

SCIENCE AND SOCIETY

The ethics of human gene transfer

Jonathan Kimmelman

Abstract | Almost 20 years since the first gene-transfer trial was carried out in humans, the field has made significant advances towards clinical application. Nevertheless, it continues to face numerous unresolved ethical challenges — among them are the question of when to initiate human testing, the acceptability of germline modification and whether the technique should be applied to the enhancement of traits. Although such issues have precedents in other medical contexts, they take on a different character in gene transfer, in part because of the scientific uncertainty and the social context of innovation.

Human gene transfer involves the application of genetic sequences or genetically modified organisms to human beings for investigational or therapeutic ends. Almost 20 years after the first human gene-transfer experiments, over 1,300 clinical studies in 28 countries have been registered on the [Journal of Gene Medicine database](#). Chinese authorities have licensed the first ever genetic medicines¹ (although what this means precisely will be discussed further below), and gene transfer techniques seem to be on the cusp of becoming standard care for certain patients with rare immunological disorders² (TIMELINE).

However, few areas of research have faced as much adversity and controversy, an indication of which can be gathered from the recent headline: “Gene therapy: cursed, or inching towards credibility?” in *Nature Biotechnology*³.

Human gene transfer presents several distinctive ethical challenges. First is the question of when, and in which patient population, to initiate human testing — how is risk assessed, what level of risk is deemed to be acceptable in this context and who should decide on these matters? Second, the approach towards clinical application (licensure) has raised underappreciated questions about risk and benefit, access to treatment and the provision of medical care across national boundaries. The final two unresolved issues are the application of gene transfer to germline tissues (whether intentional or not) and towards cosmetic ends (genetic enhancement).

What follows is a review of these main ethical challenges; other important issues are discussed briefly in BOX 1. I argue that the technical and social complexities surrounding human gene transfer present

distinctive ethical and policy challenges that justify multilayered oversight mechanisms, and restrictive approaches to cosmetic or germline gene transfer.

Protecting volunteers in early phase trials

In 1982, the US President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research issued a report examining the application of genetic engineering to human beings. It concluded that “therapeutic applications now being planned are analogous to other forms of novel therapy and can be judged by general ethical standards and procedures, informed by an awareness of the particular risks and benefits that accompany each attempt at gene splicing”⁴.

If, indeed, somatic gene transfer (sGT) represents a natural extension of already existing medical interventions, how might its clinical translation present distinctive ethical challenges?

“Gene transfer has often been characterized as permanently 5 years away from clinical application.”

Assessing risk and uncertainty. The most conspicuous ethical challenge is the assessment and interpretation of risk. Early phase clinical trials have caused two deaths — one in a trial in which adenoviral vectors were delivered to volunteers with [ornithine transcarbamylase deficiency](#)⁵ (BOX 2), and the other in an *ex vivo* protocol that used retroviral vectors on children with X-linked severe combined

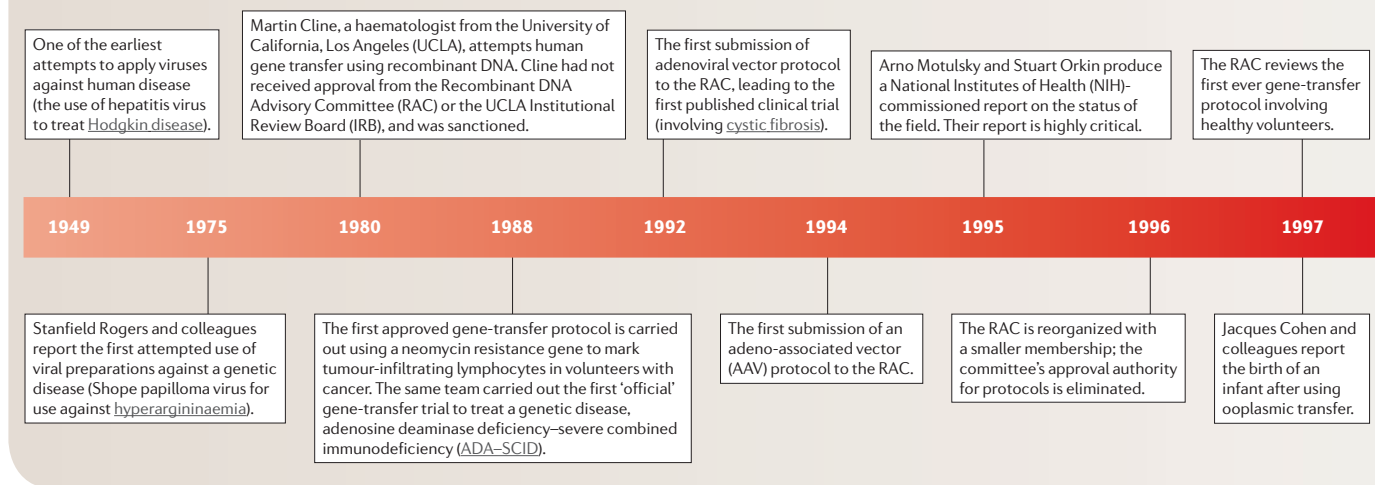
immunodeficiency (X-SCID). The latter death was caused by a leukaemia; since then, three other children in the study have also developed leukaemias.

