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Is inheritable genetic modification the new dividing line?

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1.1 Slow but clear progress in achieving gene therapeutics

The promise of gene transfer as a way to cure or ameliorate a range of genetic and acquired human diseases dates back over 40 years.[1] "Gene therapy" can be defined as the introduction of new genetic information to achieve a therapeutic goal, for instance to replace, correct, or augment parts of the recipient's genome. Generally the use of wild-type or attenuated-virus vaccines is excluded from the purview of gene therapy, although their applications may be regarded technically as forms of gene-based prevention. Gene therapeutics include gene-based immunization strategies designed to prevent or treat cancers and autoimmune disorders, which are relatively non-controversial applications that are likely to prove successful. For over 30 years, the molecular biology revolution has steadily provided tools that allow us to manipulate, synthesize, and sequence DNA, culminating in the publication of the human genome sequence in 2000.[2] There has been an accelerating rate of discoveries since the earliest sequencing of mutated genes revealed the genetic basis of many human diseases. Nowadays a month rarely passes without a new disease-causing gene being linked to one of over 4000 human diseases that have been described. But besides providing new diagnostic genetic tests and some insights into disease causation, the discovery of disease-causing genes in itself has not generally led directly to therapies.

The next logical step for the field of molecular medicine was to ask whether non-mutated versions of disease-causing genes could be used for therapy. The concept of treating life-threatening diseases with genes remains compelling in its simplicity, but implementing this idea has proven highly challenging. The problems hindering realization of the promise offered by gene therapy techniques include technical difficulties in gene delivery and control, clinical failures, and over-hyped expectations, the latter of which is shared by other areas of genetic research. However, despite these problems, there are few who doubt that one day the technology to deliver successful gene therapy will be sufficiently mature and robust to achieve widespread clinical acceptance. For many genetic

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disorders, there are no satisfactory pharmacologic or cell-based therapies, and the persuasive idea of treating the root cause of such diseases has never lost its appeal. This book addresses a question that will arise once the technical hurdles of somatic cell gene transfer (SCGT) are overcome: whether genetic modification of the human germ line and other types of inheritable genetic modification (IGM) will ever be ethically and socially justifiable.

Genes cannot function outside the context of a cell, and thus any potential gene therapy must use specific target cells as vehicles. Since stem cells are long-lived and capable of massive expansion in number, they offer an obvious, if not straightforward, cellular target for gene therapies. Assuming that medical therapy using genes is a worthwhile goal, what would be the "minimum therapeutic unit" to transfer the genetic payload, so to speak? In one sense, whole organ transplantation is a "macroscopic" version of gene therapy, insofar as organ transplantation uses tissues that contain cells, whose genes deliver a therapeutic function. These therapies have been used successfully for decades to treat particular diseases, and include transplantation of kidney, liver, lung, and/or heart tissue. For those proponents of stem cell therapy (whether involving therapeutic cloning or, less controversially, adult stem cells), a "minimum therapeutic unit" involves the transplantation of whole cells such as skin, bone marrow, or peripheral blood hematopoietic stem cells, which are commonly used to treat malignant disorders of blood cells such as leukemia. The problem confronting each of the above cellular and tissue-based therapies is immune rejection and the consequent commitment to long-term immune suppression of the recipients, which in turn makes them vulnerable to infection.

Downscaling in terms of size, those wishing to use therapies based on chromosomes or genes adopt a more reductionist approach with the aim of modifying the existing genome of the recipient's cells. Although the genetic engineering of cells could be achieved on organ-, tissue-, or cell-based levels, parsimony dictates that, all other things being equal, the smallest intervention required for success should be preferred. Of central importance to this book is the important distinction between those gene transfer procedures that could lead to inheritable changes and those that do not. Interventions that could lead to IGM consist of ooplasmic transfer, gene transfer to reproductive cells and their precursor cells, and embryonic stem (ES) cell manipulations including reproductive cloning. Current therapeutic interventions that might never be expected to lead to IGM include the whole organ transplantation procedures described above and adult stem cell therapies such as hematopoietic stem cell transplantation.

