

Human Germline Genetic Modification:
Issues and Options for Policymakers

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Executive Summary

Germline genetic modification is possible in animals, but not yet in humans. If certain technical obstacles were overcome, human germline genetic modification (HGGM) could allow human beings to create permanent heritable genetic changes in their descendants by changing the genetic makeup of human eggs or sperm, or human embryos at the earliest stages.

For many decades, the technical barriers to HGGM have seemed insurmountable. Today, however, advances in human reproductive technologies, stem cell science, and animal genetic modification have brought the possibility of HGGM much nearer than it has been before. The Genetics and Public Policy Center believes it is time for renewed consideration of this controversial subject. This report, *Human Germline Genetic Modification: Issues and Options for Policymakers*, analyzes the scientific, legal, regulatory, ethical, moral, and societal issues raised by genetic modification of the human germline, provides data about the American public's views about HGGM, and explores possible policy approaches in this area.

Science

Germline genetic modification is possible in laboratory animals, and some techniques could be translated for use in humans although none has been tried. Scientists are able to replace a faulty gene with a “normal” copy in mouse embryonic stem cells, then introduce those stem cells into an early mouse embryo where they can give rise to genetically modified sperm or eggs. The next generation of mice that results from the modified sperm or eggs will contain the “normal” copy of the gene. It is now possible to replace a gene in human embryonic stem cells, overcoming a huge obstacle to HGGM. In addition, scientists have been able to derive genetically modified sperm directly from mouse stem cells. Together, these developments suggest that HGGM may not be as far off as we thought even five years ago.

While advances in these techniques have been driven by more general research goals widely viewed as valuable, and not the pursuit of HGGM specifically, these discoveries will catapult us over what were understood to be the principal technical obstacles to HGGM.

Safety

Serious consideration of safety is and has been of utmost importance in any deliberation about HGGM. In animal research, many germline genetic modification approaches can introduce unwanted mutations that can lead to severe developmental outcomes, even death.

Most safety risks of HGGM would be to the resulting child. The proposed techniques for HGGM involve extensive manipulation of stem cells, eggs, sperm, or embryos in the laboratory prior to introduction into a woman's uterus. Such manipulation alone could alter the growth and development of the fetus in ways that are not yet well understood, resulting in health problems that in many cases could be lethal.

There is a clear need for more animal research and better data, although it is less clear how much and what it would need to show. Many questions exist about how to measure

the risks and benefits of HGGM. And although it is a basic tenet of medical practice that patients receiving medical treatment must provide informed consent, opinions are divided as to whether and when the consent of the true “patients” — the future child and future generations — could and should be assumed.

Scenarios

HGGM may become more technically feasible in the future. The question remains whether and for what purpose HGGM would be attempted. Many first applications could be imagined for HGGM and the technical feasibility and perceived demand are different for each. An example of a technically more feasible use of HGGM with low demand would be its use to prevent recessive genetic disease such as cystic fibrosis. This is more technically feasible because the single-gene mutations have been identified. However, since these diseases can be avoided by other already existing techniques, such as PGD, the perceived demand for using HGGM would be low. An example of a technically less feasible use of HGGM with unclear demand would be its use to enhance traits such as intelligence or strength. This is less technically feasible because the genetics behind these traits are largely unknown. The perceived demand is unclear because of the many ethical questions surrounding the use of HGGM for enhancement. In contrast, there may be fewer ethical objections to — and more demand for — using HGGM to enhance human health, to provide a “vaccine” against HIV for example. Feasibility would depend on both an understanding of the genetic disease at issue and the overall development of safe and efficient methods for HGGM. A table analyzing eight possible scenarios for HGGM is presented in the report.

Public Opinion

Until now, the most sustained and visible deliberations about HGGM have been within elite governmental commissions or academic institutions. Frequently, these groups have called for increased public input in the discussion, but there has been little public engagement in the issue outside of the extreme portrayals of HGGM by Hollywood or the popular press. As a result, little has been known about the views of the general public.

In order to learn more about what the American public knows, thinks, and feels about HGGM and other reproductive genetic technologies, the Genetics and Public Policy Center recently conducted a broad survey of 4,834 Americans. Our data show significant interest in HGGM as a potential means for avoiding serious genetic disease. However, concerns were expressed about how safe the technology would be, who would have access to it and who would not, and the impact of HGGM on society as a whole.

Ethics

The purposes for which HGGM might be attempted vary, from “fixing” a genetic mutation before an individual is born to enhancing children with socially desirable traits such as athletic skill or intelligence. Views differ as to which purposes are ethically acceptable and whether it is possible to meaningfully distinguish, for example, between a “therapeutic” use of HGGM on the one hand and an “enhancement” use on the other.

A vast array of ethical issues arises from HGGM. HGGM raises both the specter of humans “playing God” and questions about whether such interventions in nature would change the human gene pool, ultimately affecting the species as a whole. There are fears that HGGM will negatively affect human dignity and attitudes towards those living with disabilities, casting people as “problems” that could have been avoided and putting pressure on families to have genetically “perfect” children.

Some question whether HGGM would start society on a slippery slope to a modern version of eugenics, regardless of the purposes for which it would be used. And for those who categorically oppose manipulation or destruction of human embryos, HGGM would be unacceptable under any circumstances because it would involve one or both for the foreseeable future.

Oversight

In the United States, both the Food and Drug Administration (FDA) and the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) play a role in current federal oversight of HGGM. FDA has indicated that it would treat any proposals for HGGM the same way it treats proposals for somatic gene modification, and require an investigational new drug application (IND) to be filed before the technology may be attempted in humans. It is unclear what criteria FDA would use to evaluate such an application. At the present time, the RAC has indicated that it will not consider any proposals for HGGM.

Options

An array of policy approaches is available for future oversight of HGGM. Policymakers and the public may consider a direct ban of HGGM; increased oversight with an eye towards safety, ethical use, or both; or promotion of HGGM by providing additional resources for relevant research. International laws, United States law and regulation, and voluntary self-regulation by scientists are some of the approaches that are described, along with the advantages and disadvantages of each.

Although HGGM remains on the distant horizon, technologic advances are bringing HGGM from the imaginable to the possible. Thus it is time to consider the difficult questions about HGGM. An enriched and expanded discussion that includes both experts and the public offers an opportunity to share information and understanding about the underlying values and concerns that inform our individual and collective perspectives on HGGM. Such an approach ultimately will lead to thoughtful and robust public policies.

Introduction

Human Germline Genetic Modification (HGGM) refers to techniques that would attempt to create a permanent inheritable (i.e. passed from one generation to the next) genetic change in offspring and future descendants by altering the genetic makeup of the human germline, meaning eggs, sperm, the cells that give rise to eggs and sperm, or early human embryos. For many decades, the technical barriers to HGGM have seemed insurmountable. Thus, discussions of HGGM have focused on the correctness of the ends associated with HGGM rather than the feasibility of the means. Some have viewed HGGM as having the potential for species perfection, while others have condemned the concept as an attempt to usurp God by making “man his own self-creator.”¹

Two recent advances in stem cell research suggest that the technological barriers may soon be overcome. Scientists recently have created genetically modified mice by genetically modifying the cells that give rise to sperm, and using these resulting sperm for fertilization.^{2,3} In addition, scientists have genetically modified human embryonic stem cells.⁴ These techniques overcome what were long regarded as impenetrable technical barriers, bringing the possibility of HGGM much closer. Therefore, the time is right for a new public discussion about whether, when, and how HGGM research should proceed.

This report, *Human Germline Genetic Modification: Issues and Options for Policymakers*, is

intended to facilitate informed public discussion of HGGM. It addresses the scientific, legal, regulatory, ethical, moral, and societal issues raised by genetic modification of the human germline and lays out an array of possible policy approaches that could be adopted for HGGM research. It also includes a sample of recent public opinion research conducted by the Genetics and Public Policy Center on this topic. This report does not address issues related to chimeras (produced by mixing cells from different humans or mixing human and animal cells) or wholesale genome replacement, such as somatic cell nuclear transfer.⁵

In previous work, the Center has addressed other reproductive genetic technologies, including carrier testing, prenatal genetic testing, and preimplantation genetic diagnosis (PGD), which enables prospective parents to select embryos with certain genetic characteristics.⁶ In many cases, these technologies could be used to accomplish the same goals as HGGM. Some of the ethical, safety, and social issues are common to all the technologies. For example, reproductive genetic testing and HGGM raise similar concerns about the impact of these technologies on relationships between parents and children and on society’s views of and support for people with disabilities.

However, HGGM raises unique concerns because it seeks to alter the genetic makeup of future generations. Some worry about the significant health risks, many

unforeseeable, which would be imposed on generations to come, and about the fact that these individuals could not consent to the procedure that imposed this risk. Others worry that the intentional manipulation of the genome to produce changes that might not have arisen otherwise will have a negative effect on the overall gene pool of the human species.

In 2004, the Genetics and Public Policy Center convened a meeting, “Babies By Design: Policy Options For Human Germline Genetic Modification” to review the state of the science and explore an array of questions and concerns relating to HGGM. Conference invitees (listed at the end of this report) were selected to represent a range of disciplines and reflect a variety of perspectives, and their contributions were invaluable to the development of this report. We are grateful to the participants, many of whom have reviewed drafts of this report, for being so generous with their time and expertise. Please note that meeting participants do not necessarily agree with or endorse this report. The Genetics and Public Policy Center assumes full responsibility for the report and its contents.

Science

Genetics

Understanding the possible technical approaches to human germline genetic modification (HGGM) requires an understanding of some basic genetic concepts.

An individual's genetic makeup, known as his or her genome, is the complete set of genes that are spelled out in DNA. The human genome contains 20,000-25,000 genes.

Most of the human genome is contained in a structure within the cell called the nucleus, and is referred to as nuclear DNA (Figure 1). Nuclear DNA is packaged into 46 chromosomes, 23 of which came from the mother's egg, and 23 from the father's sperm. When egg and sperm join upon fertilization, the resulting cell, known as the zygote, contains the full complement of 46 chromosomes (Figure 2). The single cell zygote divides repeatedly, becoming first an embryo, then a fetus. Every time a cell divides, the entire genome – all 46 chromosomes – is copied so that the same information is contained in the resulting cells. Nearly all cells in the body – also known as somatic cells - contain 46 chromosomes. Eggs and sperm, which are called germline cells, contain only 23 chromosomes.

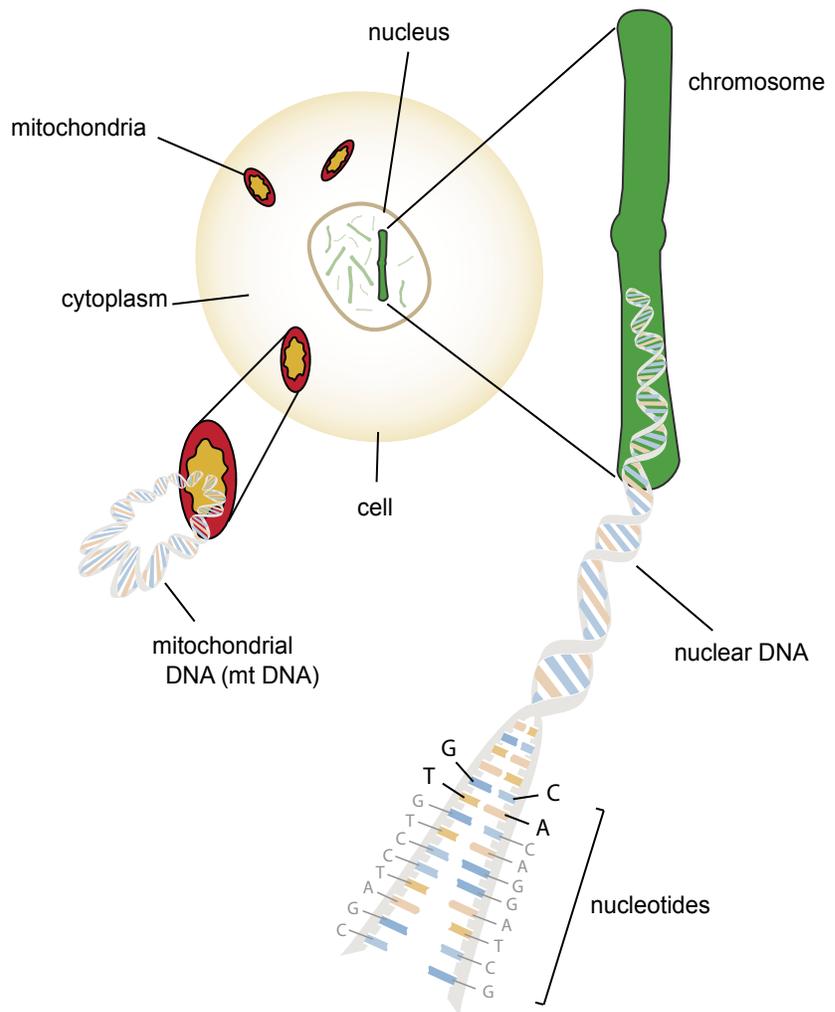
In addition to the nuclear DNA, a small portion of the human genome is found in structures within the cell called mitochondria. Mitochondrial DNA or mtDNA (Figure 1)

contains only a few genes. Unlike nuclear DNA, almost all of a person's mitochondria – and the mtDNA – comes from the mother's egg (Figure 2).

Genes and Disease

The genomes of any two people are 99.9 percent identical. The 0.1 percent difference in DNA

Figure 1: DNA and Cell Structure



Most of the DNA in a cell is packaged into chromosomes that are contained in the cell's nucleus. A small amount of DNA is contained in the mitochondria, which are found outside the nucleus in the cytoplasm. DNA consists of four chemical subunits called nucleotides – abbreviated A, T, C, G – which hold the strands together in the DNA double helix. Genes are specific segments of nucleotide sequences along the DNA double helix that contain instructions for making specific proteins.

sequence between individuals makes each person genetically unique. These differences in DNA sequence often are referred to as genetic variations. Most genetic variations carry no harmful effects. Some variations, however, can cause disease or increase one's risk of developing disease. A variation as small as one nucleotide in the DNA sequence can disrupt a gene severely; these deleterious alterations in DNA sequence are called genetic mutations. Genetic conditions such as Huntington disease, cystic fibrosis, or sickle cell disease are caused by mutations in single genes.