What distinguishes the risks of sGT trials from those for conventional drugs is not so much the level of risk — for example, gene transfer compares favourably with conventional cytotoxic drugs used in cancer⁸ — but rather their level of complexity and of uncertainty^{9,10}. Adverse events encountered in the ornithine transcarbamylase deficiency and X-SCID trials were not anticipated, in part because of the relatively primitive state of the animal models and toxicology assays that were used in preclinical safety assessment. For example, there is currently no satisfying explanation for why a trial using nearly identical conditions as the aforementioned X-SCID study reversed the disease without apparent malignancies¹¹ (or, at least, with adverse outcomes occurring on a different time scale; as this Perspective went to press, a child in the latter X-SCID protocol was reported to have developed leukaemia, bringing the total to five).

Furthermore, even though numerous trials involving retroviral vectors have been carried out, there is no widely accepted system for quantifying the risks of insertional mutagenesis¹². Other trials have also raised unexpected safety concerns — although, thankfully, without causing permanent or serious harm. For example, rises in serum transaminases and vector contamination of semen occurred in a trial that was designed to test the hepatic administration of AAV vectors for the treatment of [haemophilia B](#)¹³. Neither of the adverse events were predicted in prevailing animal models. Thus, although all clinical trials involve uncertainty, the levels are likely to be greater in the context of novel interventions such as gene transfer.

When to begin human clinical trials. A second and related question is when to initiate human testing. Later stages of clinical research have a ready-made ethical response in clinical equipoise: this refers to a situation in which the expert medical community is uncertain as to the comparative therapeutic merits of different agents being tested in a controlled clinical trial¹⁴. Yet equipoise applies awkwardly, if at all, to non-controlled studies where the main objective is safety testing. Although gene transfer researchers have often struggled with deciding when to launch first-in-human trials, neither they, policy makers, patient advocates nor ethicists have articulated a coherent

Timeline | The history and status of gene-transfer ethics



framework for confronting this question. In my view, the absence of such a framework presents one of the most striking pieces of unfinished business for research ethics. This issue is particularly visible in gene transfer, because a large proportion of studies are exploratory (that is, aimed at testing the feasibility of a strategy) or Phase 1.

Another set of questions concerns the justification of risk in gene-transfer studies. Influential ethics codes, such as the Declaration of Helsinki, state that any clinical study must have a favourable balance of risks and possible benefit. The latter is divided into two broad categories: benefits for the human volunteer (for example, the therapeutic value of the study) and benefits for society (for example, the scientific value of the study). For early phase trials, value has been conventionally defined in terms of the ability of a study to yield the information that is necessary for a later-stage trial. But as numerous commentators have pointed out, the uncertainties and technical hurdles for successful gene transfer are large, and the relationship between preclinical and clinical studies tends to have a more iterative character: clinical studies often stimulate further animal investigations, which in turn provide the basis for new studies in human beings¹⁵. This situation raises a series of questions at the ethical and scientific interface: how can gene-transfer clinical studies be designed to produce more powerful biological insights? Are gene-transfer clinical studies maximizing their scientific potential? When clinical and scientific objectives conflict, as they often do, how should

they be balanced? The key to answering the latter question is in ensuring that diverse stakeholders are represented in risk deliberations. For example, researchers (and ethics committees) might solicit input from research and patient advocates, or the broader scientific and clinical communities. In addition, full publication of preclinical studies before trial initiation helps to ensure that different stakeholders can form independent judgments about the value and risks of a trial¹⁶.

Contextual issues. Another set of ethical challenges in translating gene transfer, as with other novel medical interventions, concerns the social and economic milieu of research. Many early phase gene-transfer trials bring together a potent mixture of desperately ill research subjects, ambitious (and sometimes financially invested) clinical champions, biotechnology firms, engaged disease advocates and news media. These factors have at times produced a turbulent dynamic in which concepts are rushed into trials, preclinical and clinical results are oversold, research efforts are fragmented and adverse events go underreported.