This chapter does not examine the development of, and procedures involved in, human gene transfer in detail. A number of excellent books detail technical aspects of gene transfer and stem cell technology,[3] which also are summarized in essays in this book by John E.J. Rasko and Douglas J. Jolly, and Rudolph Jaenisch.[4] However, certain highly-publicized tragedies, failures, and mistakes have taken place in the brief history of gene therapy research that provide the

historical and experimental context out of which some of the more controversial aspects of gene transfer have emerged.

Once the recombinant DNA revolution became well-established in the 1970s, early experiments in mice suggested that gene therapy might work.[5] In 1980, Martin Cline at the University of California at Los Angeles (UCLA) sought to transfect bone marrow cells from an Italian patient and an Israeli patient with a gene in order to treat their thalassemia. As has been documented, the trial was not approved (as was required) by the UCLA Institutional Review Board; there was an intention to hide the true nature of the experiment; there was no clinical or scientific follow-up of the two patients; and there were scientific reasons at the time that argued against the likelihood of success of such an experiment.[6] Hence, Cline received severe academic punishment and ceased research in this field. This first non-viral human gene therapy trial led to substantial scientific and public furor that eventually forced the United States federal government to expand the responsibilities of the Recombinant DNA Advisory Committee (RAC) to include human gene therapy. Eventually, approved clinical trials were initiated in 1990. The first involved a 4-year-old child, Ashanti de Silva – who suffered from severe combined immunodeficiency (SCID) – being re-infused with her own gene-modified cells; and the second involved the use of gene-modified tumor-infiltrating blood cells aimed at treating cancers. Since then, over 1000 clinical trials have been undertaken worldwide involving thousands of individuals.[7] To date, no gene transfer procedure has been approved by the Food and Drug Administration (FDA) for use in the U.S.A. However, in 2004 China approved production of an anti-cancer gene therapeutic.[8] The biotechnology investment market does not tolerate delays and failures well, and the peak of over 100 biotechnology companies with a focus on gene therapy has dwindled to about one-fifth of these original numbers.

Cline's ethically- and scientifically-suspect gene transfer experiments provided an inauspicious start for the field, but worse was to come when the first fatality directly attributable to a gene therapy trial was reported. In 1999, 18-year-old Jesse Gelsinger, who suffered from a rare enzyme disorder affecting the liver, but who had been relatively healthy before participating in the trial, died soon after receiving a high dose of experimental adenovirus designed to provide gene therapy. His death shocked the gene therapy field and led to the suspension of all gene therapy trials being conducted at the time. However it was not the death of a human volunteer *per se* that caused the storm, but subsequent revelations regarding problems with trial design, informed consent, and the lack of medical caution exercised at the time of gene delivery, as well as the compromise of the chief investigator who had significant financial incentives if the trial was successful. Six years after this death, a settlement was reached between the U.S. Justice Department and the chief investigator of the trial.[9]

The final example highlights the greatest clinical achievement in gene transfer to date, which was tempered by profound disappointment and was described by

a leader in the field as "The Best of Times, The Worst of Times."[10] In a trial initiated in France, over 10 young children suffering from SCID have been treated with their own gene-modified hematopoietic stem cells because they were not able to receive a potentially-curative bone marrow transplant from a matched donor. Within a short time, it was clear that the clinical and cellular response to this gene therapy was close to miraculous, leading to the successful restoration of the immune system in recipients.[11] After a period of re-invigoration and rekindled optimism fueled by this result, the field was struck a serious blow when it was revealed that leukemia had developed in a minority of the experimental gene transfer trial participants.[12] Not only was it shown that the gene transfer itself had led to the leukemias (due to induced mutations caused by the viral gene transfer technology), but that this technical problem might affect other promising forms of experimental gene transfer. Similar trials were put on hold owing to these safety concerns until a review of the technology indicated that the unexpectedly high occurrence of leukemia was likely to be unique to this specific trial.[13] After 15 years of clinical trials, this seeming "triumph" of gene therapy has become another example of the difficulties that this novel technology has continued to experience. Despite the serious side effects, however, the French SCID trial was the first example where not only was the specific root genetic cause of a disease diagnosed, but a gene therapeutic was successfully used to treat it.

