between altering germ cells and somatic cells rests on a reasonably clear and solid scientific foundation because (i) the cells are distinct biological entities and (ii) it is possible to make measurements that distinguish between the genetic alteration of these cells. A moral rule based upon this distinction does have some advantages in setting public policy.

The second proposal for setting an ethical boundary for human gene modification posits a distinction between the amelioration of a disease and the enhancement of traits. The moral rule based upon this distinction finds it acceptable to make genetic modifications on the person, fetus, or fertilized egg if its purpose is for the treatment or cure of a disease. It would be unacceptable to alter a trait that is not associated with a disease. Some obvious examples of the latter are height, skin tone, or intelligence. Setting the moral boundary of human genetic modification between cure and enhancement seems to be gaining ground within the scientific community.

One of the difficulties with the distinction, and therefore the moral boundary, is that it has no firm scientific basis. The concept of a disease or a clinical abnormality is continuously being redefined. For example, is

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chemical hypersensitivity a disease? Any trait that has a higher association with the onset of a disease may itself be typed as a proto-disease such as fibrocystic breasts.

The most exhaustive public opinion poll taken on such matters was conducted by Louis Harris and Associates in 1986 under the auspices of the Office of Technology Assessment. A national probability sample was taken of 1,273 American adults over a 19-day period. A majority of the respondents (53%) disapproved of the use of human gene manipulation for enhancement rather than therapeutic purposes. The poll also asked respondents whether they would approve of eliminating from the germ line the genes of fatal diseases. A majority (62%) voted in the affirmative.

The poll indicates that the public is still far away from a consensus on setting an ethical limit for the genetic alteration of humans. Nevertheless, from the Harris Poll results the critical factor for policy is the distinction between using human genetic engineering to treat an individual or to eradicate the genes of a fatal disease from the gene pool and using the technology for improving qualities of clinically normal individuals or selecting traits for future generations.

This brings us to our dilemma. Moral rules based upon nebulous distinctions are most vulnerable to slippery-slope outcomes. The somatic-germ-line boundary, while relatively intact and most easily incorporable into a public policy, is less favored by the public and biomedical scientists who are at the frontiers of human gene therapy. The distinction between enhancement and medical therapy is a socially constructed category influenced by many factors that contribute to the current taxonomy of clinical disorders. Moreover, once the right of somatic cell therapy becomes established, it is doubtful that its use can be restricted to "medical therapy." Consider all the surgical techniques that are used for cosmetic purposes. It is unclear what moral rule or legal process could prevent a program of genetic cosmetology once canonical procedures of somatic cell therapy are developed. It is equally unclear how society would prevent "enhancement" interventions of the fertilized egg once standardized "therapeutic" interventions are permitted.

This leads me to the following conclusions. No satisfactory moral rule has been advanced that sets boundaries on somatic cell human genetic engineering. Therefore, we are left with two choices. We may either restrict the use of HGT to specific types of diseases (*e.g.*, life-threatening or severely debilitating) until such time as there is a strong public consensus for other applications. Or we may give up the idea of finding a moral rule and in its place substitute a decision process that operates on shifting pragmatic criteria. My own preference is with the former.

The case of germ-line intervention is quite different. First, we are not dealing with a moral agent to whom we have a responsibility. There are only spermatozoa or fertilized eggs. Furthermore, there is no social consensus on whether our responsibility for preventing disease extends to the elimination of so-called "disease genes" from the human gene pool. Second, the implications of genetically modifying germ cells are far from understood. Many agree that there are profound consequences associated with initiating such experiments, but few can even begin to anticipate the scope of these consequences. Therefore, to begin such a process without understanding its broader implications, without a reasonable idea about whether it is possible to control the process once it is begun, and without a strong consensus from an informed electorate would be socially irresponsible.

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