

CRG HUMAN GERMLINE MANIPULATION Position Paper

THE POSITION OF THE COUNCIL FOR RESPONSIBLE GENETICS

The Council for Responsible Genetics (CRG) strongly opposes the use of germline gene modification in humans. This position is based on scientific, ethical, and social concerns.

Proponents of germline manipulation assume that once a gene implicated in a particular condition is identified, it might be appropriate and relatively easy to replace, change, supplement or otherwise modify that gene. However, biological characteristics or traits usually depend on interactions among many genes, and more importantly, the activity of genes is affected by various processes that occur both inside the organism and in its surroundings. This means that scientists cannot predict the full effect that any gene modification will have on the traits of people or other organisms.

In purely biological terms, the relationship between genes and traits is not well enough understood to guarantee that, by eliminating or changing genes associated with traits one might want to avoid, one may not simultaneously alter or eliminate traits one would like to preserve. Even genes that are associated with diseases and may cause problems in one context, can be beneficial in others.

There is no universally accepted ideal of biological perfection. To make intentional changes in the genes that people will pass on to their descendants would require that we, as a society, agree on how to classify “good” and “bad” genes. We do not have the necessary criteria, nor are there mechanisms for establishing such measures. Any formulation

of such criteria would inevitably reflect particular current social biases. The definition of the standards and the technological means for implementing them would largely be determined by economically and socially privileged groups.

WHAT IS “GERMLINE MANIPULATION”?

The undifferentiated cells of an early embryo develop into either “germ” cells or “somatic” cells. The germ cells become the eggs or sperm of a developing organism and transmit its heritable characteristics. All other cells in the body are called somatic cells. While both types of cells contain genes, only the genes in germ cells are passed on to future generations.

Techniques are now available to change chromosomes of animal cells by inserting new segments of DNA into them. If this insertion is performed on specialized or differentiated body tissues, such as liver, muscle, or blood cells, it is referred to as somatic cell gene modification, and the changes do not go beyond the individual whose DNA is modified. If such changes are performed on sperm or eggs before fertilization, or on the undifferentiated cells of an early embryo, it is called germ cell or germline gene modification, and the changes are not limited to the individual organism. For when DNA is incorporated into an embryo's germ cells, or undifferentiated cells that give rise to germ cells, the altered gene or genes will be passed on to future generations and may become a permanent part of the gene pool.

Deliberate gene alterations in humans are often referred to as “gene therapy.” The Council for Responsible Genetics (CRG)

prefers to use the terms “gene modification” or “gene manipulation” because the word “therapy” promises health benefits, and it is not yet clear that gene manipulations are beneficial nor that the conditions for which proponents urge such interventions are always “illnesses.”

PROPONENTS' ARGUMENTS FOR ATTEMPTING GERMLINE MANIPULATION IN HUMANS:

If one or both sex partners carry a version of a gene that could predispose their offspring to inherit a condition they want to avoid, genetic manipulation may seem like a way to prevent the undesired outcome. The earlier during embryonic development the targeted gene or genes are altered or replaced, the less likely is the resulting individual to be affected by the unwanted gene. While the immediate goal of such a modification might be to alter the genetic constitution of a single individual, modifications made at early embryonic stages would also affect the offspring of this future person.

One use proposed for germline modification has been to “cleanse” the gene pool of “deleterious” genes. For example, Daniel E. Koshland, Jr., a molecular biologist and the former editor-in-chief of *Science*, has written, “keeping diabetics alive with insulin, which increases the propagation of an inherited disease, seems justified only if one ultimately is willing to do genetic engineering to remove diabetes from the germline and thus save the anguish and cost to millions of diabetics” (2). Another goal of germline manipulation may be to avoid the need for repeated somatic gene modifications.

Some people also suggest that germline modification would enable couples to “enhance” certain characteristics of their offspring. In the article referred to above, Koshland raises the possibility that germline alterations could meet future “needs” to design individuals “better at computers, better as musicians, better physically.”

WHAT IS THE TECHNICAL FEASIBILITY OF MODIFYING THE HUMAN GERMLINE?

Both somatic and germline modification are widely performed on laboratory animals for research purposes. Beginning in 1990, somatic gene modifications have been performed on humans, and the FDA is reviewing additional experimental protocols in increasing numbers (3).