1.2   Are there "natural" precedents for IGM?

Scientific discussions about the future of gene therapy often focus on the technologic problems that have occurred in these early trials, as reviewed above. But most ethical and social critiques of gene therapy have focused on the problematic nature of IGM, and objections to it often stem from ideas about what is "natural" and arguments against intentionally causing genetic changes in future generations. However in recent years there has been what might be considered to be a provocative "precedent" for IGM in the demonstration that there are now human babies who have three biologic parents as a result of medical intervention.

In 2001, a reproductive medicine group in the U.S.A. reported the existence of two 1-year-old children who inherited genetic material from three unrelated genetic "parents".[14] In a follow-up letter, the researchers noted that 16 babies had been conceived by the same ooplasmic transplantation method.[15] In 2002, an FDA Advisory Committee reported at least two dozen births using this method that have been supervised by three fertility clinics since 1998.[16] This experimental method of ooplasmic transfer is designed to improve successful pregnancy rates for couples who are infertile due to recurrent implantation failure. The proponents of ooplasmic transfer argue that unknown factors are defective in the cytoplasm of some oocytes, leading to loss of viability of the pregnancy. The "therapy" involves the introduction of cytoplasmic material from a healthy

donor oocyte, which is intended to provide beneficial factors and sub-cellular components, including mitochondria. However, mitochondria carry their own unique DNA, which encode almost 40 known genes not found in the nuclear DNA. The mitochondrial DNA (mtDNA) represents only one-tenth of a percent of the known genes present in cells, but abnormalities in it can transmit approximately 50 genetic diseases (e.g., Leber's Hereditary Optic Neuropathy).

What is often neglected in descriptions of classical Mendelian inheritance is that mtDNA is almost completely (about 99.99%) inherited from one's mother.[17] Because mitochondria must self-replicate independent of somatic nuclear division, and because they do not participate in the careful segregation that occurs when nuclear chromosomes replicate, they are apparently randomly allocated to daughter cells during mitosis. Thus children produced as a result of ooplasmic transfer followed by *in vitro* fertilization have one set of nuclear DNA each from the mother and the father, as well as a mixture of mtDNA from the mother and the woman who donated the cytoplasm, a phenomenon known as heteroplasmy. The female descendents of children conceived by ooplasmic transfer would receive the genetic inheritance of three parents. Such a reproductive intervention produces a situation that is scientifically akin to the ultimate aim of IGM, namely to provide therapy for, or prevent, genetic disease by the addition of new genetic material from a third source. In late 2004, an application was submitted to the U.K. Human Fertilization and Embryology Authority to perform a variant of ooplasmic transfer in which the nucleus from a fertilized egg from a woman with a genetic disease carried by her mitochondria would be transplanted into an enucleated donor egg. Thus inheritance of the woman's faulty mitochondria might be avoided, but such nuclear transfer would intentionally lead to children with three genetic parents.

Perhaps even more shocking for those who hold dear one's "right" to a "relatively fixed" genome (i.e., one inherited from two parents) is the fact that heteroplasmy occurs naturally in most animals, including humans.[18] Although the mechanism for heteroplasmy is far from clear, its existence has famously been used to resolve a genetic discrepancy in descendents of the Tsar Nicholas II who was slaughtered along with his Tsarina and their five children during the Bolshevik uprising in 1917.[19]

The simple fact is that, through ooplasmic transfer, new genetic information has been purposefully introduced into the germ line of humans, and at very least a scientific precedent has been set for intentional transfer of genes under some circumstances. Since mtDNA represents only a tiny percentage of the total genome, some have dismissed the precedent set by ooplasmic transfer as a "red herring" in terms of the ethical and social issues raised by other types of IGM. But such arguments neglect the overwhelming attention paid by some regulators and ethicists to the problematic nature of the inadvertent addition of even one gene to the genome, let alone IGM intended as therapy. Indeed, the FDA has called ooplasmic transfer a "*de facto* germ-line gene transfer"

technique and, along with the governments of China and the U.K., has effectively banned it.[20] Without doubt this technology remains experimental and the possibility that its use may predispose children to an increased risk of genetic abnormalities needs to be carefully tested using preclinical models and monitoring of the health of children already conceived in this manner.