There are two copies of every gene (except those on the X and Y

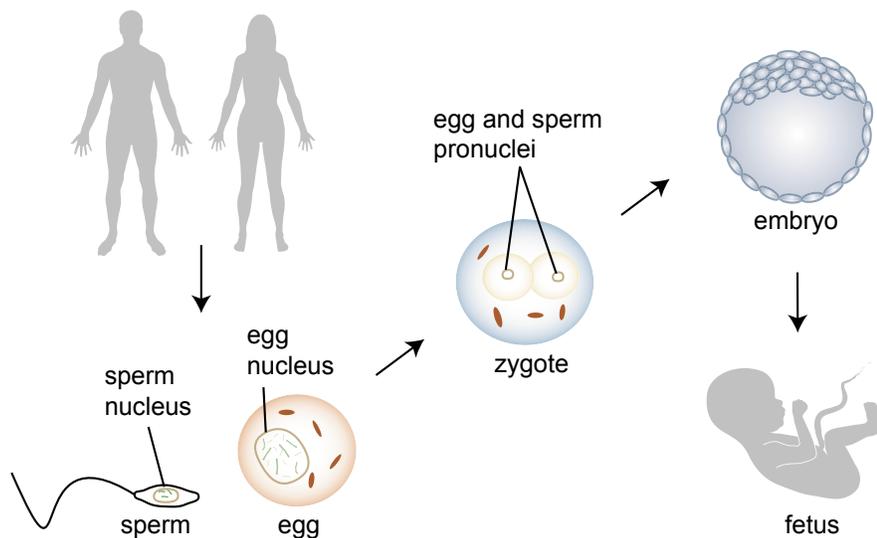
chromosomes) in each cell – one copy came from the mother's egg and the other copy from the father's sperm. For conditions known as recessive genetic disorders, such as cystic fibrosis or sickle cell disease, one develops the disease only if both copies of the gene contain a mutation. If one copy of a gene contains a mutation and the other copy does not, the person does not develop the disease; instead he or she is called a carrier. When two carriers — people who carry a mutation for the same recessive disorder — have children, each child has a 25 percent chance of receiving two copies of the mutation, one from each parent, and developing the disease. For conditions known as dominant genetic disorders, such

as Huntington disease, a mutation in only one copy of the gene is needed to cause the disease. Each child of a parent with Huntington disease has a 50 percent chance of inheriting the dominant mutation and developing the disease.

Some single gene alterations do not necessarily cause a disease but instead increase the risk of developing that disease. For example, women who carry alterations in the BRCA1 or BRCA2 genes have about an 80 percent risk of developing breast cancer by age 70 as well as an increased risk of developing ovarian cancer. Men who carry alterations in BRCA1 or BRCA2 likewise are at increased risk for breast, prostate, and other cancers. But some men or women who carry genetic alterations in BRCA1 or BRCA2 never develop cancer. Furthermore, the severity of a disease or the stage of life at which the disease may develop generally cannot be predicted based on the presence of a genetic alteration.

Not all genetic conditions result from mutations in single genes. Some genetic conditions result from chromosomal abnormalities, where a person carries too many or too few chromosomes, or chromosomes that are missing or carry extra segments of DNA. For example, an extra copy of chromosome 21 causes Down syndrome. Many chromosomal abnormalities result in pregnancy loss or stillbirth, whereas others cause birth defects, developmental delays, or mental retardation.

Figure 2: Human Reproduction



When a sperm containing 23 chromosomes from the father fertilizes an egg containing 23 chromosomes from the mother, a single cell containing 46 chromosomes, called a zygote, is formed. The zygote divides to give rise to an embryo containing two cells, then four, and so on, eventually developing into a fetus.

Lastly, some health conditions are caused not by mutations in a single gene but rather involve alterations in many genes and the interaction of those genes with the environment, which is not well understood. These conditions frequently are referred to as multifactorial diseases. Examples include heart disease, diabetes, asthma, and most cancers.

Genetics and Reproductive Technologies

New reproductive technologies have developed alongside an increased understanding of the roles genes play in disease. Preimplantation genetic diagnosis (PGD) combines genetic testing and in vitro fertilization (IVF). IVF involves collecting eggs from a woman, fertilizing the eggs with sperm in a petri dish, and transferring the resulting embryo(s) to a woman's uterus. PGD typically involves removing one or two cells from an embryo two to four days after fertilization, extracting DNA from these cells and testing the DNA for a specific genetic alteration or chromosome abnormality. Embryos free of the genetic disease being tested for or possessing desired genetic characteristics are selected for transfer into the woman's uterus.⁶

Germline Genetic Modification

If and when it occurs, human germline genetic modification would involve introducing a new genetic sequence into a person's germline cells that could be passed to future generations. The

techniques that might be used in humans draw from successful germline genetic modification studies in animals, human stem cell research, and human somatic gene therapy techniques where non-heritable genetic changes are made in an attempt to cure or treat disease.

In theory, there are several ways to modify a person's genome. An entire gene or part of a gene could be inserted somewhere into the genome. This inserted DNA sequence, sometimes called a transgene, could be a normal copy of a resident gene. Introducing a normal copy of that gene could compensate for the nonfunctioning or malfunctioning resident gene. Instead of introducing a whole gene, a transgene could be a segment of DNA that affects the function of a resident gene to turn it on or off. Alternatively, the transgene could introduce a whole new, and previously non-existent gene function into the genome. An example would be the gene for green fluorescent protein that has been introduced into a number of laboratory animals to make them glow.

All cells in an adult animal's body develop from the zygote, the fertilized egg. Because germline genetic modification seeks to modify all of the cells in the adult body, the genetic modification must be introduced into the eggs and sperm, the precursor cells that give rise to eggs and sperm, or very soon after fertilization in a zygote or very early embryo.

Cloning: Extreme genetic modification

Another technique that genetically modifies the germline is somatic cell nuclear transfer (SCNT). SCNT involves the transfer of the nucleus of an adult somatic cell into an egg from which the nucleus has been removed. The resulting zygote could be allowed to develop into an embryo that is genetically identical to the adult who donated the somatic nucleus. Although technically the resulting embryo is genetically modified in the sense that its genome has been changed, this wholesale genome replacement is considered to be cloning, which is the subject of the Center's report *Cloning: A Policy Analysis*.³⁸

There are a variety of theoretical uses of human germline genetic modification. "Therapeutic", or health-related, modifications of the genome would seek to cure or ameliorate a disease in future generations. "Enhancement", or non-health related, uses would be aimed at adding or augmenting characteristics or traits not related to disease, such as muscle mass or height. Some uses, however, are not easily categorized as either therapy or enhancement. For example, germline genetic modification conceivably could be performed to confer resistance to disease, which might be considered both therapeutic and enhancement. Such a use may best be termed preventative.¹³

Genetically modified humans living among us?

It has been theorized that “faulty” ooplasm may contribute to infertility in some couples. To compensate for this, ooplasm from a healthy donor egg – including mitochondria and mtDNA but not the nucleus or nuclear DNA – has been transferred into the eggs of infertile women. Approximately 30 babies worldwide have been born following ooplasm transfer.⁷ These cases have been called the first examples of HGGM because the resulting child’s mtDNA is a mixture of both the mother’s and the ooplasm donor’s mtDNAs.⁷ This mixture of mtDNA is known as mitochondrial heteroplasmy.^{7,8,9} Since mitochondria are passed solely through the mother, a female child with mitochondrial heteroplasmy may transmit both types of mtDNA to her offspring, leading to a heritable, germline genetic modification (Figure 3).

Ooplasm transfer potentially could be used also as a form of gene therapy to attempt to treat or cure mtDNA-related disease.¹⁰

Human eggs also can be genetically modified by a process called pronuclear transfer. For pronuclear transfer, the pronuclei – the egg nucleus and sperm nucleus – from a fertilized egg are removed and placed in a donor egg that has had its own nucleus removed. Like ooplasm transfer, the resulting child would carry genetic material from three people – nuclear DNA from the mother and father, and mtDNA from the donated egg.¹¹ No live born child has resulted from this procedure. One triplet pregnancy was reported but there were no live births. DNA studies on the fetuses confirmed the presence of maternal and paternal nuclear DNA as well as mtDNA from the donor.¹²

In theory, successful HGGM could eradicate a genetic disease in a family by permanently replacing a gene containing a mutation with a normal copy of that gene. Single-gene disorders such as cystic fibrosis or Huntington disease would be the most straightforward targets for HGGM because replacing the mutated gene should prevent the disease. Using HGGM for multifactorial diseases or to enhance complex traits such as intelligence are much less feasible because they involve many genes and many environmental factors, and the genetic contributors remain largely unknown.

Germline Genetic Modification Techniques Under Study

Germline modification techniques have been used widely in mice and other species for many years¹⁴ and these methods potentially could be employed in humans some day. Genetic modification in humans has been limited to somatic cell gene therapy where genes are introduced into target cells of the body in an effort to correct or ameliorate an existing disease or condition in that individual. Similar techniques might be adaptable for human germline

genetic modification. However, several significant technical barriers must be overcome in order for the human germline to be successfully modified.

Delivering a gene or any DNA segment into a cell requires a means of getting the gene of interest into the target cell. The three principal methods for delivering genes into a target cell are using a virus carrying the gene of interest to infect a cell, introducing a gene of interest into a cell via a non-viral mechanism, and introducing an entire artificial chromosome containing a gene, or many genes, into a cell. Each approach has advantages and disadvantages, and each approach varies in its likelihood of being applied successfully to human cells for HGGM.

Twenty-five years of research in somatic gene transfer have yielded some success in using viral vectors to deliver a gene of interest into target cells.^{15,16,17} The gene of interest is placed in a virus that has been modified such that it infects cells but can no longer cause disease. This engineered virus then infects the target cell and the viral DNA usually inserts itself and the gene it carries somewhere into the genome.

A gene also can be delivered into a cell by a non-viral method. Four non-viral methods of gene delivery are: direct microinjection of DNA segments carrying the gene of interest into the nucleus of the cell; electroporation, whereby an electrical current is applied to the cell, causing it temporarily to

open small holes in its outer layer to allow entry of the DNA vector carrying the gene of interest; lipofection, whereby the vector carrying the gene of interest is packaged into a fatty substance that can easily pass through the cell's outer layer and release its contents into the cell; and transposable elements, which are segments of DNA that can insert themselves into chromosomes. And, although most gene delivery studies have focused on targeting the nuclear genome, it may be possible also to introduce genes into the mitochondrial genome.^{18,19}

Researchers also are experimenting with the possibility of using artificial human chromosomes to introduce genes of interest into target cells for somatic gene therapy.²⁰ Artificial chromosomes are larger in size

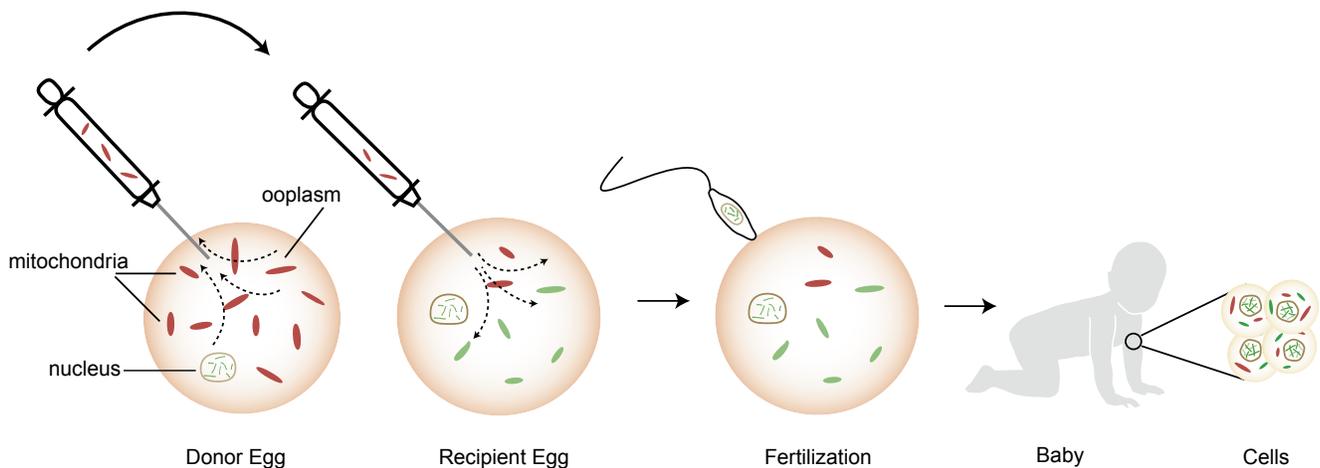
than the typical DNA vector and can carry all of the genetic sequences necessary for a gene to function properly. In order to be effective in germline modification, however, an artificial chromosome would have to exist alongside the standard 46 chromosomes in each cell and be copied and transmitted reliably when a cell divides into two. Artificial chromosomes have shown varied success in other organisms such as yeast, bacteria, and some mammalian cells.²¹ However, artificial chromosomes have not yet proven to be feasible in humans.²⁰ If this technology could be perfected for somatic gene transfer, it might be possible to use human artificial chromosomes in HGGM as well.