No published reports have yet appeared on germline modification in humans, but articles proposing such procedures are appearing with increasing frequency (4, 5). In mice and other animals that have been employed as models for human biology, germline modification has actually proved technically easier than somatic modification. The cells of early embryos incorporate foreign DNA and synthesize the corresponding functional proteins more readily than do most differentiated somatic cells. In the first widely-reported successful experiment using the germline technique, an extra gene that promoted the synthesis of growth hormone was introduced into fertilized mouse eggs and the unusually high levels of the hormone made the mice grow to twice their normal size. Germline techniques are also being used to modify farm animals in attempts to increase yields of meat or enhance its nutritional quality, to cause them to produce pharmaceuticals in their milk, and to make their organs more suitable for human transplantation.

Given what has been accomplished in animals and the availability of *in vitro* fertilization, there appear to be no technical obstacles to initiating germline modification experiments in humans.

WHAT ARE THE TECHNICAL PITFALLS?

Current methods for germline gene modification of mammals are inefficient, requiring the microinjection of DNA into numerous eggs before one egg is successfully modified. Furthermore, introduction of a foreign gene into an inappropriate location in an embryo's chromosomes can have unexpected consequences. For example, the offspring of a mouse that received an extra

copy of a normally present gene, while appearing unaffected at birth, developed cancer at 40 times the rate of the unmodified strain of mice (6). In another experiment, disruption of a normal gene by insertion of foreign DNA into mouse embryos resulted in mice that lacked eyes, the semicircular canals of their inner ears, and in anomalies of the tissue that mediates the sense of smell (7). This second case highlights the fact that the techniques used for making germline modifications can produce developmental disruptions in the manipulated embryo itself.

Techniques to introduce foreign DNA into eggs, however, are constantly being developed and will eventually be portrayed as efficient and reliable enough for human applications. For example, it may soon be possible to place a gene into a specified location on a chromosome while simultaneously removing the unwanted gene. This will increase the accuracy of the procedure, but it will not eliminate the possibility of creating genetic changes or combinations that will be harmful to the modified embryo and its descendants. Such inadvertent damage could be caused by technical error, but more importantly, it could also arise from biologists' inability to predict how genes or their products interact with one another and with the organism's environment to give rise to biological traits. It would have been impossible to predict, a priori, for example, that someone who has even one copy of the gene associated with the blood protein known as hemoglobin-S would be protected against malaria, whereas a person who has two copies of this gene would develop sickle cell disease.

This unpredictability applies with equal force to germline genetic modifications intended to correct presumed disorders and to those introduced to enhance desired characteristics.

SOCIAL AND ETHICAL IMPLICATIONS OF GERMLINE MANIPULATION

The attempt to improve the human species biologically is known as eugenics, and formed the basis of a popular movement in Europe and North America during the first half of the twentieth century. In the 1920's and 1930's, eugenics was advocated by prominent

scientists across the entire political spectrum, who represented it as the logical outcome of the most advanced biological thinking of the period. In the United States, eugenic thinking resulted in state laws permitting forced sterilization of individuals regarded as inferior because they were variously disabled or "feeble minded or paupers." In Europe, the Nazis took up these ideas, and their extermination programs led to widespread revulsion against the concepts of eugenics.

Today, public discussion in favor of influencing the genetic constitution of future generations has gained new respectability with the increased possibility for intervention presented by in vitro fertilization and embryo implantation technologies. Although it is once again espoused by individuals with a variety of political perspectives modern eugenic programs are now defended as driven by individual need and "choice." But the doctrine of social advancement through biological perfectibility underlying the new eugenics is even more potent than the older version: its supporting data seem more scientifically sophisticated, and the alignment between the State, through its support of the market, and the individual exercising so-called free choice, is unprecedented. The result could be similar to the organized eugenics programs so avidly embraced prior to the Second World War.

It is important to recognize that the dream of eliminating "harmful" gene variants (such as those associated with cystic fibrosis or Duchenne muscular dystrophy) from the entire human population could be realized only over time scales of thousands of years, and then only with massive coercive programs of germline manipulation monitored by special genetic police. Such programs would be neither feasible nor morally acceptable. In practice, then, any presumed beneficial effects of germ line modification would affect only individual families and are not likely to yield a public health benefit unless accompanied by unacceptable compulsion. This is in contrast to harmful genetic effects, which are likely to be widely disseminated given patterns of human reproduction and migration.