The facts that heteroplasmy occurs naturally in human populations and may be experimentally introduced by ooplasmic transfer highlights a question, and a theme, of this book: is IGM really a dividing line that should not be crossed or even considered? The question considered in various ways by the authors of the essays in this book is whether IGM is intrinsically morally objectionable, and what limits (if any) should be placed on it.

1.3   Why focus on "IGM"?

Early in this project, we decided to define the types of genetic interventions to be examined in terms of their intended and potentially-realizable effects (i.e., IGM), rather than in terms of the biologic materials or means used in their application (e.g., germ-line gene modification). This distinction arose because we consider intentional inheritability to be the essential characteristic of the interventions in question, which distinguishes them from other types of interventions that have been argued to be less ethically problematic (e.g., SCGT), and that the tissues and means of mediating them are secondary aspects of the process.

The term "IGM" hence indicates those procedures where the material and means used have the capacity to facilitate the intended transmission of particular genetic alterations to future generations. If our primary focus was on the secondary aspects of the interventions (i.e., the tissues targeted for modification), our considerations could have been confounded by the definitional problems that have characterized discussions about intentional IGM of humans for the last 20 years, namely, the blurring of the boundaries between somatic and germ-line tissues, and between intentional and inadvertent effects. For example, we might have argued about whether ooplasm does or does not constitute part of the germ line, and we might have concluded that it does not, probably on the basis that its genetic content is too small to contribute significantly to the total genetic make-up of an individual. But, as discussed above, the recent history of assisted reproductive technology makes this question difficult to answer, as it is not clear that the answer to it lies in quantitative estimates of genetic contribution.

In choosing to use the term "IGM" instead of "germ-line gene modification," we are not rejecting the idea of the "germ line" in any sense. The germ line has a definite existence and is a clearly definable biologic tissue (despite its various other interpretations). It constitutes the reproductive cells of an organism (i.e., the germ cells, including their products, and gametes) that can transmit genetic information from one generation to the next. The germ line has the major role to play in inheritable genetic interventions and is essential to discussions about them.[21]

In rejecting the term "germ-line gene modification" for general use in this book, we hope to prevent confusion between the aims of IGM and of germ-line engineering, which are often quite distinct. For example, one could aim to engineer the germ line for the sole purpose of introducing a genetic change into every cell of an individual (while controlling tissue-specific expression) without wishing for the change to be inherited by his or her progeny. In this situation, one would have to figure out how auxiliary chromosomes could be blocked "from passing through the sexual cycle to the next generation."[22] The rationale behind this aim is that rapid development of the science means that each new generation will want to have more up-to-date versions of the change and not be tied to a fixed version embedded within it.

Alternatively one might aim to engineer the germ line for the purposes of introducing a genetic change into every cell of an individual (while controlling tissue-specific expression) and *want* the change to be inherited by his or her progeny. In this situation, one would have to determine how auxiliary chromosomes could be consistently passed through the sexual cycle to the next generation. The rationale behind this aim is that each new generation would not have to undergo modification (i.e., the disease phenotype in question would be removed from future generations). These two situations show how useful the term "germ line" is, and at the same time how confusing the term "germ-line gene modification" can be (at least as it has been used in the literature to date), and how IGM more precisely describes the subject of this book.

