Germline gene therapy: its time is near

Morris Fiddler¹ and Eugene Pergament²,³

¹School for New Learning, De Paul University and ²Section of Reproductive Genetics, Department of Obstetrics and Gynecology, Prentice Women's Hospital and Maternity Center, Northwestern University School of Medicine, 333 East Superior Street, Chicago IL 60611, USA
³To whom correspondence should be addressed

For almost two decades, bioethicists, legal scholars and writers in the popular press have debated the ethics and consequences of gene engineering and gene therapy. Much of the discussion has focused on germline therapy, that is, artificially-designed alterations in the human genome that would not be limited to somatic tissues but would be passed on to succeeding generations. Currently, strategies for gene therapy that would result in alteration of the germline are not considered appropriate. Scientists and health professionals have become well-sensitized to the issues and arguments concerning germline therapy but, for the most part, have not participated openly in the debate on its potential benefits and harms. Based on existing technologies in human reproduction and on expected advancements in gene therapy technology, we believe that the debate on germline gene therapy must now also become the purview of scientists and health professionals. We have in fact already advanced beyond the theoretical considerations that have fuelled debate on germline gene therapy and must now begin to examine the issues based on clinical experiences. Indeed, for the popular press, prenatal genetic diagnosis, including preimplantation diagnosis via embryo selection (e.g. Handyside and Delahanty, 1993), is considered a form of germline gene therapy, and 'there (has been) not a murmur of dissent' (Lyon and Gorner, 1995).

Critical assessment demonstrates rather convincingly that perspectives favouring the pursuit of germline gene therapy hold sway over those against. An overview of the full range of positions expressed in support or opposition to germline therapy supports this conclusion. The primary arguments in opposition to germline therapy (Juengst, 1991) can be reasonably summarized into five categories: (i) uncertainty and risk; (ii) 'slippery slope', particularly in regard to 'genetic enhancement'; (iii) lack of consent by future generations; (iv) inappropriate allocation of health resources; and (v) intrinsic immorality.

While uncertainty and risk may accompany the application of gene therapy to the germline, it is difficult to reconcile singling out germline gene therapy as any more risky than the introduction of other interventions, such as pharmaceutical agents, invasive procedures, or any other technologies having an impact on health, now and into the future. It is more than likely that by the time gene therapy trials that could affect future generations through alteration of the germline are approved, we will have accumulated a significant level of experimental data on its impact in model systems. However, in and of itself, the fear of uncertainty and of risk seem hollow arguments in contrast to a positive call for agreement on guidelines to assess, limit, and address uncertainties and risks (Zimmerman, 1991; Lee, 1993).

Concerns over the 'slippery slope' to 'genetic enhancement' is a reasonable outgrowth of past experiences with eugenics, e.g. immigration and sterilization laws in the US; the philosophy and practices of Nazi Germany in the 1930s and 40s. We, however, cautiously suggest that 'genetic enhancement' is neither an easy term to define nor a concept to be avoided at all costs. What if resistance to viral and bacterial infections, including human immunodeficiency virus (HIV), could come in the form of a gene(s)? Would it not make sense to provide this gene(s) to an individual and, through systemic delivery, to his/her offspring? Why not offer resistance to gout through the introduction of the gene for uricase, an enzyme absent from the human complement (Caskey, 1992)? Why not provide members of cancer families the genetic means to prevent not only developing cancer but also passing on the mutated gene to succeeding generations, e.g. the BRCA1 gene in familial breast cancer. Although this is not a blanket advocacy of genetic manipulation for enhancement purposes, we do urge that 'genetic enhancement' be treated in the same context as 'uncertainties and risks' and that it be rationally investigated.

Concern over allocation of resources is ultimately an expression of societal values and priorities and, as such, is an outcome rather than an ethical premise. When approached as a question of whether germline therapy is, or promises to be, a more effective therapeutic strategy than other approaches to health care, the issue of 'allocation of resources' is reduced to a judgment call; this is not unlike other decisions made in democratic societies in which health care concerns must be prioritized. The rationale for limiting resources cannot be based on a rejection of new knowledge and science and, consequently, scientists and health professionals must be continuously cautious as to who and what perspectives are influencing social and economic policies.
This brings us to the concerns over lack of consent by members of future generations to alterations in genetic inheritance, changes that permit them to survive when they otherwise may not have. Certainly, we have phrased this issue in the bias of our position; however, we believe that this is the realistic way future generations will view germline gene therapy. We rarely ask questions of future impact with as much stridency when addressing social and cultural changes in our society that are likely to be more widespread and pervasive than any current vision of germline gene therapy. Also, it should be recognized that the technology that allowed for genetic transformations in one generation leading to non-consensual changes in subsequent generations will not only be available for reversal or other alteration, but will more than likely be further refined in future generations (Ledley, 1993; Pergament and Fiddler, 1996).

Although these are not the only arguments against the development and application of germline gene therapy, they are representative of the major positions of disapproval. We believe that the counter-arguments convincingly refute any objection to the advancement of germline gene therapy, however, we also believe that a clear rationale for its pursuit is as important. The overriding perspective of scientists and health professionals should be that the pursuit of germline gene therapy is not any different from other decisions affecting future generations (Moseley, 1991). There are at least four specific rationales justifying undertaking germline gene therapy: (i) medical utility; (ii) medical necessity; (iii) prophylactic efficiency; and (iv) parental autonomy.

A major mission of medicine and of the medical profession is to provide the public with technologies that can cure or prevent genetic diseases, particularly pathology that results in disability, physical and mental pain, or premature death. This is its moral place in society as well as the source of its essential contribution to improving the welfare of society. From a utilitarian perspective, gene therapy is likely to be the most successful and most useful approach to preventing or correcting pathology and therefore pursuing gene therapy becomes nothing less than a categorical imperative. The possibility of gene therapy providing a true cure for many genetic disorders, and its capacity to prevent the transmission of disease-causing mutations, thereby preventing the need for repeated somatic therapy generation after generation, justifies making germline gene therapy an imperative to be developed, applied and refined. Furthermore, medicine would not only be fulfilling its social and scientific mandate but would also be providing parents at high reproductive risk for genetic disease an option for the birth of an infant with markedly improved prospects for a healthy life. It is, therefore, in the interests of all of us to support germline gene therapy whatever through whatever means is suitable and acceptable to, and for, the common good (see also Pergament and Fiddler, 1996).

For many years to come, as best we can tell, germline gene therapy will be discussed in terms of single gene replacement or alteration for Mendelian inherited conditions. At this time, concern about gene therapy applied to social behaviours, deviant personalities, and enhanced human development (e.g. skills in music, mathematics or athletics) appear to be ill-conceived and deliberately inflammatory to the debate. We do not know as yet how far we will be able to carry gene therapy into the unresolved complexities of the human genome. But, unless we proceed with conviction, albeit with great caution, we certainly will have failed our responsibilities as scientists and health professionals if we avoid this opportunity for reasons derived from ethical premises grounded in fear and inexperience. It is entirely possible that as we continue to integrate an understanding of our biology into our social and spiritual dimensions, one of the truly great repercussions of this new technology called gene therapy will be a widespread reformulation of our moral assumptions. Until then, germline gene therapy is likely to be considered as just another incremental addition to our capacity to improve our health and that of our children. And, perhaps, that is the best way to think about it.

References