Even without access to germline modification,

people could avoid having a child who manifests a trait they do not want to pass on. Prenatal diagnosis and abortion are available options; so are obtaining eggs, sperm or embryos from people who do not carry the trait in question; and so indeed is adoption. As disability rights advocates have pointed out, most disabilities are acquired and not inherited, and we have in no way exhausted the social measures that could be implemented to enable people with disabilities to live ordinary lives. Given that there are alternatives for avoiding the inheritance of “unwanted genes”, the main selling point of germline modification over the long term would appear to be the prospect of “enhancement” of desired traits—designer children.

While, as noted above, unsuccessful attempts at germline modification can profoundly perturb ordinary biological function and introduce new, harmful genetic variants into the gene pool, even “successful” attempts will for the first time bring production of human beings into the realm of designed items. Like all such items, these human specimens will be subject to the fashions of the times.

These considerations make the social and ethical problems raised by germline gene modification very different from those raised by genetic manipulations that target specific non-reproductive tissues and organs of individual patients, as with somatic cell gene modification.

Health conditions targeted in clinical trials of somatic gene modification include cystic fibrosis, lung cancer, malignant melanoma, breast cancer, brain cancer, and muscular dystrophy. Such trials are being conducted at many major medical research institutions. Violations of regulations and conflicts of interests in these trials have been pervasive (8,9), and have led to deaths of research subjects. Like the testing of new pharmaceuticals, somatic manipulations affect only the individual who undergoes them. However, these treatments are not strictly analogous to other therapies that incur individual risks. Radiation, chemotherapy or drug treatments can be stopped if they prove harmful to patients, while some forms of somatic gene

modification cannot. Subjects thus forfeit their right to withdraw from a research study because the intervention cannot be stopped, whether it proves harmful or not. While it appears that somatic gene modification techniques will be used increasingly in the future, the CRG urges that they be used with great caution and only for life-threatening conditions.

While a policy of proceeding with caution may be suitable for somatic gene modifications, the goal of which is to cure or alleviate health problems of existing individuals who are able to consent to the intervention, such a policy is not appropriate for germline modification. Many of the ethical arguments against germline modification are similar to those that pertain to somatic cell modification. In addition the following arguments lead us to unequivocally oppose germline modification:

(1) Germline modification is not needed in order to save the lives, or alleviate the suffering, of existing people. Its target population are “prospective people” who have not even been conceived.

(2) The cultural impact of treating humans as biologically perfectible artifacts would be entirely negative. People who fall short of some technically achievable ideal would be seen as “damaged goods”, while the standards for what is genetically desirable will be those of the society's economically and politically dominant groups. This will only increase prejudices and discrimination in a society where too many such prejudices already exist.

(3) There is no way to be accountable to those in future generations who are harmed or stigmatized by wrongful or unsuccessful germline modifications of their ancestors.

The Council for Responsible Genetics therefore calls for a permanent ban on germline gene modification.

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ABOUT CRG The Council for Responsible Genetics fosters public debate on the social, ethical, and ecological implications of genetic technology. Founded in 1983, CRG is a non-profit/ non-governmental organization based in Cambridge, Massachusetts (USA). In addition to producing educational materials on various issues raised by biotechnology, CRG also publishes a bimonthly magazine, *GeneWatch*, the only national magazine that continually monitors the ethical, social, and ecological impacts of biotechnology as they apply to both humans and the environment. CRG has **position papers and question-answer sheets** on a variety of topics, including genetic discrimination, human cloning, predictive testing, genetically engineered food, the "gay gene," life patents, and germline engineering. Other resources include **The Genetic Bill of Rights**, a **Genetic Discrimination Legislation database**, and **selected books** on biotechnology and genetics. CRG also runs a **competitive internship program** for exceptional college and graduate students.

Council for Responsible Genetics 5 Upland Road, Suite 3 Cambridge, MA 02140 USA
Tel 617.868.0870 Fax 617.491.5344 Web www.gene-watch.org Email crg@gene-watch.org