Based on our criterion of intentional heritability, IGM is a biomedical intervention (molecular, genetic, or cellular) that alters the set of genes that a subject has available to transmit to his or her offspring. It includes all interventions performed at an early enough stage in an organism's development to have inheritable effects on its germ cells (gametes and gamete-forming tissues). Audrey Chapman and Mark Frankel, among others, have relied on this definition when discussing these types of interventions.[23] Thus this book focuses on intentional IGM by the application of techniques such as the use of artificial chromosomes, viral vectors, oligonucleotides, cell fusion, and sub-cellular component transplantation (e.g., mitochondria). Other potentially powerful mediators of IGM such as social and cultural practices, alteration of the environment (e.g., by nuclear radiation), and side effects of non-genetic treatments for infertility or other diseases (e.g., by chemotherapeutic agents) are not considered. Germ cell and ES cell modification constitute the major IGM subtypes.

1.4 What about the "dividing line"?

Discussions about the potential for biotechnologic alteration of human germ cells and whole human beings reflect concerns about benefits, risks, safety, and consent among other ethical, biomedical, and social issues. They also reflect a deep concern about the destiny of "human freedom, equality, and dignity,"[24] as

well as human identity and where the limits of human intervention should be drawn. They are a sign of deep fears that hitherto natural attributes will be brought "within the sphere of social control, and thereby within the domain of justice."[25] Hence commentators have traditionally focused on constructing dividing lines between what should and should not be permissible, and on determining the conditions that must be satisfied before these lines might be crossed, if ever.

All discussions are partly shaped by the language used in them, and debates about intentional inheritable genetic interventions are no exception, as overt "dividing line" language has been used for over 20 years.[26] Dividing lines have been constructed, and then invariably deconstructed, between the natural and the social or technologically-engineered; the somatic cell and the germ line; enhancement and therapy; the intentional and the inadvertent; and humans and other species. The language of the "dividing line" is often accompanied by that of the "slippery slope" – the idea that once a technology has begun to be implemented, its application cannot be controlled, and some dividing line will inevitably be crossed between what is moral and what is immoral. The dividing line was further blurred by the appeal of some commentators to the "principle of double effect," whereby ethical difficulties are not associated with crossing moral lines, so long as the "crossing" is unintentional, or a sort of side effect of another, morally just action.[27]

Science has also blurred these lines, sometimes by crossing them in unexpected ways. The somatic cell/germ line divide has been crossed by somatic cell nuclear transfer (SCNT) in animals;[28] the enhancement/therapy divide is becoming untenable as enhancement and therapy are becoming less distinguishable as disease is being constantly redefined;[29] the intentional/inadvertent divide is not sustainable in terms of moral consequences;[30] and there does not appear to be a unified definition of species.[31] The problem with "dividing line" language is that it polarizes debate and competing, diametrically opposed, positions are compared with one another, often in isolation from other possible combinations of diverse positions.

It is our hope that while use of the term "IGM" is unlikely to fully dissolve the barriers to constructive discussion, it will invoke a different type of dividing line that facilitates social, ethical, and biologic assessment of intentional inheritable gene interventions by allowing clear distinctions between targets, and tissues, means, intentions, effects, and consequences, and their inter-comparison, without attempting to "solve the moral questions by artful redefinition or by denying to some morally crucial element a name that makes clear that there is a moral question to be faced."[32] In using the term "IGM," and even in grounding this book at the outset with technical and scientific explorations of these and related technologies,[33] we have no desire to create a new barrier to discussion by "subordinating social and ethical issues to technical and scientific debate in the regulatory arena."[34] At the same time, we support Katherine

High's wise counsel that we must "stay grounded in science and the realities of drug development if we wish to develop novel therapeutics."[35]

The term "IGM" conveys a change in focus within the field of gene transfer research from the question of "can we find a disease in which we can justify attempting [IGM]?", to the question of "can we use the new tools to identify a safe basis from which to proceed?"[36] It also emphasizes the need to move towards using the more ethically and technically appropriate language associated with experimental trials rather than "therapy" language, particularly given the nascent status of this field. We generally avoid using the term "germ-line gene therapy" (except where used in its strictest meaning to indicate something that is actually intended to be therapeutic) in part because human IGM, at this stage, is experimental. But in addition, if IGM were to be implemented on a widespread basis, in many cases its primary aim would be to prevent a genetic condition in a potential, future individual, rather than to treat a disease condition in the individual receiving the transferred gene(s).[37]

1.5   IGM as a tool for ethical debate

Against this background, the essays in this book are designed to examine ethical and policy issues associated with IGM and related technologies using a range of disciplinary approaches. Rather than viewing ethical debate as narrowly grounded in science, the biomedical/clinical context, or moral philosophy, the contributors to this book explore ethical issues within their wider scientific, political, social, cultural, and legal contexts. There is considerable confusion amongst members of the public (and even many expert commentators) as to the connections between technical/biologic and ethical issues in this domain, and many essays in this book attempt to disentangle this new Gordian knot.