Taken together, novel sGT research protocols each present multiple ethical and technical difficulties. Are conventional ethics review committees up to the task of oversight? Several countries, including the United States, the United Kingdom, Australia and the Netherlands, maintain centralized review bodies for sGT studies. Some have criticized these bodies for avoiding fundamental ethical questions, such as

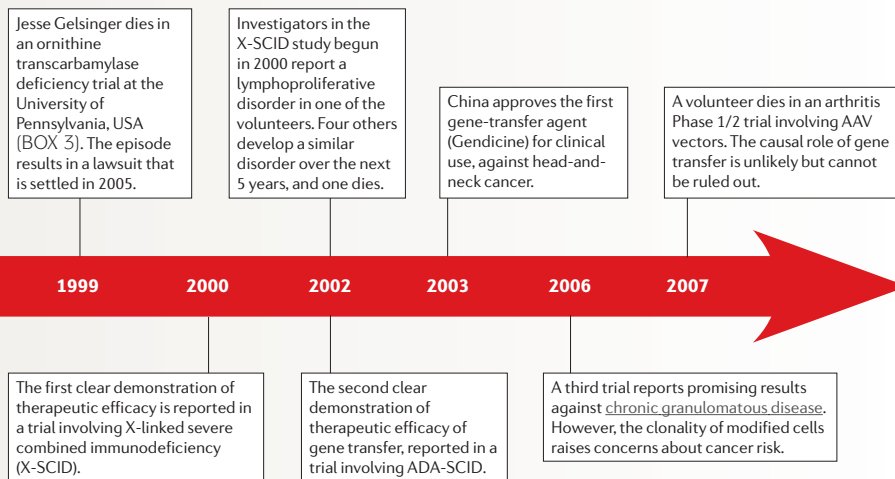
whether modifying germ tissues is ethical, and for focusing instead on conventional issues of safety and consent¹⁷. However, in the United States at least, the Recombinant DNA Advisory Committee (RAC) performs numerous functions that enhance the capacity of local review structures while mitigating problematic dynamics mentioned in the previous paragraphs¹⁸. For example, the RAC has a system in place to allow the reporting of adverse events, organizes conferences aimed at categorizing knowledge on safety or study design and is committed to almost total public transparency.

Entering clinical application

Gene transfer has often been characterized as permanently 5 years away from clinical application. Notwithstanding the problems encountered in translating sGT (BOX 3), there are indications that the technology is slowly progressing towards licensure. For example, in the 1990s only four Phase 3 protocols were submitted for review to the RAC. From 2004 to 2007 inclusive, the number is ten, according to the [Genetic Modification Clinical Research Information System \(GeMCRIS\) database](#).

Assessing risk before and after licensure.

At least three sets of ethical challenges have been raised by the approach of gene transfer into clinical practice. The first concerns the level of risk and evidence required of a novel category of intervention. Take the example of retroviral gene transfer for X-SCID. On the one hand, SCID patients who lack donors with matched human leukocyte antigen (HLA) face a highly morbid prognosis.



On the other hand, current sGT strategies against X-SCID carry serious risks. At what point should regulatory agencies decide that the safety issues are well enough understood to warrant licensure of a product¹⁹?

A different set of post-licensure questions has already been hinted at: because many sGT interventions involve continuous, lifelong exposure to a transgene and vector, certain side effects are not likely to become manifest within the time scale of a clinical trial⁹. The high degree of uncertainty surrounding latent sGT risk might justify the establishment of a more robust system of post-marketing surveillance for stable sGT interventions.

The challenges of cost and access. A second set of looming challenges is access. Advocates of sGT often present the approach as a low-cost alternative to chronic drug treatment regimens. Less commonly acknowledged, however, are the many serious obstacles to improved access that are particular to sGT. First, sGT involves extraordinarily high development costs. Second, many sGT strategies target orphan diseases (that is, diseases that are very rare), which involve notoriously expensive treatments. Third, one-time interventions concentrate expenditures at the time of initial treatment, rather than spreading the cost across the course of an illness^{20,21}. Together, these factors limit the extent to which sGT can deliver on its potential to improve domestic and global treatment access.

Consider the case of severe haemophilia. Defenders of sGT trials conducted in the developing world argue that a durable,

one-time procedure would obviate annual patient expenditures on factor-replacement therapy, which currently costs US\$60,000–\$150,000 (REF. 22). However, one news article estimated that Avigen, which was pursuing an AAV-based treatment for haemophilia B, would price its product at \$400,000 per shot, with each injection lasting “several years”²³. Although this might produce cost savings, it seems unlikely to markedly improve access.

Globalized gene transfer. A third and related set of issues is the globalization of sGT. Until recently, sGT research was confined to Europe, North America, Japan and a few other high-income countries.

However, countries such as China, Brazil, Mexico and the Philippines are increasingly pursuing their own sGT research programmes. Although English-language information is sketchy, the Chinese experience provides some hint of issues confronting a globalized sGT.

The first issue concerns the ethics of clinical testing. According to some reports, one reason gene transfer cancer research has thrived in China is the easy availability of a “large number of highly cooperative patients” whose cancer treatments are not covered by the Chinese healthcare system²⁴. However, a good many of the beneficiaries of this research (assuming these interventions are efficacious) are, at least for the present, medical tourists whose countries of origin have not licensed the intervention²⁵. A second concern is the global marketing of products for which clinical efficacy is unproven. The products approved in China were licensed on the basis of surrogate rather than clinical responses, and the Chinese State FDA is said to maintain “looser efficacy requirements”^{24,26}.