Germline genetic modification could be performed in egg or sperm cells or the cells that

give rise to eggs and sperm, the gametocytes. Recent studies in mice have shown that mouse ovaries continue to produce eggs throughout the mouse's reproductive lifespan.²² If true in humans, it may be possible to genetically modify a woman's gametocytes by targeting her ovary. Eggs produced by that ovary would in theory contain that genetic modification. Likewise, male gametocytes in the testis also could be targeted so that it would produce genetically modified sperm. Some early experiments in animals have been successful^{23,24,25} but this approach has not been tried in humans.

Germline genetic modification also could be performed in an embryo, but it must occur at a very early stage of development – perhaps at the single cell zygote

Figure 3: Ooplasm Transfer



The ooplasm of the donor egg is transferred into the recipient egg. Since this process transfers mitochondria, the recipient egg now contains mitochondrial DNA from two different people (donor and recipient). After this egg is fertilized and transferred into a woman's uterus, the resulting baby carries DNA from three people – nuclear DNA and mtDNA from the mother, nuclear DNA from the father, and mtDNA from the ooplasm donor.

Is human germline genetic modification technically realistic?

In 2000 the American Association for the Advancement of Science (AAAS) released a report called *Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious and Policy Issues* that concluded human germline genetic modification “cannot presently be carried out safely and responsibly on humans. Current methods for somatic gene transfer are inefficient and unreliable because they involve addition of DNA to cells rather than correcting or replacing a mutated gene with a normal gene. They are inappropriate for human germline therapy because they cannot be shown to be safe and effective. A requirement for inheritable germline modification, therefore, is the development of reliable gene correction or replacement techniques.”³⁴

Two recent advances have brought us significantly closer to the possibility of germline genetic modification in humans. The first advance is that gene targeting by homologous recombination – replacing a mutated gene with a “normal” copy – recently has been demonstrated in human embryonic stem (ES) cells.⁴

The second advance is getting stem cells to differentiate into germline cells – either sperm or eggs. Adult mouse sperm precursor stem cells have been isolated, genetically modified by gene targeting and coaxed into becoming mature sperm.^{2,3} These genetically modified sperm have been used for successful fertilization to give rise to genetically modified mice.

Mouse ES cells have also been coaxed into producing eggs³⁵ and sperm^{36,37} (Figure 4). These sperm have been used for fertilization and developed into mouse embryos.⁴ It remains unknown if these embryos can give rise to live born mice, but further research might support this approach as a viable technique for germline genetic modification.

Gene targeting studies in human ES cells will continue and likely be improved in the process of studying the molecular basis of human disease and in developing new treatments. Similarly, deriving functional sperm or eggs from stem cells also will be pursued as a means of developing genetically modified model organisms for biomedical research. While advances in these techniques will be driven by relatively uncontroversial research goals, and not the pursuit of HGGM, they effectively will catapult us over what were identified heretofore as the principle technical obstacles to HGGM.

stage – in order to ensure that the cells that will develop into the egg or sperm carry the gene of interest. Genetic modification of older

embryos (consisting of hundreds of cells) has been successful in many animal models by introducing genetically modified

stem cells into the developing embryo. However, because not all cells of the resulting embryo are genetically modified, the germline cells may remain unmodified. This condition is referred to as mosaicism. Mosaicism also can occur if the introduced gene becomes lost in some cells of the animal when the cells divide during development.²⁶ If the germline cells in a mosaic animal are not genetically modified, the modification will not be passed to the next generation.

Stem cells are another potential target for HGGM. Human stem cells can be isolated from many different tissues: Human embryonic stem cells (ES cells) are derived from the cells of a young embryo; embryonic germ ridge cells are isolated from young human fetuses; and adult stem cells can be isolated a number of tissues. Stem cells have the ability to develop into many cell types found in the adult human body.^{2,27,28,29} Stem cells offer significant advantages as targets for genetic modification. For example, they can grow indefinitely while remaining undifferentiated, meaning they do not develop into specialized cell types like muscle or skin. Because they can be grown in a petri dish in a laboratory, stem cells can be genetically manipulated and subjected to genetic tests to verify that the genetic modification is present. Mouse embryonic stem cells have been modified successfully in this manner.^{30,31}

Recent significant advances in mice involve genetically modifying

adult sperm precursor stem cells and causing them to develop into mature sperm, which then are used to fertilize eggs, giving rise to genetically modified mice (Figure 4). In addition, mouse embryonic stem cells have been modified, coaxed into developing into sperm, and used to create mouse embryos.³²

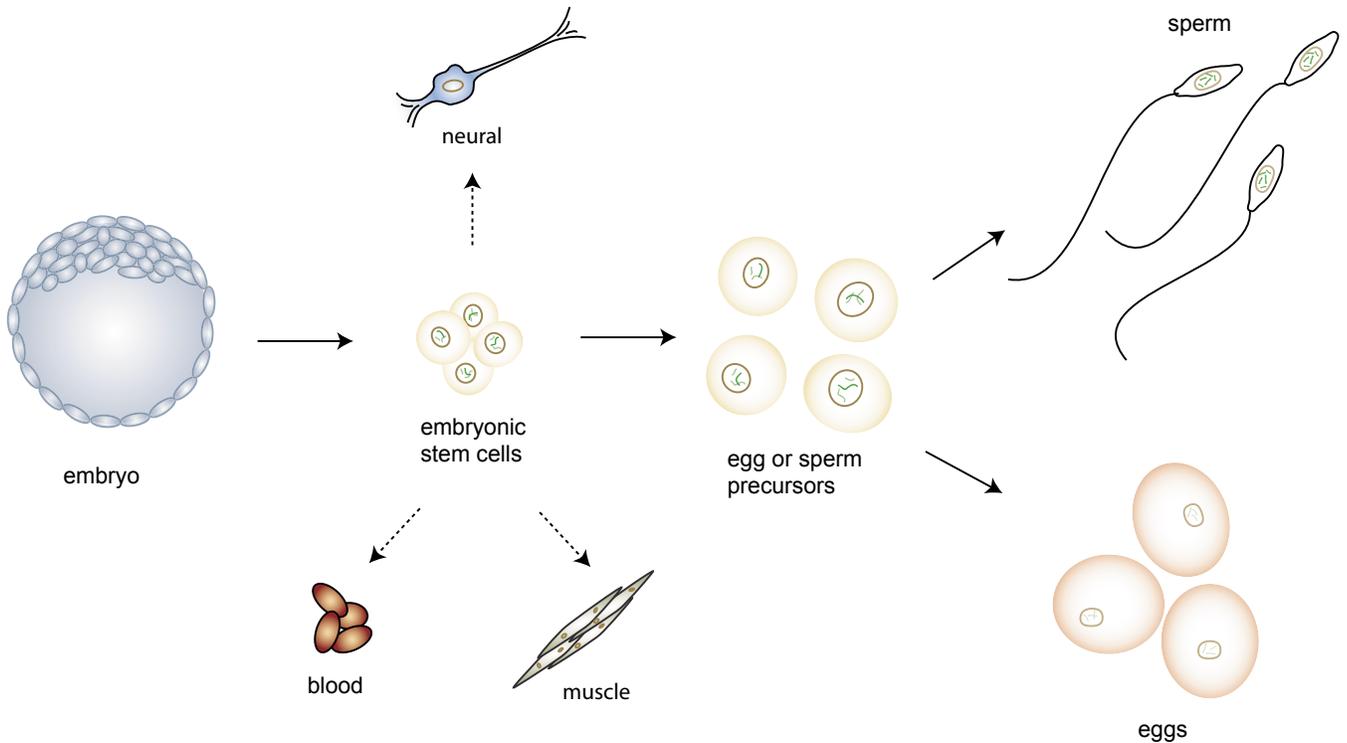
Germline genetic modification also could be performed in stem cells that could then be implanted into a developing embryo. Although this has not been done in humans, it is used frequently in mouse studies.³⁰

Some major technical challenges in gene modification involve uncontrolled insertions of the new gene or genes into the DNA of the target cell; improper gene function of the inserted gene; accidental mutation of a healthy gene; failure to remove the original, mutated gene; and separation of the newly introduced gene from the mutated gene.

With many methods of delivering a gene to a target cell, genes tend to be introduced at random locations in the genome. The inability to specifically and efficiently target a specific site

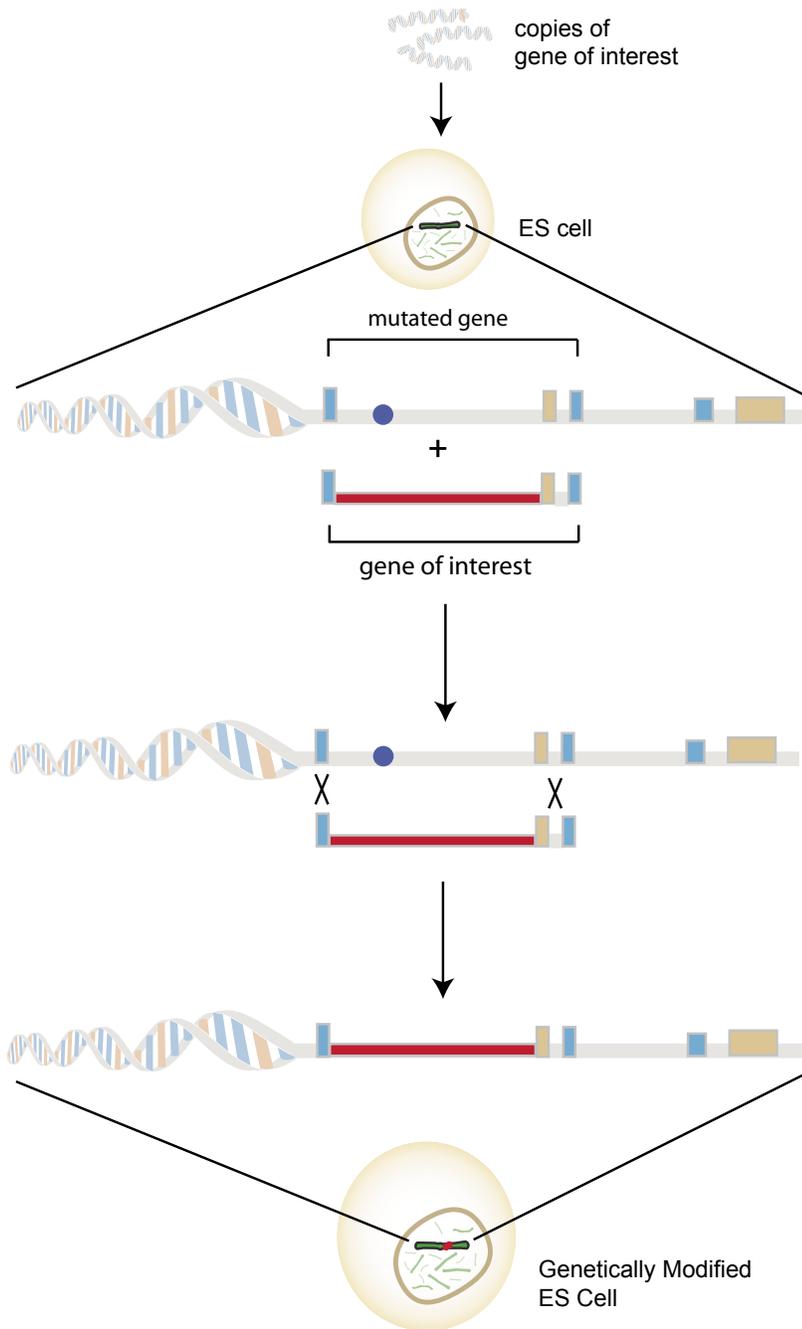
of the genome poses a number of problems. First, accidental insertion of a gene into a normal resident gene can disrupt its function, a problem called insertional mutagenesis. The risk of insertional mutagenesis is difficult to predict but it occurs at a significant rate in animal studies.¹⁴ Insertional mutagenesis also has occurred in human somatic gene therapy clinical trials.³³ Second, random insertion of the introduced gene also can result in abnormal expression of the added gene. Third, too many copies of a gene also can be inserted, leading to unwanted outcomes. Fourth,

Figure 4: Sperm and eggs derived from ES cells



Embryonic stem cells are able to develop into all types of cells in the body such as blood, muscle, and neurons. Recently, mouse embryonic stem cells have been coaxed to develop into egg or sperm precursor cells – germline cells. These egg or sperm precursor cells can develop into mature eggs or sperm. Deriving germline cells from human embryonic stem cells has not been reported.

Figure 5: Gene targeting by homologous recombination



A mutated gene in an embryonic stem cell – indicated by the blue dot – can be replaced by introducing a “normal” copy of that gene into the cell. The “normal” copy pairs up with the mutated copy and effectively swaps places so that the “normal” copy ends up in the chromosome and the mutated copy is lost.

random insertion could result in the introduced gene being located on a different chromosome from the mutation-containing resident gene. And, because chromosomes are shuffled and separated from each other during formation of egg and sperm, this shuffling could lead to the introduced gene ending up in a different egg or sperm cell from the mutated resident gene, which would lead to the disease reappearing in future generations.

Another significant limitation of gene delivery techniques is that these techniques typically do not remove the original, mutated gene. Introducing a normal copy of a gene aims to replace an existing, non-functioning, or malfunctioning gene. This approach could work when introducing a functional copy of a gene is all that is required for the desired effect. But certain genetic mutations, particularly dominant mutations, cannot be corrected by introducing a healthy copy of the gene.

The problems associated with random gene insertion and the failure of many techniques to remove the original mutated gene could be avoided by using gene targeting to introduce the gene or segment of DNA of interest into a precise location on a chromosome in the target cell by a process called homologous recombination (Figure 5). Homologous recombination can occur between two identical or nearly identical segments of DNA; these two pieces of DNA effectively swap places with each other. If the gene on the chromosome contains

a mutation or alteration, gene targeting through homologous recombination could replace it with a normal copy of that same gene. Gene targeting in mice has been successful and usually results in a single copy of the gene being inserted into the proper place within a chromosome, ensuring relatively normal gene function.¹⁴ Homologous recombination in human embryonic stem cells recently has been reported.⁴ If this technique can be perfected in humans, it could be a major advance for somatic gene transfer and remove a major technical obstacle to HGGM.