Several essays take the form of thought experiments, imagining a range of potential futures and how we might react to them, or perhaps prevent them from occurring. For instance, Peter Singer introduces the volume using Robert Nozick's metaphor of the "genetic supermarket" to lay out a framework that can be used to examine moral questions related to genetic technologies for enhancement.[38] Singer also questions what counts as therapy and as disability, in order to project for us a picture of a future where IGM and other genetic technologies might become more widely available, for those who can afford them. The crucial questions then become not whether or not we should permit enhancement, or what counts as therapy, but instead whether these technologies should be privately or publicly controlled, and by what mechanisms. The themes of public policy and control in a not-so-distant future are echoed in Roberta Berry's essay, which claims that "bioethics can speak helpfully to politics about gene transfer by explicating both the past and an imagined future."[39] To reflect in a useful manner on any potential future for IGM requires a solid grounding in our past

history of uses and abuses of genetic medicine, eugenics, and genetic coun-selling, as well as clear reflection on what our societal norms have been, and what norms should be furthered in public policy.

Françoise Baylis and Jason Scott Robert imagine a different future, one where intentional IGM has become widespread, in order to consider how some fundamental boundaries, or perhaps dividing lines, might be crossed.[40] They use the concept of "radical rupture" as a heuristic device to explore the ways in which volitional IGM could cause major disruptions to our concepts and ideas associated with genetic inheritance, genetic legacy, and species. Eric T. Juengst, in contrast, examines a future that is already here: one of strange alliances forged on the basis of shared commitment to prohibiting IGM.[41] He argues that although talk of "preserving the species" (such as that used in draft legisla-tion promoted to the United Nations) may initially seem attractive, it smuggles in dangerous, essentializing assumptions not only about the human species and genetics, but about how we assign moral rights. As he argues, "The human gene pool, unlike the sea, has no top, bottom, or shores: it cannot be 'preserved.' The reservoir of human mutual respect, good will, and tolerance for difference, however, seems perennially in danger of running dry. *That* is the truly fragile heritage that we should work to preserve in monitoring genetic research on behalf of the future." Denis Kenny undermines a different set of dangerous assumptions, namely those that envision our universe as static and nature as given, with human beings having no right to intervene in this order in any sig-nificant ways.[42] Instead, he advocates a notion of a "creative universe" with an alternative cosmology, one that might lead us to conclude that in fact IGM is part of our responsibilities to ourselves and this universe.

The fragility of various concepts – notably disease, normality, and human identity – is taken up in several essays, most notably by Jackie Leach Scully in her examination of IGM in relation to disability.[43] She argues that we must look at the ethical and social issues about these technologies from a disability perspec-tive, not only because disabled and chronically ill people are likely to be those for whom IGM and related technologies will have the greatest and most pressing impacts, but also because disabled people have novel perspectives particularly with regard to identity and other fundamental aspects of human life. Isabel Karpin and Roxanne Mykitiuk[44] take a feminist legal approach to investigate leg-islative controls on reproductive technologies and particularly those associated with genetic modifications which provide limits on scientific innovation in order to ensure safe and ethical research, but also reveal how such legislation and its language is attempting to dictate what is to count as "normal" reproduction. Thus as also argued by Rosemarie Tong,[45] rather than rehearsing the usual bioethical debates, disability and feminist perspectives should lead us to recast the very questions that we ask, and to whom we address those questions.

Indeed, rather than addressing our questions about genetic technologies, IGM, and other bioethical dilemmas solely to bioethical experts or policy