Germline gene transfer

Germline gene transfer (gGT) — that is, the genetic modification of tissues that are passed on to a recipient’s progeny — presents an especially contentious set of ethical questions. First, is it ethical to inadvertently modify the germ line in the process of pursuing sGT? Second, is gGT ethically appropriate when applied to eliminating serious diseases or for enhancement purposes?

Box 1 | Other major ethical issues in gene transfer

Biosecurity

Many gene-transfer strategies involve the genetic manipulation of viruses. Gene-transfer investigators have also been pressed into action in biodefence research. Both research areas raise a series of ethical challenges surrounding public health, dual-use applications, security and secrecy⁵¹.

In utero gene transfer

Researchers have yet to submit protocols for intervening during human fetal development. Although the approach offers numerous therapeutic advantages, it also involves greater uncertainty compared with somatic gene transfer, risk to an additional party (the mother) and ethical questions similar to those that arise in the context of germline gene transfer (gGT; see main text)^{52,53}.

Regulation of research into germline gene transfer

How might studies that are aimed at characterizing the safety and efficacy of gGT be conducted ethically? According to some commentators, existing regulatory and review systems are not well suited to assess the ethics of intergenerational research⁵⁴.

Animal gene transfer

The same techniques that are being applied in human beings for therapies are being used in animals to create transgenic models of human disease. Although improved animal models of human disease and more extensive animal testing represent assets for protecting human subjects, engineering animals for serious disease is not without ethical consequences⁵⁵.

Inadvertent germline gene transfer. The question of whether it is ethical to inadvertently modify the germ line became highly topical in 2001, when the US FDA placed a hold on a sGT study involving haemophilia after investigators detected vector contamination in the semen of study volunteers²⁷ (further testing ruled out transduction of germ cells, and the hold was soon lifted). Two main arguments have been advanced in defence of braving accidental gGT.

First, some argue that germline modification is routine in standard medical practice (for example, the use of ionizing radiation) and that inadvertent occurrences are likely to be swamped by a background of naturally occurring genetic alterations caused by retrotransposition²⁸. However, this set of arguments hinges on the assumption that mutagens and retrotransposons are identical to gene-transfer vectors with

respect to their biological effects. For instance, whereas chemical mutagenesis involves the alteration of existing genes, gene-transfer vectors that integrate insert entire, new and functional genetic elements⁹. Moreover, can we assume that integrating vectors and transposons have similar propensities to insert at particular genetic loci?

A second argument holds that “a willingness to take future risks for the sake of improving health today is well within the accepted standards of medical treatment” and is grounded within a utilitarian tradition²⁹. Perhaps among the most cogent responses to this position is offered by Nancy King, who has argued that too little is resolved about the nature and consequences of inadvertent gGT to categorically proclaim its risks acceptable. She further argues that inadvertent germline modification

courts the far more troubling possibility of pre-empting an open policy debate about deliberate gGT³⁰. In the absence of such a debate, King and others make a credible case for a highly restrictive approach to inadvertent gGT.

Intentional germ-line gene transfer. Even more controversial is the prospect of intentional gGT — either for the purposes of eliminating disease or for genetic enhancement. Scientists are many years away from efficient and effective germline genetic interventions; however, debates that were once academic and hypothetical acquired greater policy relevance in the late 1990s, when reproductive biologists reported the use of ooplasmic transfer to treat infertility³¹. The technique involves transferring cytoplasm from healthy donor eggs to compromised ova; because cytoplasm contains mitochondria, and mitochondria carry their own genome, the procedure is an oblique form of gGT.

Largely motivated by uncertainties surrounding the risks of heteroplasmy, the US FDA began regulating the procedure by requiring that clinics wishing to perform it submit investigational new drug applications³². This substantially restricted the procedure in the United States, but overseas clinics continue to offer ooplasmic transfer with little to no regulatory oversight³³.

What if the physical risks of such gGT interventions were deemed acceptable? Commentators such as John Robertson, who defend a strong presumption of reproductive autonomy, find no convincing arguments for enacting policy bans on gGT³⁴. Yet many jurisdictions have implemented a ban (for example, the European Community³⁵, Canada³⁶ and India³⁷), in some instances less on the basis of risk than of dignity. However, it is not entirely clear what is meant, precisely, by ‘human dignity’, or what it is about a ‘natural’ genetic endowment of human beings — particularly those involving serious disease states — that demands strict protection.

The main concerns many commentators have with intentional gGT is the possibility that it will lead inexorably towards designer babies, and that precedents that are established for serious diseases — which, after all, can be prevented through pre-implantation diagnosis with considerably less risk and without an increased loss of embryos³⁸ — will weaken social opposition towards cosmetic applications (which, at this point, is strong³⁹).