Safety and Scenarios

Safety

Germline genetic modification currently poses significant safety risks that research has not adequately addressed. Most risks are to the resulting child. The proposed techniques for HGGM involve extensive manipulation of stem cells, eggs, sperm, or embryos in the laboratory prior to introduction into a woman's uterus. Such manipulation alone could alter the growth and development of the fetus in ways that are not yet well understood.³⁹

If a gene fails to be inserted into the genome or if it becomes inserted but fails to function, the resulting child likely would be no worse off than he or she would have been without the attempted genetic modification.⁴⁰ However, if an introduced gene malfunctions or if too many copies are introduced, serious health consequences could result.⁴⁰ Likewise, the insertion of a gene into the wrong region of the genome can lead to insertional mutagenesis, where gene insertion causes a mutation in an otherwise normally functioning gene.⁴¹ Animal research has shown that insertional mutagenesis can lead to severe or lethal effects to the developing fetus.^{42,43} Human somatic gene therapy clinical trials to correct the "bubble boy" disease known as X-SCID (X-chromosome linked severe combined immunodeficiency) resulted in three patients developing leukemia as a direct result of insertional mutagenesis by a viral gene delivery system.³³ Animal research also has indicated that inserting

viral DNA into the genome carries significant health risks.^{14,41}

Some potential HGGM techniques also could put parents at risk. Germline genetic modification techniques that target ovaries or testes could pose risks to parents by damaging the cells that give rise to mature eggs or sperm.^{44,45} Injecting viral vectors into testes to genetically modify sperm in animals has resulted in male infertility.⁴⁵ A similar outcome could occur in females as well.⁴⁶

The safety of germline genetic modification is further complicated by the fact that some problems might not be evident until well after the genetically modified child is born or reaches adulthood, when the problems already could have been passed to the next generation.⁴⁷ Introducing a gene into an embryo does not guarantee that gene will function at all, much less be passed on and function in future generations.⁴⁸ If a genetic modification is lost, the disease that was corrected very well may re-appear in future generations.

Given current safety concerns, it remains unclear whether human germline genetic modification ever will be, or ever should be, developed. The potential risks (and potential benefits) are not fully understood, thus difficult decisions would need to be made about whether, and under what circumstances, human research and clinical trials would be tolerable.⁴⁹

Scientists and regulators agree that safety and effectiveness must be demonstrated clearly in animal models before HGGM ever is attempted. However, there is disagreement about how safety should be demonstrated, how long the research should continue and what level of success should be required. Some observers believe multigenerational data from animals will be needed before human trials can begin. Given that it may take sixty to eighty years to obtain multigenerational data from some animal species, questions exist about whether animal data would ever be sufficient to warrant human clinical studies.⁵⁰ Another view is that the level of efficacy in animals achieved before attempting HGGM should be greater than that which typically is required before beginning clinical trials. Proponents argue that currently, an intervention is considered adequate if it works as expected 70 percent of the time, but that such a standard would be far too low to justify attempting to create a child using HGGM.⁵¹ Some say the standard of success in animals should be close to 100 percent, and scientists must understand from animal models what would make a person an appropriate candidate for germline modification, in order to exclude from participation those who would be unlikely to benefit or would face significant risk.⁵² Some believe that HGGM should not occur at all until it is scientifically possible to both detect and correct the problems that may be introduced through genetic modification.⁵²

Measuring Risks and Benefits

Even if agreement were reached regarding the appropriate quantity and quality of animal data, attempting HGGM in humans nevertheless would pose potential harms. Animal studies cannot predict with 100 percent accuracy what will happen in humans. Whenever new therapeutic interventions are contemplated, researchers and regulators consider the potential risks and benefits in deciding whether to proceed. Some have argued that HGGM requires a risk/benefit analysis no different from that applied to any other proposed therapy.⁵³ Others, however, counter that the usual risk/benefit calculus is insufficient for the evaluation of HGGM.

Both the magnitude and likelihood of potential adverse outcomes from HGGM would need consideration. However, while some risks of attempting HGGM will be identified and quantified, the severity of some outcomes likely is to be variable, and some adverse outcomes simply will not be foreseen.

Some argue that consideration of risks must include potential harms that may be experienced by unspecified future generations. Some also argue that consideration of risks should not be limited to potential physical harms but should encompass the risk of ethical and societal harms as well. However, the amount of weight that should be given to that risk when compared to a potential near-term benefit to a specific person is difficult to determine.

There also is disagreement concerning what should be considered a benefit. Whether and to what extent HGGM would provide benefits will depend on both objective and subjective factors, including the expected outcome of the modification, why it is being attempted, and how one views the impact of the modification on the life of the future child and future generations.

Risk/benefit calculations typically include a consideration of alternatives – a high risk, potentially life-threatening therapy may be justified for a dying patient with no treatment alternatives but not justified for a mild or chronic disease for which there are alternative treatments. In the case of HGGM, however, there is disagreement regarding the alternatives against which HGGM should be compared, and how the risks and benefits should be measured.

Some say the new technology must be shown to be no more risky than the normal process of conception and birth.⁵⁴ Another view is that the risks of germline interventions for future generations “should be no greater than their risks of being born with the genetic condition at issue.” In other words, the risks to the child of attempting HGGM should, at worst, leave the child no worse off than if the child were born with the genetic disease HGGM is targeting.⁵⁵

On the other hand, law professor John Robertson has

made the argument that the risks of new reproductive technology should not be compared to risks faced by children born after traditional reproduction. According to Robertson, the relevant question is whether the person born after the use of reproductive technology is better off than if he or she were never born. This view is based on the assumption that existence is in most if not all cases preferable to non-existence.⁵⁶ However, others contend if HGGM involves modifying an embryo, then the child already exists, albeit as an embryo. The alternative to HGGM for these future children is not non-existence but rather continued existence in an unmodified state. Therefore, prospective parents would be putting future children (as well as future generations) at greater risk by using HGGM than they would without the technology.⁵⁵

Given that there are often alternatives to HGGM, many believe it would be a rare case in which the benefits of HGGM would outweigh the risks. Currently, families seeking to prevent passing a heritable single-gene disorder to their offspring have several options including PGD, the use of donor eggs or sperm, and in some cases, somatic gene transfer or non-genetic therapies once the child is born.⁵⁷ Attempting HGGM for a health-related use when alternatives are available would be viewed less favorably than cases where HGGM is the only possible option.⁵⁸

One possible model for assessing risks and benefits is the Federal Human Research Subject Protections, specifically those rules that apply to research on children. These federal regulations require consideration of the circumstances of the children under study, the magnitude of risks or discomforts that may result from participating in the research, and the potential benefits the research may provide to the child or to other children with the same disease or condition.⁵⁹

Under these regulations, there are four possible categories of research: a) Research that does not involve greater than minimal risk to the children, b) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child involved in the study, c) Research involving greater than minimal risk and no prospect of benefit to the individual child in the study, and d) Research not otherwise approvable under one of the above categories but that is determined to present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.⁵⁹

These rules would provide some standards to an oversight body or an individual weighing the risks and benefits of HGGM, but how one performs the risk/benefit analysis is difficult to separate from one's perspective on HGGM. For example, the possibility of risks to generations many decades hence may seem small to an adult

suffering from a serious genetic disease who wishes to prevent his or her future child from suffering from the same disease. On the other hand, an observer concerned that HGGM will have a devastating impact on the human species may believe no "benefit" to an individual is so great that it could compensate for this risk. These concerns would not fit readily into the current human subjects regulations, where under most circumstances the risks and benefits are to a single child and harms to society are not easily considered.

Informed Consent

It is a general principle of human subjects research that researchers must secure the voluntary informed consent of participants before proceeding.⁶⁰ It is unclear what information would need to be provided to prospective parents in order to inform them adequately of the risks associated with HGGM, given that many of these risks are unknown. It also is unclear whether obtaining consent only from the prospective parents would be adequate. Because HGGM alters individuals who are not yet conceived or born, some might argue it would be unethical to ever attempt HGGM because the informed consent of the future "patients" could not be obtained. However, parents generally are authorized to consent on behalf of their children or future children. For example, many parents pursue genetic testing of a fetus through amniocentesis or other means, or pursue fetal surgery even though the fetus is unable to give consent

for such testing or treatment. Children often receive treatments and the informed consent of the parent stands in for the informed consent of the child. However, although parents may have the right to make decisions on behalf of children, or even future children, it may be argued that they do not have the legal or moral authority to do so for generations to come.

Some believe the imperative to obtaining informed consent from future children is overstated, and that their interests simply need to be considered reasonably.⁶¹ For example, it may be possible to rely ethically on parental consent in cases where the alternative – the genetic disease in question – is so severe (for example, suffering and death in very early childhood) that the risks of HGGM safely can be said to be acceptable.

The need to conduct long-term, possibly multigenerational, follow-up studies also could pose a challenge. Researchers may want prospective parents to agree to have their children, and perhaps several generations thereafter, studied from birth.⁵⁷ However, it would not be possible to guarantee participation in a study, as participants are always free to withdraw. Some have argued that multi-generational effects should be studied in animals but that human trials should follow subjects only for the first generation.⁵³ There have not, to date, been any comprehensive long-term follow-up studies in the United States on the long-term health effects of other reproductive

technologies, such as in vitro fertilization and PGD.

Scenarios for HGGM

Given current scientific knowledge, HGGM is widely viewed as unsafe to attempt in humans. Yet as described above, recent scientific developments suggest that HGGM may become more technically feasible in the future. The question remains whether and for what purpose HGGM would occur.

Scientists' willingness to invest the time and research to develop the technology may be limited by the many existing alternatives to HGGM (including PGD, prenatal genetic testing followed by termination, adoption, embryo or gamete donation, and somatic therapy). On the other hand, several factors may create consumer demand. Prospective parents, those with sick children or genetic disease in the family, and patients themselves may create a demand for HGGM. For some patients, any possibility of treatment or cures is worth pursuing.^{62,63} The fame and fortune HGGM could bring to scientific and medical pioneers and the companies that back them may spur interest in the technology.⁵¹ And although there may be alternatives to "therapeutic" uses, the potential to "enhance" a future child, rather than prevent a heritable disease may create its own consumer demand.⁶⁴

The chart at right examines specific circumstances under

which HGGM could occur, and compares the **technical feasibility** of HGGM and possible **consumer demand** for HGGM under each set of circumstances.

Table 1:

Technical feasibility considers the extent to which the genetic factors at issue are known and can be manipulated, and whether the necessary technique exists or is foreseeable.

Consumer demand considers whether alternative treatments are available, the number of people affected by the disease or condition, and whether the targeted genetic characteristic likely is to be viewed as a serious disease or as a more ethically problematic enhancement.

Table 1: HGGM Applications: Technical Feasibility and Consumer Demand

Scenario	Examples	Technical feasibility	Consumer demand
Prevention of mitochondrial disease	Transfer donor ooplasm in order to provide unaffected mitochondria and mtDNA	Most feasible Ooplasm transfer and pronuclear transfer have been performed in humans.	Less demand Mitochondrial disease is extremely rare.
Genetic vaccine	Confer genetic resistance to HIV infection (e.g. CCR5)	Moderately feasible Some genes have been identified; feasibility is dependent on efficient genetic modification techniques.	Moderate demand Non-genetic modification alternatives more likely.
Prevention of recessive disease with two affected parents	Prevent cystic fibrosis in child of two affected parents.	Moderately feasible Genes have been identified; feasibility is dependent on efficient genetic modification techniques.	Less demand Extremely rare cases. Adoption, donor gametes or embryos are alternatives.
Prevention of late onset dominant disease with homozygous parent	One parent has two copies of BRCA1 mutation.	Moderately feasible Genes have been identified; feasibility is dependent on efficient genetic modification techniques.	Less demand Cases are extremely rare: homozygosity of many dominant disease-related gene mutation often has severe effects that preclude survival to reproductive age.
Prevention of recessive disease	Prevent sickle cell disease, cystic fibrosis, thalassemia in children of two carriers.	Moderately feasible Genes have been identified; feasibility is dependent on efficient genetic modification techniques.	Less demand PGD is an effective alternative.
Enhancement of physical characteristics, mental capacity or behavior	Change or add gene to influence height, improve memory, intelligence, creativity or confidence.	Less feasible Genetic contributors to these characteristics are unclear.	Uncertain demand Ethical objections to enhancements.
Multiple genetic modifications	Add immunity, athletic skill, etc.	Least feasible Numerous genetic contributors not known, may require use of artificial chromosomes.	Uncertain demand Ethical objections to multiple enhancements may be particularly high.
Extensive changes	Add armored skin, functional wings	Least feasible Genetic contributors are currently only imagined.	Any level of demand by parents is questionable.

Ethics: Expert and Public Views

For decades, many have questioned whether human germline genetic modification is or ever could be “ethical,” however one defines that term. Because it aims to make permanent changes to DNA that would affect generations not yet born, HGGM raises unique ethical issues.

For some, the most significant ethical challenge stems from the significant safety risks outlined in the previous chapter. Such risks are viewed as ethically unacceptable in the absence of substantial countervailing benefits.

For others, the societal impact of HGGM is the paramount concern. Pressures to “cure” inherited disease in future descendants could change family relationships, particularly those between parents and children. Human germline genetic modification has the potential to create the expectation that all babies should be born without genetic health conditions, and might thereby decrease society’s tolerance for and willingness to support and treat those living with disabilities. Many have raised the specter that notions of equality and fairness would be upended by a technology that created “enhanced” children only for those who could afford the treatment.

Concerns about HGGM also stem from deeply held religious perspectives on the morality of the techniques that would be used to perform HGGM. For those who categorically oppose the manipulation or destruction of human embryos, HGGM would

be ethically problematic because it involves one or both, at least for the foreseeable future.⁶⁵

In the United States, discussion of the ethics of human germline genetic modification largely has been confined to academic circles and government commissions, without significant input from the public. This section summarizes many significant contributions to the literature on the ethical dimensions of human germline genetic modification. It also describes findings from our own public opinion research in this area.

Previous Ethics Discussions

A quarter of a century ago, representatives of three major religious organizations raised concerns about the fundamental moral, ethical, and religious questions related to new genetic technology, and called upon President Jimmy Carter to address the lack of adequate oversight and control in this area.⁶⁶ In response, President Carter charged the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research to examine the social and ethical implications of “genetic engineering” or “gene splicing” – as it was then called – as it applied to humans. The Commission considered gene splicing, as well as somatic cell and germline gene modification. At that time, the technique of gene splicing was less than a decade old and had been used only in laboratory research. Many concerns at that time

revolved around the potential for accidental release of novel, genetically modified organisms and possible harms to humans and the environment. At the same time, many foresaw the potential benefits of using gene splicing and related technologies to alleviate human disease.^{67,68}

The Commission’s report, *Splicing Life: The Social and Ethical Issues of Genetic Engineering*, was intended to stimulate long-term discussion rather than to provide premature conclusions.⁶⁹ Nevertheless, the Commission made several findings and recommendations. The Commission concluded that while public anxieties were “exaggerated,” genetic engineering techniques were a “powerful new tool for manipulating nature” and a reminder of “human obligations to act responsibly.”⁷⁰ The Commission found that genetic engineering techniques had great potential to alleviate human suffering.⁷⁰ However, it recommended that particularly close scrutiny be given to procedures that would create inheritable genetic changes in humans. Interventions aimed at enhancing healthy people as opposed to remedying genetic disease were seen as problematic, although drawing the line between treatment and enhancement was viewed as subjective.⁷¹ Responding to the critique that genetic engineering was impermissibly “playing God,” the Commission stated that while the scientific procedures were not “inherently inappropriate,” such concerns deserved serious attention and

served as “a valuable reminder that great powers imply great responsibility.”⁷¹ The Commission recommended that the National Institutes of Health extend the scope of its existing Recombinant DNA Advisory Committee (RAC) to examine the safety of applications such as human gene therapy, and signaled a profound need for an oversight body, preferably one that would include participants from diverse backgrounds including government representatives, scientists, industry, lawyers, ethicists, religious leaders, and members of the public.⁷²

Although its primary focus was on somatic gene modification, the Commission specifically considered the potential use of genetic engineering in germline cells. In particular, the Commission focused on what it termed “zygote” therapy, i.e., the potential genetic modification of a fertilized egg. The Commission described safety concerns about genetic engineering and numerous cases where alternatives to “zygote” therapy might be possible. With respect to ethics, the Commission noted that some had raised eugenic concerns about altering the gene pool to eliminate undesirable traits.⁶⁵

In the late 1990s, HGGM increasingly entered ethical debates as a potential variation of emerging attempts at somatic gene therapy. In the RAC, the gene therapy pioneer, W. French Anderson, submitted two “pre-protocols” for *in utero* gene therapy. Although the research

in question actually was not ready to move forward, the RAC agreed to discuss these protocols in order to provide both a framework for continued discussion of the science, safety and ethical issues, and a guidance document for this area of research.⁷³ The ongoing discussions also considered the possibility that *in utero* genetic modifications could have germline effects.

In 1998, a public symposium at UCLA, “Engineering the Human Germline,” considered the prospects for HGGM. The symposium explored the social and ethical dilemmas raised by the technologies, and gave members of the public in attendance the opportunity to express their views.^{74,75}

In 2000, the AAAS issued a report, *Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues*. The report concluded that HGGM could not at that time be carried out in humans safely and responsibly and that few scenarios existed in which HGGM would be the only option to prevent genetic disease in one’s offspring. The report also stated that the impact of HGGM on future generations raises serious ethical concerns because of its potential to alter attitudes towards human beings, the nature of reproduction, and the parent-child relationship, as well as its potential to exacerbate existing societal inequalities – particularly if HGGM were used to “enhance” a child rather than avoid a serious or fatal disease.³⁴

Among its recommendations, the report noted the absence of sustained public deliberation on the subject and the need for such deliberation to occur in advance of technological possibility in order to influence whether, how, and to what extent HGGM moved forward. The report echoed the Presidential Commission’s recommendation that public oversight and public discussion were necessary. It recommended creating both a public body to monitor and oversee research developments in HGGM as well as a mechanism for assessing short and long term risks and benefits, before any protocol moves forward. The report stressed that society would need to determine whether HGGM would be socially, ethically, and theologically acceptable. Finally, the report recommended that public funding should not support clinical development of technologies for HGGM until a system of oversight is in place.³⁴

Most recently, the President’s Council on Bioethics briefly addressed HGGM. In its report *Reproduction and Responsibility*, the Council describes the safety, ethical, and regulatory issues related to HGGM while strongly emphasizing that HGGM is purely speculative “for now, and for the foreseeable future.”⁷⁶

What Does the Public Know and Think about HGGM?

As described in the previous section, the most visible deliberation about HGGM has been confined to elite

governmental commissions or scholarly groups. These same entities frequently have called for a broader public input into what, if any, use of HGGM might be appropriate.^{77,78} Yet, until now, little has been known about what the American public knows or thinks of HGGM.

Much of the American public has had little access to accurate information about HGGM. Instead, “information” about HGGM has come from Hollywood in the form of disquieting, sometimes horrific portrayals of the results of irresponsible scientific tampering or accidental mishaps (see box).

Most films and television shows play upon the public’s fears of scientists running amok and the erosion of liberty in the name of technological progress. The popular press also sends strong messages to the American public about HGGM. In a 2003 Time Magazine cover story celebrating the 50th anniversary of the discovery of DNA, seven prominent scholars speculated about how genetics will change our lives. Each presented an optimistic vision of a future in which genetic knowledge and manipulation lead to longer, healthier lives.⁷⁹ With genetic breakthroughs reported almost weekly, some view media reports as overwhelmingly positive and have criticized the media for building unreasonable expectations about the potential of genetics to transform our lives.^{80,81} Some comments reported by the media have been particularly extreme. James Watson, one of

HGGM at the movies

In the 1982 film “Blade Runner,” genetically enhanced humanoids known as “replicants” were created to colonize distant planets. But society’s obsession with creating a better human being backfired. After a bloody mutiny on an off-world colony, replicants are declared illegal and terminated upon detection.

In the 1997 film “Gattaca”, individuals who are not genetically ideal are relegated to a lower status and face discrimination in many forms. The lead character must purchase the identity of a genetically perfect human in order to have any hope of rising beyond his lowly position in society.

Recent film versions of the Spiderman comic departed from the Marvel comic original. In these stories, a genetically modified spider bites Peter Parker and gives him all his powers.

The television show “Mutant X” is Hollywood’s latest foray into the world of HGGM. In this drama, a geneticist accidentally creates genetically modified humans with superpowers. He must fight to protect these misunderstood superheroes from those who would destroy them.

Human genetic modification even makes an occasional appearance in children’s shows, such as the Disney films and television cartoons “Lilo and Stitch.” The likeable but destructive character Stitch is the product of a genetic experiment by a mad scientist in outer space. Stitch crash lands on Hawaii and is befriended by a young human child, Lilo. Stitch and his other friends from the experiment wreak havoc while the three-eyed alien mad scientist attempts to contain them.

the co-discoverers of DNA, said in 2003 that intelligence and appearance were fair game for germline genetic modification: “People say it would be terrible if we made all girls pretty. I think it would be great.”⁸²

How has the public absorbed these messages? Is HGGM something to be feared? Or does the public believe that genetic modification holds great promise for health and happiness? In order to better understand the public’s attitudes, hopes, and

concerns about HGGM and other reproductive genetic technologies, the Genetics and Public Policy Center conducted an ambitious research project including surveys, focus groups, and interviews.^{83,84,85,86}

The public’s views of HGGM do not necessarily reflect the extreme messages from the entertainment industry or media. In our focus groups and interviews, members of the public show significant interest in HGGM’s potential to provide treatments and cures.

“Well, if we can get rid of diseases like cystic fibrosis or colon cancer, I think that would be wonderful... My goodness. I would have done anything to do that if we had the chance at the time.”
(Interview with father of child with cystic fibrosis)

“It’s almost just like we are eliminating polio, any other disease, why wouldn’t I want that (HGGM for sickle cell disease) for my baby if we could do this.”
(Participant in African American male focus group, Tennessee)

However, members of the public do have fears about the development of these technologies. Some focus group participants specifically raised the specter of mad scientists who are willing to try anything for fame, and biotechnology companies in a relentless quest for profit.

“You are a reasonable person. We are responsible people here, but some of those scientists, because of the science and because of their warped mind, they will do something stupid like that, and you know they can, and they will.”
(Participant in Mexican Catholic female focus group, California)

“[W]ith the medical profession, I think...they’re brilliant and they do amazing things, but some of what drives the medical

community is ego and accomplishment. How do you know when they’re going to cross that line just because they want to be the one?... [T]hey’re willing to take risks or, ‘Well, I know this one’s not going to turn out right. I’ll tell them that it will be right because the next five, by learning what I can from this, then five people down the road [may benefit].”
(Participant in mixed sex/race focus group, Massachusetts)

“There are very few people who are pure researchers who don’t have any financial motivation for the success of their research.”
(Participant in Protestant female focus group, Massachusetts)

Other participants were skeptical that the use of HGGM would stop at serious medical issues.

“I like the idea of this one thing [HGGM for cystic fibrosis], and maybe a few other life threatening, horrible disease kinds of things, but I know it would never stop.”
(Participant in Evangelical female focus group, Colorado)

“It’s all or nothing. If you’ve gone down this road at all, you’ve gone down completely. You can talk about matters of degree, but you’re playing God....if we can actually do it, I think that’s great. But there is a lot of downside that

goes with it. We’re talking about the best intentions of medicine, and assuming that this is all going to be for good. But how many movies have we seen [with] so many nightmare scenarios of people manipulating this. So opening that door at all means its open, regardless of the degree.”
(Participant in Caucasian male focus group, Colorado)

For some focus group participants, the long-term impact of HGGM raised serious concerns.

“[W]ho knows the long-term effects of doing all this gene fixing? And then, as the generations that follow – that we created, or whatever – what happens with that, their DNA’s when they mix? And I don’t know – it just seems all very difficult and scary to some point.”
(Participant in Mexican American female focus group, California)

“What if you made a correction, what if there was an error and you created something worse?”
(Participant in mixed sex/race focus group, Massachusetts)

Additional issues, such as access to new technologies were also important to some participants:

“I mean, obviously this is not going to be available to everybody, regardless of whether it’s subsidized by insurance or whatever. There

are going to be some people that are able to have super kids, or improved kids, and a lot that aren't."

(Participant in Caucasian male focus group, Colorado)

Some participants discussed the use of reproductive technologies in terms of the role of suffering in people's lives. Most view suffering as something best avoided, yet a few described affliction as an important aspect of existence that allows individuals, families, and society to grow and learn:

"[E]veryone has got obstacles in life to get through, and if you terminate all of [these] from the very beginning to where people have an almost perfect existence, that eliminates a little challenge from life. And having things like this ... sometimes they can give people a reason to try harder, or a reason to build themselves up to be better than they are."

(Participant in young male focus group, Tennessee)

And finally, concerns were expressed about how individuals view themselves and their children:

"People get caught up in making the perfect child. You are trying to create the perfect life and making the perfect child, and that is not synonymous."

(Participant in African American female focus group, Tennessee)

"I just still think it goes against nature's way of maintaining order and balance on the planet. We are not meant to have a planet of complete, perfect individuals that are going to live to a hundred years old."

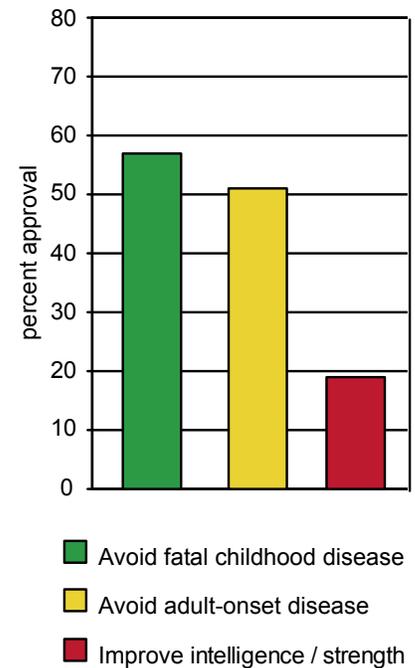
(Participant in Mexican American male focus group, Los Angeles)

The Center's 2004 survey of 4,834 Americans found higher levels of approval for the use of HGGM (as well as other reproductive genetic technologies) for health-related reasons. In general, however, Americans appear to be ambivalent about HGGM. For example, 57 percent approved of HGGM to avoid fatal childhood disease while 19 percent approved of the use of HGGM to have children with desirable "traits" (Figure 6).

For What Purpose?

There are multiple potential uses for HGGM if it becomes technically possible. HGGM could "fix" an inherited genetic disease before a child is born, and prevent the passing of the disease to future generations. These uses often are referred to as therapeutic or health-related, although the exact meaning of these words often depends on who uses them. HGGM also could be used for enhancement, to create children with particular genetic "traits" desired by the parents – traits that are not necessary for good health but that are perceived as enhancing the child. Again, the exact meaning of many of these terms

Figure 6: Americans' Approval of HGGM



Source: Survey 2004

and the lines between disease and trait are far from clear.