Box 2 | The Gelsinger debacle: translational clinical research and the morality of risk

In 1999, gene transfer recorded its first ever casualty when an 18-year-old man, Jesse Gelsinger, died in a Phase 1 dose escalation study involving ornithine transcarbamylase deficiency. Although the adenoviral-based intervention was designed to treat infants suffering from acute episodes of hyperammonaemia, Gelsinger — like the other volunteers in the study — was able to control his disease through medication and diet. The episode quickly came to symbolize failings in the field of gene transfer, human protections, research ethics, academia and drug regulation. As such, it has become a sort of moral Rorschach for assigning blame and moral responsibility in contemporary translational clinical research.

The most familiar view is that Gelsinger died from physiological derangements brought on by a massive immune response against a high dose of adenoviral vectors. This represents an almost fatalistic position in that it eliminates human agency from the tragedy. Although we might agree that Gelsinger’s death was accidental and involved a physical trigger, whether it was completely unforeseeable is debatable. Indeed, when the protocol was first presented to the Recombinant DNA Advisory Committee in 1995, several panellists expressed major concerns about the trial’s safety and subject selection.

The United States Food and Drug Administration, which is charged with protecting the safety of volunteers in clinical trials, viewed the death as a result of numerous protocol violations and irregularities: eligibility criteria had been fudged, stopping criteria had been ignored and the agency had not been apprised of the most current safety information⁵⁶. Other policy makers saw the death as vindicating concerns that were raised a few years earlier about the performance of local ethics review committees.

Gelsinger’s father, and many others, viewed Jesse’s death as a sort of sentinel case exposing the hazards of merging academia and the private sector. Genovo, which held licensing rights to the study intervention, provided US\$4 million to the institute pursuing the study. The parent institution held a 5% equity interest in Genovo, and lead investigator James Wilson’s stake was 30% — double the university’s normal limit for clinical researchers.

Not surprisingly, many ethicists saw the episode through the lens of informed consent⁵⁷. Some faulted the consent-based justification for enrolling medically stable adults instead of dying infants and their desperate parental proxies (although another factor in the decision to enrol adults was the protocol’s request for liver biopsies, which would have been difficult to justify in children). Others saw a derogation of standard consent practices in the study team’s failure to inform volunteers about the deaths of several rhesus monkeys in preclinical studies, the primitive state of gene-transfer research and the financial interests of investigators pursuing the study.

These widely varying interpretations of the Gelsinger debacle give some indication of the complexity that is involved in managing and disclosing risk when testing novel interventions. Try as we might to characterize and quantify the risks of somatic gene transfer (sGT) in preclinical studies, any estimate will inevitably be embedded in various assumptions about the behaviour and performance of investigators, oversight bodies and institutions. The fact that incentives, rules, relationships and practices in cutting edge research rapidly mutate further confounds the management of risk in first-in-human sGT research.

Genetic enhancement

This brings us to one of the most hotly debated ethical issues in gene transfer: genetic enhancement. As above, an issue that once seemed speculative has gained increasing currency as researchers confront problems that might more appropriately fall under the category of enhancement. One early example was a 1999 protocol testing the use of adenoviral vectors against unilateral retinoblastoma⁴⁰. The goal of the study was to develop an intervention that would obviate removal of the diseased eye. However, because the children in this study had one healthy eye, the study's objectives were seen by many to serve 'quality of life' objectives⁴¹. Other recent examples of sGT that are aimed at improving the quality of life include a protocol involving erectile dysfunction⁴² and one involving genetically modified bacteria for the prevention of dental caries⁴³. Finally, numerous sGT trials that involve serious disorders would have obvious applications in performance enhancement. An example is a muscle-building protocol targeting cachexia (physical wasting) for patients with cancer⁴⁴.

Most commentators acknowledge two main difficulties in articulating an ethics of enhancement. The first is the problem of distinguishing between therapy and enhancement: at what point does surgery to fix facial disfigurement cross into cosmetic surgery? The second is the difficulty of drawing a firm moral boundary between uncontroversial forms of enhancement (for example, vaccinations, which are a form of immunological enhancement) and those raising deeper concerns (for example, cognitive enhancement of one's children).

Objections to genetic enhancement technologies. Secular objections to the more controversial types of genetic enhancement divide into concerns about means, ends and unintended consequences. Consider the example of cognitive enhancement of one's children through sGT. A means-oriented critique argues that other ways of achieving cognitive enhancement, such as training and education, are morally preferable because the child participates in his or her self-making, and because education has value in itself (for example, in providing the experience of accomplishment)⁴⁵. The ends-oriented critique views the impulse behind genetic enhancement as intrinsically problematic because it endangers important social values like unconditional love toward one's children and humility in the face of privilege⁴⁶. Finally, the unintended

Box 3 | The regulation of gene transfer

In the United States, gene-transfer protocols typically undergo review by at least four different bodies⁵⁸. Many other countries have similar review mechanisms — although some, like Canada, do not require centralized ethical review⁵⁹.

As for any other drug trial, researchers must submit their protocols to the Food and Drug Administration (FDA) and a local ethics committee (institutional review board). In addition, researchers that are affiliated with institutions pursuing recombinant DNA research that is funded by the National Institutes of Health (NIH) also submit their protocols for review to the Recombinant DNA Advisory Committee (RAC) and to a local institutional biosafety committee. The RAC has no approval authority and only conducts full public review of novel protocols. Nevertheless, its recommendations are forwarded to IRBs for consideration.

Once a protocol is initiated, researchers pursuing novel strategies are also expected to submit ongoing results to data-safety monitoring boards; they are also expected to report all serious and unexpected adverse events to the NIH.

Many researchers find the oversight system burdensome and duplicative. Nevertheless, the multilayered approach has two justifications. First, it is consistent with the position that oversight be proportionate with uncertainty, risk and ethical challenge. Second, redundancy is a well-established institutional (and, I might add, biological) mechanism for managing risk.

consequences critique occasionally rejects the suggestion that genetic enhancements are, as a general rule, intrinsically suspect. Indeed, some exponents of this critique argue that, in certain circumstances, enhancements might prove to be as ethically obligatory as vaccination is today⁴⁷. Their concerns centre more on the likelihood that an unregulated approach to genetic enhancement would exacerbate existing inequalities or erode the liberal democratic society if access were determined by the ability to pay⁴⁸.

By no means do these views represent consensus positions in the bioethics literature. Nevertheless, the concerns they express are credible and recurrent, and provide grounds for limiting certain forms of genetic enhancement.

By contrast, two other sets of questions have received considerably less attention. The first concerns whether and how to enact policies that would regulate, deter or bar certain genetic enhancements⁴⁹. A second has even greater immediacy. Ethical analysis of genetic enhancement has tended to argue from extreme premises: in these accounts, interventions aim at lurid and perfecting traits, absolute safety is assumed and the relationship between genetic modifications and traits is determinate. However, the first two decades of gene transfer belie problems with the latter two assumptions — at least for the foreseeable future. What seems to be needed is an ethical framework applicable for the sorts of imperfect, risky and variably effective genetic interventions that are likely to be encountered in the near future.

Conclusions and genetic exceptionalism

Are any of the ethical challenges described above unique to gene transfer? In what ways

are the problems described in the first two sections distinct from those for any novel intervention? Do we not already mould future generations by shaping the world that they will inhabit? Is genetic enhancement any different than surgical or pharmacological enhancement? In short, is it productive to think of gene transfer as presenting a unique set of ethical challenges?

Many thoughtful commentators answer no, but would nevertheless argue that gene transfer offers an occasion to revisit ethical issues that have slipped our attention for medical practices that, by now, are considered more prosaic. They would thus reject genetic exceptionalism, but defend sustained attention to the ethics of genetic interventions^{18,50}.

But perhaps the question misses an important point. Gene transfer is characterized by a cluster of issues — for example, high degrees of technical uncertainty, interventions that are irreversible, direct alteration of the genetic 'circuitry', the use of 'live' therapies, control over future generations, and powerful interests. Each individual issue arises in other medical contexts or can be reduced into simpler ethical terms, but together they mark gene transfer as presenting special challenges. Far from receding into irrelevance as it approaches clinical application, the ethics of gene transfer continues to present a rich and productive line of scholarly inquiry — at least to this admittedly biased student of the subject.

Jonathan Kimmelman is at the Department of Social Studies of Medicine, Biomedical Ethics Unit, McGill University, 3647 Peel Street, Montreal, QB H3A 1X1, Canada.