The availability of alternative reproductive technologies such as PGD, and the technical impediments to HGGM have meant that for many years HGGM has been what bioethics professor Eric Juengst has called a "bioethicists' problem." Given the many alternatives for addressing genetic disease, it seems HGGM's usefulness would be limited to enhancement purposes, which are widely regarded as unethical. Discussing policy schemes to regulate research and assess risks and benefits sometimes has been seen as prematurely

encouraging questionable uses of the technology.⁸⁷

Some policy schemes would make any germline techniques or enhancement uses off-limits and would allow only therapeutic use of somatic gene transfer.^{13,92,94} However, possible inadvertent germline effects have been reported in somatic gene transfer.⁹⁵ Some suggest such effects should be considered in context of the severity of the disease that is being treated, and should not necessarily preclude scientists from developing effective somatic treatments (see arrow A in Figure 7).⁹⁶

In addition, some scientists believe HGGM will be a more effective way of accomplishing the therapeutic goals of somatic gene transfer. For example, geneticist Mario Capecchi has argued that intentional germline methods will be more efficient and effective than somatic methods at delivering new genetic material to an adequate number of cells to produce the desired therapeutic effect.⁹⁷ If true, intentional germline approaches to enhancement, such as improving intellect or strength, may also be more effective than somatic approaches. In sum, germline modification could occur as a means to or side effect of somatic modification (see arrow A in Figure 7).

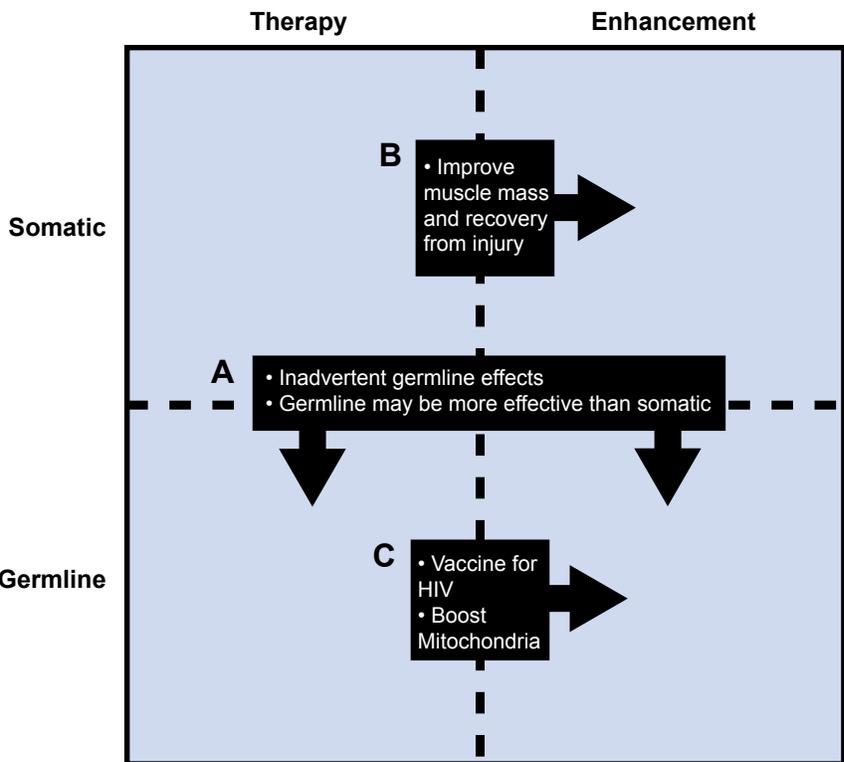
The line between using HGGM for therapeutic, or improved health purposes, and using HGGM for non-health related, or “enhancement” purposes, also is difficult to draw. In the context of somatic gene modification,

scientists already have succeeded in creating mice and rats that have 20%–30% greater muscle mass, recover from injury more quickly, and live longer than normal mice, changes that could be viewed as enhancement rather than therapeutic^{98,99} (see arrow B in Figure 7). HGGM could be used for overall health enhancement rather than to prevent a particular known inherited disease such as sickle cell disease. For example, prospective parents might be able to provide their offspring with heightened immunity to disease through a germline “vaccine”

against conditions such as HIV (see arrow C in Figure 7).¹⁰⁰

The intentional replacement of ooplasm containing mitochondria and mtDNA may be a therapy for rare mitochondrial disease (Figure 3). This would be a therapeutic use of HGGM. But, it is also possible to imagine using a similar technique for enhancement: mitochondria, which control the cell’s energy levels, could be manipulated in an attempt to boost a person’s overall energy level (see arrow C in Figure 7).

Figure 7: HGGM for What Purpose? The Challenge of Drawing Lines



This figure is based on slides presented by Eric Juengst at the Genetics and Public Policy Center’s “Babies By Design” meeting. Leroy Walters, W. French Anderson and others also have mapped the possible purposes for HGGM.^{88,89,90,91,92,93}

If, in the future, genes that significantly influence appearance or intelligence are identified, some prospective parents may be interested in using HGGM to pursue these traits in their offspring and future descendants.¹⁰¹ Whether or not society officially deems such uses appropriate, determined prospective parents might be able to find providers willing to help them pursue such goals.

These potential uses suggest that the traditional framework of dividing the uses of HGGM between “therapy” and “enhancement” may be too limited. It has been argued that an additional category, prevention, could include the use of HGGM to prevent disease by enhancing the body’s natural immunity.^{13,102,103}

However, depending on the user and the context, “prevention” may be difficult to define. Prevention could include interventions to prevent a genetic disease that is certain to develop, which may be indistinguishable from therapy. It might include preventing diseases that are the result of natural and universal processes like aging, strengthening the body in ways that seem superhuman, which may be indistinguishable from “enhancement.”^{13,92} And HGGM sometimes may be viewed not as “preventing” a disease in an individual but as preventing the birth of the original individual by changing who that individual is with the goal of reducing or eliminating the occurrence of the disease in a population.¹⁰²

Playing God

Some argue against HGGM by equating it to “playing God” and interfering with life as God intended it to develop. Paul Ramsey, a prominent theologian in the 1960’s and 70’s argued, “Men ought not to play God before they learn to be men, and after they have learned to be men, they will not play God.”¹⁰⁴ Theological discussions about HGGM often turn on the question of whether new technologies such as HGGM further God’s will or attempt to usurp it.

“I would love to have a child free of disease, and...no one gets sick, but it’s again, to me, it’s God’s will....The negative effect is playing God, and I don’t think God is going to like that.”
Participant in Mexican male focus group, California

“It’s the old argument, you know, if God wanted you to fly, he’d give you wings. Well, you know, we got past that. We fly now. You know?”
Participant in mixed sex/race focus group of people over age 55, California

However, in some religious traditions, such as Judaism and many Protestant traditions, the notion of playing God is not necessarily negative.¹⁰⁵ Rather, the belief is that human beings act as partners with God, taking responsibility for the pursuit of healing.¹⁰⁶ Some theologians argue that new technologies may be consistent both with theological conceptions of humans as co-creators and with more secular

ideas about moral duties to promote human flourishing and well-being.¹⁰⁷

Impact on Human Dignity

Human dignity is a difficult quality to define. Leon Kass, chair of the President’s Council on Bioethics, has referred to it as “that elusive core of our humanity ... the profoundly special character of human beings and the special virtue to which we may rise.”¹⁰⁸ Dignity may also be seen as a quality that enables human suffering to be redeemed, that drives us to strive on and engage in the world. Some view it as a human quality bestowed by God while others believe it comes from society or from our innate nature and rational capacity.^{109,110}

Religious and secular scholars alike have argued that HGGM would threaten human dignity by creating children in a utilitarian way, raising questions about whether every individual will be afforded the dignity he or she deserves.⁵² As the President’s Council on Bioethics has written,

A child who is designed to certain specifications might be viewed as more of an artifact – or more answerable to the will of his or her parents – than a child who is merely selected for his or her existing characteristics... turning procreation into a form of manufacture; promoting a new eugenics, where parents and society seek only the ‘best’ children; allowing individuals or

society to alter the native human capacities of offspring in a direct way, and perhaps to engineer novel capacities not hitherto present in human beings; and binding the next generation to a genetic fate that suits the will of the present one.”¹¹¹

HGGM and Eugenics

Eugenics is a term coined by Sir Francis Galton in the late 19th century to refer to the “study of agencies under social control that may improve or impair the racial qualities of future generations, whether physically or mentally.”¹¹² Galton and his followers believed that characteristics such as intelligence, wealth, and success were hereditary. His theories spawned eugenics movements, including in the United States, during the late 19th and early 20th century. These included programs of “positive” eugenics, aimed at encouraging those considered to have particularly good heritable characteristics to have more children, and of “negative” eugenics, aimed at discouraging or actively preventing those considered unfit from having children. Many states enacted laws permitting the involuntary sterilization of institutionalized persons and 40,000 eugenic sterilization operations were recorded in the U.S. between 1907 and 1945.¹¹³ One such law was upheld by the Supreme Court. In *Buck v. Bell*, Supreme Court Justice Oliver Wendell Holmes, Jr. opined that those that “already sap the strength of the State” must make sacrifices to prevent our being

swamped with incompetence,” and reached the now infamous conclusion that “three generations of imbeciles are enough.”¹¹⁴

The government-sponsored eugenics practiced in Nazi Germany is the starkest example of the implementation of eugenics-based policies. Noted scholar and member of the President’s Council on Bioethics Francis Fukuyama has described Nazism as “the last important political movement to explicitly deny the premise of universal human dignity.”¹¹⁵ The Nazi “racial hygiene” movement espoused the view that the Nordic race was genetically ideal and that non-Nordic races were genetically inferior and weakened society. Jews in particular were singled out for elimination, first through professional and social exclusion and then through extermination. The Nazis also sought to prevent reproduction by Germans with those whose genes were considered inferior. Under the 1933 “Law for the Prevention of Congenitally Ill Progeny,” which authorized sterilization of those with one of nine conditions including “feeble-mindedness,” an estimated 400,000 Germans were forcibly sterilized. Additionally, an estimated 200,000 Germans – including babies with Down syndrome and elderly psychiatric patients – were killed.¹¹³

For some observers, powerful parallels exist between the eugenics movement of the early 20th century and HGGM. Those who view HGGM as a form of modern eugenics fear it will be used to permit only those with

“ideal” genes to come into being. They worry that the allure of what the Council for Responsible Genetics calls “biological perfectibility” will result in organized eugenics programs.¹¹⁶ As the President of the American Association of People with Disabilities has stated:

“One would hope that reactions to the Holocaust and the advent of the disability rights and independent living movements in the U.S. and around the world would have put an end to the eugenic efforts to eliminate people with disabilities.... Unfortunately, if we examine the rhetoric of some influential modern scientists and ethicists, we can see the emergence of a new eugenics tied to the rapid advances in scientific understanding of the human genome.”¹¹⁷

Impact on Human Species

Some argue that changing the genetic makeup of individuals to prevent disease or enhance characteristics will change the overall genetic composition and diversity of the human race with unpredictable and perhaps disastrous consequences. For example, the Council of Europe has stated, “Whilst developments in this field may lead to great benefit for humanity, misuse of these developments may endanger not only the individual but the species itself.”¹¹⁸ Indeed, health problems such as developmental syndromes have appeared during

genetic experiments with mice: the concern is that HGGM similarly would alter the “natural order” and may result in new genetic diseases in humans.^{51,119}

Others have argued, however, that the risks of HGGM to the human species as a whole are overstated. They point out that every medical treatment or procedure that allows people who otherwise would have died to survive and reproduce changes what genes would “naturally” continue to exist.¹²⁰ They believe that “[t]he whole practice of medicine is a comprehensive attempt to frustrate the course of nature. If we always preferred the natural as a matter of principle, we would have to abjure medicine altogether.”¹²¹ Some add that HGGM is “not likely to have a significant effect on the human gene pool,”¹³ and that we need to keep in mind the baseline level of genetic change that occurs without human intervention.⁹⁶ For example, genetic material can change position or “jump” in unexpected ways. One study found that one in eight sperm contains new genomic sequence caused by “normal” movement of genetic material.^{122,123}

Although the intent of HGGM may be to improve humans, some believe “the outcomes will be quasi- human or less than human,”¹¹⁹ and those who have been altered may lose the rights to which they otherwise would be entitled.¹²⁴ However, others have argued that it is impossible to contemplate truly “preserving” the species because

humans are changing the species all the time through medical or other interventions.¹²⁵ As one commentator put it, “We are all new ‘population variants,’ constantly generated by the interaction of our genomes and epigenomes with the natural and technological world.”¹²¹ Unless HGGM were to become easy, inexpensive, efficient, widespread, and accessible to many, the changes confined to just some individuals seem unlikely to affect the human race as a whole: “A handful of rich people genetically modifying their children for greater height or intelligence would have no effect on species-typical height or IQ.”¹²⁶

Impact on Society

Similar to concerns about other reproductive genetic technologies, there are concerns about the impact of HGGM on society, particularly whether its use would exacerbate existing societal inequalities. HGGM is likely to be extremely expensive and only those who could afford it would benefit. The most basic health care is not available to many members of society, and inequalities in access mean that HGGM would only be available to a few, reinforcing or increasing existing disparities and widening the already existing class divide.¹²⁷

A troubling and sinister relationship between the genetically enhanced and non-enhanced members of society could arise as a result of the divide: “Ultimately, it almost seems inevitable that genetic

“Well, you know, it’s unfortunate; but there probably would be this whole competition thing... people perceive that if you are more perfect or closer to perfection then you have more value as a human being... And we might end up being a society... you know, that doesn’t take care of everybody but that certain individuals have more value than other individuals because they’re closer to perfection.”