e-mail: jonathan.kimmelman@mcgill.ca

doi:10.1038/nrg2317

1. Guo, J. & Xin, H. Chinese gene therapy. Splicing out the West? *Science* **314**, 1232–1235 (2006).
2. Booth, C. *et al.* Management options for adenosine deaminase deficiency: proceedings of the EBMT satellite workshop (Hamburg, March 2006). *Clin. Immunol.* **125**, 139–147 (2007).
3. Branca, M. A. Gene therapy: cursed or inching towards credibility? *Nature Biotechnol.* **23**, 519–521 (2005).
4. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Splicing Life: A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings*. (US Government Printing Office, Washington, 1982).
5. Raper, S. E. *et al.* Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. *Mol. Genet. Metab.* **80**, 148–158 (2003).
6. Baum, C. What are the consequences of the fourth case? *Mol. Ther.* **15**, 1401–1402 (2007).
7. Kaiser, J. Clinical research. Death prompts a review of gene therapy vector. *Science* **317**, 580 (2007).
8. Horstmann, E. *et al.* Risks and benefits of Phase 1 oncology trials, 1991 through 2002. *N. Engl. J. Med.* **352**, 895–904 (2005).
9. Kimmelman, J. Recent developments in gene transfer: risk and ethics. *BMJ* **330**, 79–82 (2005).
10. Dettweiler, U. & Simon, P. Points to consider for ethics committees in human gene therapy trials. *Bioethics* **15**, 491–500 (2001).
11. Gaspar, H. B. *et al.* Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped γ -retroviral vector. *Lancet* **364**, 2181–2187 (2004).
12. Will, E. *et al.* Importance of murine study design for testing toxicity of retroviral vectors in support of Phase I trials. *Mol. Ther.* **15**, 782–791 (2007).
13. Manno, C. S. *et al.* Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by host immune response. *Nature Med.* **12**, 342–347 (2006).
14. Freedman, B. Equipoise and the ethics of clinical research. *N. Engl. J. Med.* **317**, 141–145 (1987).
15. Orkin, S. H. & Motulsky, A. G. *Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy*. (National Institutes of Health, Bethesda, Maryland, 1995).
16. Kimmelman, J. Stable ethics: enrolling non-treatment-refractory volunteers in novel gene transfer trials. *Mol. Ther.* **15**, 1904–1906 (2007).
17. Evans, J. H. *Playing God: Human Genetic Engineering and the Rationalization of Public Debate*. (University of Chicago Press, 2002).
18. King, N. M. RAC oversight of gene transfer research: a model worth extending? *J. Law Med. Ethics* **30**, 381–389 (2002).
19. Ashcroft, R. E. Gene therapy in the clinic: whose risks? *Trends Biotechnol.* **22**, 560–563 (2004).
20. Danzon, P. & Towze, A. The economics of gene therapy and of pharmacogenetics. *Value Health* **5**, 5–13 (2002).
21. Danzon, P. & Towze, A. The genomic revolution: is the real risk under-investment rather than bankrupt health care systems? *J. Health Serv. Res. Policy* **5**, 253–255 (2000).
22. National Hemophilia Foundation. Financial and Insurance Issues. [online], <http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=34&contntid=24&rptname=bleeding> (2006).
23. Herper, M. Avigen Leads Gene Therapy Charge. *Forbes* [online], <http://www.forbes.com/2000/11/28/1128avigen.html> (2006).
24. Ja, H. & Kling, J. China offers alternative gateway for experimental drugs. *Nature Biotechnol.* **24**, 117–118 (2006).
25. Jia, H. Controversial Chinese gene-therapy drug entering unfamiliar territory. *Nature Rev. Drug Discov.* **5**, 269–270 (2006).
26. Jia, H. Gene therapy finds welcoming environment in China. *Nature Med.* **12**, 263–264 (2006).
27. Marshall, E. Gene therapy. Panel reviews risks of germ line changes. *Science* **294**, 2268–2269 (2001).
28. Kazazian, H. H. An estimated frequency of endogenous insertional mutations in humans. *Nature Genet.* **22**, 130 (1999).
29. Kaplan, J. & Roy, I. Accidental germ-line modifications through somatic cell gene therapies: Some ethical considerations. *Am. J. Bioeth.* **1**, w13 (2001).
30. King, N. M. Accident & desire. Inadvertent germline effects in clinical research. *Hastings Cent. Rep.* **33**, 23–30 (2003).
31. Cohen, J., Scott, R., Schimmel, T., Levorn, J. & Wiladsen, S. Birth of infant after transfer of nucleate donor oocyte cytoplasm into recipient eggs. *Lancet* **350**, 186–187 (1997).
32. Zoon, K. C. Letter to sponsors/researchers: human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei. *FDA Center for Biologics Evaluation and Research*. [online], <http://www.fda.gov/CBER/itr/cytotrans070601.htm> (2001).
33. Firfer, H. How Far Will Couples Go To Conceive? *CNN* [online], <http://edition.cnn.com/2004/HEALTH/03/12/infertility.treatment/index.html> (2004).
34. Robertson, J. A. Oocyte cytoplasm transfers and the ethics of germ-line intervention. *J. Law Med. Ethics* **26**, 211–220 (1998).
35. Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. European Treaty Series **164** (4 Apr 1997).
36. Hébert, M., Chenier, N. M. & Norris, S. Bill C-6 Assisted Human Reproduction Act. Statutes of Canada, chapter 2 (2004). Available at http://www.parl.gc.ca/common/Bills_ls.asp?Parl=37&Ses=3&ls=C6
37. Indian Council of Medical Research, New Delhi. Ethical guidelines for biomedical research on human participants. [online], http://icmr.nic.in/ethical_guidelines.pdf (2006).
38. Steinbock, B. in *Designing Our Descendants: The Promises and Perils of Genetic Modifications*. (eds Chapman, A. R. & Frankel, M. S.) 179–198 (Johns Hopkins University Press, Baltimore, 2003).
39. Genetics and Public Policy Center, Johns Hopkins University. Attitudes about Reproductive Genetics. [online], <http://www.dnapolicy.org/images/reportpdfs/PublicAwarenessAndAttitudes.pdf> (2002)
40. Garber, K. RAC urges changes to retinoblastoma plan. *Science* **284**, 2066 (1999).
41. RAC Department of Health and Human Services National Institutes of Health Recombinant DNA Advisory Committee. Minutes of meeting, June 14 1999 [online], <http://www4.od.nih.gov/oba/rac/minutes/6-99RAC.pdf> (1999).
42. Melman, A., Bar-Chama, N., McCullough, A., Davies, K., Christ, G. hMaxi-K gene transfer in males with erectile dysfunction: results of the first human trial. *Hum. Gene Ther.* **17**, 1165–1176 (2006).
43. RAC Department of Health and Human Services National Institutes of Health Recombinant DNA Advisory Committee. Minutes of meeting, March 10 2004 [online], http://www4.od.nih.gov/oba/rac/minutes/RAC_minutes_03-04.pdf (2004).
44. Baoutina, A., Alexander, I. E., Rasko, J. E. & Emslie, K. R. Potential use of gene transfer in athletic performance enhancement. *Mol. Ther.* **15**, 1751–1766 (2007).
45. Parens, E. Is better always good? The enhancement project. *Hastings Cent. Rep.* **28**, S1–S17 (1998)
46. Sandel, M. J. *The Case Against Perfection: Ethics in the Age of Genetic Engineering*. (Harvard University Press, Cambridge, 2007)
47. Buchanan, A., Brock, D. W., Daniels, N. & Wikler, D. *From Chance to Choice: Genetics and Justice*. (Cambridge University Press, New York, 2001).
48. Mehlmán, M. J. Genetic enhancement: plan now to act later. *Kennedy Inst. Ethics J.* **15**, 77–82 (2005).
49. Mehlmán, M. J. & Rabe, K. M. Any DNA to declare? Regulating offshore access to genetic enhancement. *Am. J. Law Med.* **28**, 179–213 (2002).
50. Parens, E. Should we hold the (germ) line? *J. Law Med. Ethics* **23**, 173–176 (1995).
51. Imperiale, M. J. Gene therapy and biosecurity. *Mol. Ther.* **15**, 648–649 (2007).
52. Billings, P. R. *In utero* gene therapy: the case against. *Nature Med.* **5**, 255–256 (1999).
53. Waddington, S. N. *et al.* *In utero* gene therapy: current challenges and perspectives. *Mol. Ther.* **11**, 661–676 (2005).
54. Dresser, R. Genetic modification of preimplantation embryos: toward adequate human research policies. *Milbank Q.* **82**, 195–214 (2004).
55. Dennis, M. B. Welfare issues of genetically modified animals. *ILAR J.* **43**, 100–108 (2002).
56. Massiello, S. A. Warning letter to James M. Wilson, Institute for Human Gene Therapy. *FDA Freedom of Information* [online], http://www.fda.gov/foi/warning_letters/archive/m3435n.pdf (2000).
57. Munson, R. in *Outcome Uncertain: Cases and Contexts in Bioethics*. (Munson, R. ed) (Wadsworth, Toronto, 2003).
58. Cornetta, K. & Smith, F. O. Regulatory issues for clinical gene therapy trials. *Hum. Gene Ther.* **13**, 1143–1149 (2002).
59. Spink J. & Geddes, D. Gene therapy progress and prospects: bringing gene therapy into medical practice: the evolution of international ethics and the regulatory environment. *Gene Ther.* **11**, 1611–1616 (2004).

Acknowledgements

I regret that, owing to the brevity of this Perspective, many important contributions to the literature on gene-transfer ethics went unmentioned. The work of the author is funded by a Canadian Institutes of Health Research Maud Menten New Principal Investigator Award.

DATABASES

OMIM: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>
 ADA-SCID | chronic granulomatous disease | cystic fibrosis | haemophilia B | Hodgkin disease | hyperargininaemia | ornithine transcarbamylase deficiency | X-SCID

FURTHER INFORMATION

Jonathan Kimmelman's homepage: <http://www.mcgill.ca/biomedicaethicsunit/faculty/kimmelman>
 Database of gene-transfer clinical trials in the United States: <http://www4.od.nih.gov/oba/RAC/GeMCRIS/GeMCRIS.htm>
 Genetic Modification Clinical Research Information System (GeMCRIS) database: http://www.gemcris.od.nih.gov/Contents/GC_HOME.asp
 Guidance on informed consent for gene-transfer trials from the National Institutes of Health: <http://www4.od.nih.gov/oba/rac/ic>
 Information on the status of human gene transfer: http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml#status
 Information on the regulation and status of human gene transfer in Europe and elsewhere: <http://www.euregenethy.org>
 Journal of Gene Medicine database: <http://www.wiley.co.uk/genmed/clinical>
 Overview of ethical issues and literature surrounding human gene transfer: <http://bioethics.georgetown.edu/publications/scopenotes/sn24.htm>

ALL LINKS ARE ACTIVE IN THE ONLINE PDF