Interview with mother of child with cystic fibrosis

engineering would move *Homo sapiens* into two separable species: The standard-issue human beings would be seen by the new genetically enhanced neo-humans as heathens who can properly be slaughtered and subjugated. It is this genocidal potential that makes species-altering genetic engineering a potential weapon of mass destruction and the unaccountable genetic engineer a potential bioterrorist.¹²⁸

There is a rich history of discussion about the impact of new reproductive technologies on people with disabilities. Many have raised concerns about using these technologies to prevent the birth of babies affected by genetic disease, maintaining that this trend could make society less tolerant of people living with disabilities. Disabilities rights advocates also argue that the disabilities sought to be prevented through technologies such as prenatal diagnosis, PGD and potentially HGGM, need not be considered disabilities at all but reflect society’s unwillingness

to accept and accommodate people with variations from some arbitrary standard of what is considered “normal.”

Modifying children to eliminate disabilities conflicts with the notion that living with a disability need not be detrimental to that individual, his or her family, or society at large. Such decisions by prospective parents reduce a disabled person to a single trait and reinforce the idea that the problem is disability, rather than society’s failure to provide adequate measures so that those who are disabled can function well.¹³⁰

Preventing or treating a disease or condition in an existing individual may be viewed as less problematic than using PGD or prenatal diagnosis followed by abortion to prevent the person from existing in the first place. As bioethicist Ruth Faden has written,

[T]reating the prevention of the birth of children who would have a disease or disability as morally equivalent to preventing illness or disability in persons already living involves a morally unacceptable view of the worth of such persons. It suggests that the lives of some persons with a disability or illness are not worth living, that such persons are to be understood only as social or economic drains and never as sources of either independent value or enrichment for the lives of others.¹²⁹

If HGGM were to be considered treatment, then perhaps it is more morally acceptable than the alternatives. HGGM may be viewed by some as preserving the person, rather than rejecting the person because of his or her disability.¹³¹ It might be considered a “less odious form of selection because it is attempting to provide health and capacity to some new being rather than excluding from coming-into-being a person who will have what is considered diminished health or diminished capacity.”¹³²

Indeed, the disability critique of HGGM may change as the technology changes. Decades from now, HGGM may be more like a treatment for a future person, allowing a person to come into existence free of disease – prospective parents undergo a procedure that transforms their eggs or sperm, allowing offspring to be born “pre-treated” or prevented from having a specific genetic disease or disorder. On the other hand, if and when HGGM first occurs, for many years it will undoubtedly require couples to go through IVF and create embryos, either to perform HGGM on the embryos themselves or to make sure the HGGM worked before proceeding with pregnancy. Such a process, practically speaking, would raise the same issues as PGD – choosing (and discarding) embryos based solely on a genetic finding.

Regardless of the techniques, prospective parents using HGGM to “fix” a future child before birth would reinforce the fact

that society continues to make it difficult for individuals and their families to live with a disability. If and when HGGM becomes available, parents may feel social and financial pressures to pursue it. Some are concerned that insurers may someday demand that prospective parents undergo any number of measures, including HGGM, to prevent the birth of a child with genetic disorders.¹²⁷

Impact on Families

HGGM has the potential to change family relationships. Prospective parents may decide to pursue HGGM for any number of reasons: some because of cultural norms or personal opinions about what is desirable, others because of lack of complete information about what HGGM might or might not offer. A modified child, once mature enough, may object to the changes that were made and resent the parents for making them. Alternatively, an unmodified child may resent not having been given the very best genes available.

By changing human reproduction in the search for “perfect children,” some believe germline genetic modification and other reproductive technologies will change the nature of the love parents have for their children by making children a commodity that parents have produced to their specifications rather than a gift to be loved “to the point of irrationality.”¹³³ This result may harm children who, although they may be less than “perfect” in their parents’ eyes, still need their unconditional support. One fear

is that adverse outcomes from HGGM that result in children born with malformations or genetic disease will lead to the modified offspring being rejected by their families and society and becoming “entities distanced not only from the physiological reproductive process but from human forebears with any socially prescribed responsibility for them”.¹³⁴

An opposing argument is that parents and society have a responsibility to try to bring into the world the healthiest possible children for the next generation.⁵³ Parents often make decisions on behalf of their children because they “want the best for them,” be it attempting to change the child’s appearance through orthodontia or choosing their schools. Some distinguish between wanting to give children new “tools” (schools, music lessons, orthodontia) and trying to change the child’s innate capacities. Erik Parens of the Hastings Center has distinguished these examples of parental intervention: the advantages bestowed by new “tools” are limited by a person’s innate abilities or “draw in the genetic lottery” whereas genetic manipulation aims to change the innate abilities themselves.¹³⁵

There are a number of moral issues related to parents pursuing reproductive technologies to “help” their children, whether for health or enhancement reasons. For some, the willingness to take such risks, particularly for non-fatal or non-serious diseases, has been viewed as proof of

parental attitudes already gone awry. Writing about PGD, which raises similar concerns, John Kilner, President and CEO of The Center for Bioethics and Human Dignity, states “The demise of unconditional acceptance and love that usually exists when a parent has a child, whether they be healthy or not, does not bode well for the inevitable situations when other unwanted problems arise in a child’s life.”¹³⁶ These concerns are not unique to the use of new reproductive technologies as people often have children for reasons that may be viewed by some as the “wrong”: to fulfill their own personal desires and meet expectations that have nothing to do with the individual the child wants to become.

Oversight

Most national and international policy making bodies that have considered HGGM have expressed deep concerns about its safety and ethical ramifications and have taken steps to prevent it.

International Approaches

In 1997 the Council of Europe issued the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, which included the Article on Interventions on the Human Genome. The Article appears to condemn both intentional germline genetic modification and somatic gene transfer for enhancement purposes. It states:

“An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.”¹⁶⁴

Also in 1997, the United Nations Educational, Social, and Cultural Organization (UNESCO) adopted a non-binding Universal Declaration on the Human Genome and Human Rights, signed by 186 nations. Article 24 instructs UNESCO’s International Bioethics Committee to study “practices that could be contrary to human dignity, such as germline interventions.”¹⁶⁵ The International Bioethics Committee of UNESCO issued a report in 2003 stating:

“Correction of a specific genetic abnormality in germ cells or early stage embryos (germ-line intervention) has not yet been carried out in medical practice. Because of the many technical problems and uncertainties about possible harmful effects on future generations, germ-line intervention has been strongly discouraged or legally banned.”¹⁶⁶

Many countries, including Australia, Austria, Brazil, Canada, Costa Rica, Finland, France, Georgia, Germany, Hungary, Italy, Japan, the Netherlands, Norway, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom have laws banning the use of HGGM in most circumstances.¹³⁷ Israel has established a moratorium that will expire in 2007. Many other countries are considering legislation that would ban HGGM.¹³⁷

Federal

The United States Congress has not passed any law that explicitly addresses HGGM but existing laws, notably the Federal Food, Drug and Cosmetic Act and the Public Health Service Act, have been interpreted as providing sufficient authority to federal health agencies to regulate research on human genetic modification, sometimes termed gene therapy. Two agencies of the Department of Health and Human Services, the National Institutes of Health (NIH) and the Food and Drug Administration

(FDA), have policies in place to govern gene therapy research in humans. Over time, the roles and responsibilities of NIH and FDA have shifted in response to changing circumstances. This section briefly traces the history of oversight of human gene modification, both germline and somatic, by these two entities and the current oversight functions played by each.

National Institutes of Health

NIH oversight is limited to institutions or researchers that receive federal funds, which encompasses most academic institutions in the United States. However, NIH regulations and policies often “set the tone” for privately funded research.

In 1974, the NIH established the Recombinant DNA Advisory Committee (known as the “RAC”). The impetus for establishing the RAC was not human gene transfer; indeed, it would be more than a decade before the first human gene therapy trial took place in the United States. Rather, the RAC was formed in response to public concerns relating to the safety of the newly developed techniques of “recombinant DNA.”¹³⁸ Initially, the RAC focused on safety concerns relating to the inadvertent release of microorganisms containing recombinant DNA into the environment.¹³⁹ In 1976, the RAC issued guidelines requiring institutions undertaking federally funded recombinant DNA research to establish an Institutional Biohazard Committee for local

oversight of such research.¹⁴⁰ These guidelines have been updated and modified over time.¹⁴¹

In 1980, the actions of a researcher at the University of California at Los Angeles brought human gene transfer research into the spotlight and led the RAC to broaden its scope of oversight. The researcher, who was funded by the NIH, conducted somatic human gene therapy experiments overseas without prior authorization by University's institutional review board (IRB).¹⁴² In response to recommendations of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research,¹⁴³ the RAC formed the Working Group on Human Gene Therapy in 1983. The Working Group, which included scientists, clinicians, lawyers, ethicists, policy experts and a representative of the public, recommended that the RAC broaden its scope to include review of protocols for human gene transfer. The Working Group also drafted over 100 questions relating to both science and ethics that scientists seeking to conduct gene therapy experiments in humans would be required to address in submissions to the RAC.¹⁴¹ Consistent with the Splicing Life report by the President's Commission, the Working Group from its inception took the position that it would not consider protocols for human germline gene transfer.¹⁴⁴

The first somatic gene therapy clinical trial occurred at NIH in 1990. In that trial, researchers

used a viral vector to deliver a functioning gene for the enzyme adenosine deaminase (ADA) to a four-year-old girl with severe combined immunodeficiency (SCID). As more researchers, both academic and industry-based, sought to conduct somatic gene therapy investigations in humans, concerns were raised regarding the burdensome and public nature of the RAC review process and whether NIH was the appropriate locus for oversight of gene therapy. As FDA assumed a central role in the regulation of gene therapy, some viewed independent review of protocols by the RAC as unnecessarily duplicative. Others, however, feared that a reduction in RAC oversight would threaten the safety and public accountability of such research.¹³⁹

The RAC began to redefine its role in the mid-1990s and moved from independent review and approval of individual gene therapy protocols to considering the ethical implications of new applications of human gene transfer. For example, in 1997, NIH sponsored a conference to discuss the use of gene therapy for "enhancement," meaning non-life-threatening conditions such as baldness.¹⁴⁵

Currently, gene therapy protocols funded by NIH or conducted at or sponsored by NIH-funded institutions must be submitted to the RAC, and NIH maintains a registry of these protocols. Submission to the registry is voluntary for protocols funded solely with private funds and not conducted at or by an

institution receiving NIH funding. The RAC reviews protocols to determine if they raise novel issues and facilitates public discussion of such protocols.¹⁴⁶ For example, in 1998, the RAC discussed two "pre-protocols" for in utero gene transfer experiments designed to treat SCID and thalassemia. The RAC considered the possibility that in utero genetic modifications could have germline effects. In discussing these protocols, the RAC sought to (1) provide a "framework for continued discussion" of the science, safety, and ethical issues surrounding gene transfer in prenatal medicine, and (2) stimulate "the development of a guidance document for this novel area of research within the context of the NIH Guidelines."¹⁴⁷ In 1999, RAC committee members issued a consensus statement that while the RAC "continues to explore the issues raised by the potential of in utero gene transfer research," it is "premature to undertake any human in utero gene transfer experiment" at the present time.¹⁴⁸

The RAC has adopted an explicit policy precluding review of protocols for human germline alteration. Germline alteration is defined as "a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring."¹⁴⁴ If the RAC were to modify its current policy and agree to consider HGGM protocols, at least some HGGM research likely would be precluded from receiving federal funds because

of a 1996 Congressional ban on federal funding of any research in which an embryo is created, destroyed, or subjected to more risk than is permitted for a fetus in utero.²⁴⁵ This ban could limit some HGGM research involving human embryos to the private sector.

Food and Drug Administration

From the early days of gene therapy research, FDA has consistently maintained that it has authority under the Federal Food Drug and Cosmetic Act (FD&C Act) and Public Health Service Act (PHS Act) to regulate clinical applications of gene therapy,¹⁴⁹ and this position has never been challenged. In 1984, FDA signaled its intention to regulate human gene therapy. According to the FDA, “nucleic acids used for human gene therapy trials will be subject to the same requirements as other biological drugs.”¹⁵⁰ FDA took the position that gene therapy is not fundamentally “different” from other types of therapies and thus would not require new oversight mechanisms.

Since 1984, FDA has communicated the regulatory requirements for gene therapy through a series of increasingly detailed notices and “guidance documents.”¹⁵¹ Guidance documents are not legally binding on the regulated industry. However, because these documents reflect FDA’s most current interpretation of its statutory authority, the regulated industry often views them, as a practical matter, as having the force of law.

In 1991, the Center for Biologics Evaluation and Research (CBER), the part of FDA that oversees gene therapy, told manufacturers which scientific issues and safety concerns FDA believed were important to take into account in manufacturing and testing gene therapy products.¹⁵²

In 1993, FDA issued a notice in the Federal Register further explaining the legal basis for its regulation of gene therapy.¹⁵³ The document reiterated that existing FDA statutory authorities, “although enacted prior to the advent of ... gene therap[y], are sufficiently broad in scope to encompass these new products and require that areas such as quality control, safety, potency, and efficacy be thoroughly addressed prior to marketing.” The document defined gene therapy as “a medical intervention based on modification of the genetic material of living cells.” Such cells “may be modified *ex vivo* for subsequent administration or may be altered *in vivo* by gene therapy products given directly to the subject.” The genetic manipulation “may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans.” According to the document, “[f]inal products containing the genetic material intended for gene therapy are regulated as biological products ... or as drugs ...”¹⁵³ In other words, the regulated “product” of gene therapy is the DNA that is administered to the patient and the delivery system (e.g., virus) used to transport that DNA. As a result, these generally require the premarket submission of an

application and approval of such application by FDA before they may be used to treat patients.

FDA oversight of somatic or germline gene therapy requires that the researcher submit an “investigational new drug” (IND) application with preclinical (e.g., animal or laboratory) data sufficient to justify use of the product in humans. The IND rules also require that the researcher has obtained approval from an Institutional Review Board (IRB). Since the death of gene therapy research subject Jesse Gelsinger in 1999, FDA and NIH have taken additional steps to protect participants in gene therapy trials.^{154,155,156} Currently, FDA oversees approximately 210 active INDs for somatic cell gene therapy studies.¹⁵⁹ FDA has not yet approved for sale any human gene therapy product.

In 2001, after the birth of children following ooplasm transfer (Figure 3), FDA sent a letter to researchers asserting broad FDA authority over research in human “involving the transfer of genetic material by means other than the union of gamete nuclei.” This included the transfer of genetic material contained in cell nuclei and ooplasm, which contains mtDNA. The letter further stated that this research requires the submission of an IND.¹⁶⁰

Thus, FDA has made clear that it will regulate HGGM. It is not possible, however, to know for certain whether FDA has received any INDs for germline genetic

modification or what criteria the agency would use to review such applications.

Federal Human Subject Research Protections

All institutions receiving federal funds are required to follow federal rules to protect human subjects of medical research.¹⁶¹ Research conducted pursuant to an IND or to support an application for a new drug or biological product is also subject to these regulations. The regulations include review of research protocols by an Institutional Review Board (IRB), informed consent of the research subject, and periodic reporting. Because HGGM research would require an IND, and might occur at a federally funded institution, it would be subject to these requirements.

State Laws

No states regulate somatic or germline genetic modification directly. However, existing laws of more general applicability could indirectly affect HGGM research.

First, laws prohibiting research with human embryos could limit HGGM research. Currently, laws in several states prohibit embryo research. In a few instances such laws have been challenged successfully as unconstitutionally vague and/or unconstitutionally interfering with procreative liberty.^{162,163}

Second, research subjects who believe they were injured as a

result of participation in HGGM research could sue the researchers and the institution at which the research took place under a variety of state or common law principles, such as negligence. No court has had occasion to issue an opinion in this area.

Professional Guidelines

Medical and scientific professional organizations are a potential source of oversight for the research, development, and use of germline genetic modification. For the most part, professional guidelines are voluntary, sometimes serving an exhortative role, setting the standard for appropriate conduct by providers. To date, no professional guidelines for HGGM have been developed.

Options and Considerations for Policymakers

HGGM is not yet possible, nonetheless there has been considerable discussion of the scientific, ethical, and safety issues that surround it, and a number of recommendations have been made for specific policy changes.^{34,69} In this section, we present policy options that respond to the many divergent perspectives regarding HGGM.

For some, the appropriate policy choice is clear and simple: HGGM should be **banned**. Those holding this view are motivated by either the perceived physical risks or ethical risks posed by the technology, or both. Therefore they support policies to ensure that HGGM is not attempted.

Others believe there may be acceptable uses of HGGM in the future, but want to be sure that **appropriate limitations** are set, through government or other oversight, to ensure safe and ethical use.

Still others want to **encourage innovation** in HGGM. From this perspective, regulation, if any, should allow prospective patients and scientists considerable autonomy to move forward in attempting germline modification in humans.

Ban it

At the present time, the safety risks of attempting HGGM greatly outweigh the benefits, leading many to conclude that an outright ban is warranted. In addition, many alternatives to HGGM, including PGD, would often

allow prospective parents to have children free of inherited genetic disease. Given these alternatives, some proponents of a ban assume the technology's primary use would be to create "designer babies" with enhanced attributes or capabilities, and argue that most Americans view this application as inappropriate, with the potential to alter social relationships and society as a whole in a dramatic and negative manner. Further, advocates of a ban argue that the benefits to the few couples who might desire to use HGGM to avoid serious genetic disease need to be weighed against the safety concerns and the risks to the future of humanity. Based on this calculus, they conclude that the risks of HGGM are too great to allow it to develop at all.¹⁶⁷

In the United States, several approaches could be used to ban HGGM. Congress or state legislatures could pass a law explicitly prohibiting HGGM and imposing penalties on those who attempt it. Congress could also enact prohibitions of limited duration, imposing "sunset clauses" that would require reauthorization of the ban at some point in the future.

FDA could articulate a policy not allowing clinical research using HGGM to proceed. While it appears that FDA has not yet received any proposals for HGGM, there may come a time when researchers seek FDA authorization for clinical research, and an explicit policy would provide clarity in such circumstances.

Supporters of a U.S. ban on HGGM point to prohibitions enacted in other countries as examples of sound policy and would like to see Congress pass a similar law. Some suggest that an international approach would be preferable because it would provide the most comprehensive protection from changes to the human species, ensuring that countries would reinforce each other's prohibition in this area.

The United Nations could play a role in implementing a ban through an international convention against HGGM.¹⁶⁷ George Annas, a professor of law at Boston University, and others have drafted a "Convention on the Preservation of the Human Species" and have advocated for its adoption by the members of the United Nations. Such a treaty would ban "species-altering" activities, including human reproductive cloning and human germline genetic modification. This approach aims to preserve the "human species" globally by preventing scientists interested in pursuing these technologies from seeking a "home country" with the most permissive laws.¹²⁴ However, a truly universal ban ultimately may be impossible: one country permitting the technology could provide a refuge for those who wish to develop or use HGGM.

Several critiques of the international approach have been raised. As a practical matter, it may be difficult to obtain support from a sufficient number of countries. Even those countries that do sign a treaty may not comply with it and

there is limited ability to enforce these agreements because there are few international enforcement mechanisms. In addition, a one-size-fits-all policy ignores unique social and political characteristics that may dictate approaches that best fit a particular country.

One challenge to crafting an effective ban would be defining the technology at issue. Some countries have laws that purport to ban HGGM but leave enormous loopholes. For example, Finland's law states: "Research on embryos and gametes for the purpose of developing procedures for modifying hereditary properties shall be prohibited, unless the research is for the purpose of curing or preventing a serious hereditary disease." It is unclear when the exception for "curing or preventing a serious hereditary disease" would apply.¹⁶⁸

The challenges to instituting a ban on HGGM are significant but those who support a ban do not believe them insurmountable, particularly given the potential harms they foresee if HGGM is permitted.

An alternative to governmental prohibition is a voluntary agreement by scientists that they will not pursue germline genetic modification in humans. Such a consensus would be difficult to achieve and virtually impossible to enforce.

Regulate HGGM to Ensure Safe and Ethical Use

Oversight of HGGM could be aimed at ensuring the safety of the technology, its ethical use, or both.

Under current law, the FDA may have adequate authority to effectively oversee the safety of HGGM. The agency can require review and approval of an IND for any HGGM attempt, but deliberations are not open to the public. The agency could create an advisory committee specifically to inform its review of HGGM proposals. FDA advisory committees typically include researchers, clinicians, patients, caregivers, industry, and consumers and their meetings are open to the public. Creating such a committee to consider HGGM would give the public more access to the deliberations that inform FDA decision making, and would provide FDA with expert opinion and insight regarding the public's concerns. FDA frequently makes use of such committees. For example, when scientists reported the birth of babies resulting from ooplasm transfer, FDA asked an advisory committee to consider this issue, and solicited presentations on ethics as well as safety and effectiveness.¹⁶⁹

With input from an advisory committee, FDA could develop additional guidance concerning the type of data they would require in an IND application to study HGGM. The issuance of guidance documents would be consistent with FDA's approach to other developing technologies;

indeed, FDA has issued numerous, progressively more detailed guidance documents for somatic gene therapy research to keep pace with new developments.

In addition, FDA could address the long-term outcomes of children born after HGGM and the well-being of future descendants. Longitudinal studies could be mandated federally as part of IND approval, and could receive federal funding as well. Such studies would provide critical data about potentially harmful effects of HGGM, but could raise confidentiality concerns, depending on how information is collected and maintained. In addition, the feasibility of following patients and their descendants for generations is uncertain, and current regulations would prohibit the government from mandating participation.

Any guidance FDA develops could clarify what human research subject protections it would apply to the area of HGGM and what standards IRBs should apply as well. Law professor Rebecca Dresser suggests that a new HGGM-specific human subjects research protection policy is needed.⁴⁹

In contrast to the FDA, whose processes and deliberations are largely private and focus primarily on safety and efficacy, the RAC's deliberations are public and include consideration of other ethical and societal issues. However, the RAC's current policy is not to consider germline proposals. If this policy were to

change, the RAC could function as a forum for discussing the social and ethical issues raised by HGGM, as it has for somatic gene transfer research.^{55,170}

However, even if the RAC did consider germline proposals, it no longer has the authority to approve them, with the exception of those funded by NIH. Moreover, the RAC is inherently limited in its capacity to oversee research not funded by NIH. Thus some have suggested that an alternative oversight body may be necessary, particularly to consider ethical issues related to HGGM.^{55,110}

Chief among the ethical questions about HGGM, perhaps, is the purposes for which it should be permitted. For example, HGGM could be permitted for non-medical, enhancement reasons. Conversely, HGGM could be reserved only for illnesses that are fatal or deemed serious. An entity overseeing ethical use would need to consider and define what uses are permitted under what circumstances. Drawing these lines would be challenging and enforcement probably would be difficult. An oversight body would need to stay abreast of any new proposed uses and what their implications might be.

Numerous equity and justice concerns have been raised about HGGM's impact on society. Many of these concerns implicate broader societal and policy issues and would be difficult to address through policy narrowly aimed at HGGM. Policymakers could, however,

explore alternative approaches to address these concerns such as anti-discrimination laws, better access to medical treatment, more support for individuals and families dealing with genetic diseases, and other approaches to reduce the perceived need for HGGM and concerns about its negative impact on society. While some might argue that such indirect approaches could not address meaningfully the many societal issues that have been raised about HGGM, such reforms might provide broader societal benefits.

International bodies such as the United Nations also could play a role in the oversight of HGGM by convening interested stakeholders from around the world and considering possible international treaties or other restrictions aimed at guaranteeing safe and ethical use. However, most countries outside of the United States that have chosen to address the issue of HGGM have banned it entirely, making it unlikely they would agree to a less-restrictive international model. In addition, these international entities have limited ability to enforce such restrictions.

Finally, those interested in HGGM, including scientists and prospective parents, could develop voluntary guidelines for HGGM. Such guidelines, created in advance of the technology being ripe for consideration by FDA and/or RAC, could help guide its scientific development and proposed uses. However, given their voluntary nature, these

guidelines are unlikely to satisfy those interested in enforceable governmental limits.

Questions remain about whether oversight of germline proposals *should* be treated any differently from somatic genetic modification by entities such as RAC or FDA, international bodies, voluntary societies, or a new entity in the future.¹⁷¹ On the one hand, germline modification could be seen as inherently suspect and have to overcome a presumption of being unsafe and/or unethical.^{167,172} On the other hand, the safety and ethical issues could be considered in the same manner and by the same oversight bodies that consider somatic proposals.⁵³

Encourage Innovation

Some believe that HGGM holds tremendous promise for preventing genetic diseases⁷⁵ and that society should pursue policies to promote or encourage successful HGGM in the future. Currently, governmental funding supports animal research that could be used to support an application to investigate germline modification in humans. Although not undertaken in pursuit of HGGM, this research provides data that has helped overcome some of the technical obstacles to HGGM. Increased funding for such research could provide additional data that could help lead to HGGM in the future. In addition, policymakers could consider funding research explicitly to advance HGGM techniques. However, for many Americans, new funding of HGGM research

would be profoundly disturbing,
particularly in the absence of
clearly stated and widely accepted
objectives for the uses of this
technology.

Conclusion

Despite widely divergent policy options to address HGGM, there is some agreement among experts and the public alike on several issues that will need attention in the future.

Many questions remain about the safety and potential uses of HGGM. Considerable research would be needed to demonstrate HGGM's safety, if society chooses to allow it to occur. Much is unknown about the potential market for this technology and what the effect of limitations or oversight might be on forces pushing for or against the technology. For example, is it more likely that insurers will demand that families use HGGM to avoid having children affected by genetic disease – or more likely that insurers will refuse to pay for it, leaving HGGM only in the hands of the rich who can pay for it themselves?

Constructing policy that reflects and is responsive to public opinion requires greater attention than has been paid thus far to what the public thinks about HGGM. There is a rich and robust history of deliberation about HGGM among the experts, with far less opportunity for the public to weigh in, despite many calls for more formal public engagement.

Some participants in the Center's "Babies By Design" meeting that helped inform this report expressed the view that the fears of the public have been underestimated and undervalued, even laughed at, by those at the forefront of the

debate.^{173,174} Decision making about human germline genetic modification historically has been entrusted to government advisory commissions. Sociology professor, John Evans argues that these entities require a "formally rational type of argumentation of bioethicists"¹⁷⁵ and that the tone and structure of the discussion within these government bodies precludes some from participating fully in the public debate. Evans argues that those who tend to support technologies such as HGGM, such as scientists and bioethicists, are better able to participate in such forums than those whose concerns come across as more emotionally or morally based, including theologians and those whose opposition to the technology does not fit neatly into a model of "calm unemotional logical discussions."¹⁷⁶ Thus the conclusions of government bodies may not, in the end, reflect a broad array of viewpoints.

It is clear that the "experts" and the "public" need better opportunities in which to share and compare views. Discussions of HGGM would benefit from input from more voices, including patients, families of those living with genetic disease, and organizations focused on a range of issues including civil rights, women's issues, the environment, business interests and religious concerns. In planning the Center's 2004 "Babies By Design" meeting, it became clear that few organizations had considered, or were willing to discuss publicly, what the impact of HGGM might be on their constituents. All

of these groups need a way to educate themselves and consider the possible risks and benefits of HGGM. Open and public deliberation should occur before new policies are implemented, and excellent models exist for inclusion of divergent views in productive discussion.¹⁷⁷

Although HGGM remains on the distant horizon, advances in technology are bringing HGGM from the imaginable to the possible. Thus, this is a propitious time to consider the most difficult questions about HGGM. Will we attempt HGGM – or work to ban it? What government entities are most appropriate for an oversight role – and what oversight is most appropriate? An enriched and expanded discussion that includes the "experts" and the "public" offers an opportunity to share information and understanding about the underlying values and concerns that inform our individual and collective perspectives on HGGM.

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