Genetic Modification of Preimplantation Embryos: Toward Adequate Human Research Policies

REBECCA DRESSER

Washington University

Citing advances in transgenic animal research and setbacks in human trials of somatic cell genetic interventions, some scientists and others want to begin planning for research involving the genetic modification of human embryos. Because this form of genetic modification could affect later-born children and their offspring, the protection of human subjects should be a priority in decisions about whether to proceed with such research. Yet because of gaps in existing federal policies, embryo modification proposals might not receive adequate scientific and ethical scrutiny. This article describes current policy shortcomings and recommends policy actions designed to ensure that the investigational genetic modification of embryos meets accepted standards for research on human subjects.

In the late 1990s, a group of scientists—including James Watson, codiscoverer of the structure of DNA; Daniel Koshland, former editor in chief of *Science*; and Leroy Hood, a leading molecular biologist—participated in a symposium on human genetic engineering (Stock and Campbell 1998). Citing advances in transgenic animal research and the disappointing results of human somatic cell genetic interventions, these scientists joined several other symposium participants in arguing that the genetic modification of early embryos offers great promise for advancing human health and welfare (Stock and Campbell 2000b). Accordingly, they called on researchers, scholars, and

Address correspondence to: Rebecca Dresser, Washington University School of Law, One Brookings Drive, Box 1120, St. Louis, MO 63130 (e-mail: dresser@wulaw.wustl.edu).

The Milbank Quarterly, Vol. 82, No. 1, 2004 (pp. 195–214)

policy officials to consider when and how to study this form of human genetic modification.

Those taking a positive view of preimplantation embryo genetic modification (PGM) emphasize its possible future benefits. For example, they say, the approach could enable someone with two copies of the gene for Huntington's disease to have a biological child unaffected by the disease. It also could allow parents to "enhance" their children by promoting resistance to HIV infection or cancer (Capecchi 2000).

Besides extensive animal and other laboratory studies, human trials would be required to evaluate whether genetic modifications in embryos were safe and effective for clinical use. In such trials, embryos created through *in vitro* fertilization would be genetically modified and then transferred to a woman's uterus for gestation. Thus, the health and welfare of later-born children would be a major ethical and policy concern.

Studies involving the genetic modification of preimplantation embryos would raise significant human subjects issues requiring extensive expert and public deliberation. If investigators were to propose a human PGM study, however, the current oversight system would be ill prepared to respond. Because of the gaps in the current federal policies protecting human subjects, PGM studies might not receive adequate scientific and ethical scrutiny.

In this article, I examine PGM studies in light of U.S. oversight policies designed to protect human subjects. First, I discuss the relevant scientific developments and argue that scholarly analyses have not devoted enough attention to the human research phase of PGM. Second, I describe current policies governing research involving human gene transfer, research involving human embryos, and research involving human subjects. Third, I point to policy omissions and uncertainties that could contribute to the inadequate oversight of PGM research. I conclude with recommendations for policy action. My goals are to alert scholars and policy officials to regulatory deficiencies and to create an opportunity to remedy the problems before PGM studies are undertaken.

Research Developments

The current research efforts to modify human genes incorporate somatic cell gene transfer interventions. This form of investigational intervention is designed to modify somatic (nonreproductive) cells in the subject's

body. Researchers conducting somatic cell gene transfer studies try to deliver properly functioning genes to children and adults, with the most common techniques using genetically modified viruses. In a successful intervention, the virus infects the appropriate target cells; the normal genes are integrated into the cell's genome; and the normal genes assume their correct function (Walters and Palmer 1997). Although numerous studies have been conducted since 1990, the approach has fallen short of earlier expectations. To date, no somatic cell intervention has produced sufficient evidence of safety and efficacy to gain approval for clinical use (FDA 2000).

Somatic cell intervention is distinguished from a second approach, called *germ line genetic intervention*, which involves modifying genes in germ (sperm or egg) cells. Such modifications become part of the genetic material that may be inherited by the initial subject's descendants. Most discussions of germ line modification stress its potential effects on future generations. On the one hand, if a germ line genetic modification had adverse effects, the burdens could fall not only on direct subjects but on their descendants as well. On the other hand, successful germ line interventions could enable a direct subject's descendants to avoid genetic disease, to avoid being a carrier of genetic disease, or to benefit from mental and physical enhancements (Walters and Palmer 1997).

Because PGM would be performed in the cells of very early embryos, the modification would be maintained as the cells differentiated and thus would be present in the germ cells of later-born individuals (Resnik, Steinkraus, and Langer 1999). The effects on the descendants of genetically altered individuals are, however, of only secondary interest to PGM supporters. Instead, they see interventions in the early embryo as the most efficient way to alter genes in a later-born child. They contend that genetic alterations at the embryonic stage are more likely to have the desired functional effects than are somatic cell interventions performed after birth. In response to concerns about adverse effects in later generations, they suggest that future research will produce methods of blocking the transmission of germ line alterations to the direct subjects' offspring (Capecchi 2000).

Although the enthusiasm about PGM rests in part on some promising results in animal studies involving the genetic modification of embryos, the current techniques are unacceptable for humans. The existing methods of producing transgenic animals cause extensive damage to many embryos and surviving animals. Because most methods produce animals

with different levels of foreign gene expression, further breeding is required to produce animals with stable and properly functioning foreign genes (Frankel and Chapman 2000; Friedmann 2003). The use of artificial chromosomes, embryonic stem cells, cloning, and other innovations could improve the outcomes in animals, but these techniques may not be suitable for human application (Friedmann 2003; Willard 2000). Furthermore, the disappointing results in human somatic cell gene transfer show that what makes sense in theory may not be successful in practice. In sum, it is difficult to reconcile the optimism regarding human PGM with the state of the science. At the same time, the rosy predictions about PGM support the need for an adequate oversight system to prevent premature human applications.

Inadequate Attention to Human Research Issues

Scholarly discussions of modifying inheritable genes have focused on the ethical and policy issues that would ensue if modifications were widely available. For the most part, those who contend that such modifications are desirable and inevitable and those who challenge this view emphasize the technology's broad ethical and social implications, often overlooking the ethical issues that would arise earlier in the technology's development. For example, the editors of a recent book asked the contributors to discuss whether genetic modifications "no more risky in humans than natural conception" would be acceptable and desirable (Stock and Campbell 2000a, 97). Another recent discussion analyzed the major ethical arguments for and against such modifications on the "optimistic assumption that the methods will gradually be refined until they reach the point where gene replacement or gene repair is technically feasible and able to be accomplished in more than 95% of attempted gene transfer procedures" (Walters and Palmer 1997, 80).

Although some analysts have voiced concern about the ethics of human testing, they have not examined the research issues in detail. For instance, a working group convened by the American Association for the Advancement of Science (Frankel and Chapman 2000) described the preclinical research advances that would be necessary before human trials should be considered. The group did not, however, evaluate inheritable genetic modifications in light of the federal policies governing human

subjects research. In the same vein, a recent philosophical analysis acknowledged that human trials of germ line genetic interventions would present serious risks and uncertainties but nonetheless simply called for "careful scrutiny of any protocols for experiments involving those interventions" (Buchanan et al. 2000, 194).

The ethics and policy literature has neglected the human research stage of technology development. Scholars and other writers have not devoted enough attention to the human research that would be necessary to ascertain whether PGM would be an acceptable health intervention. In turn, policymakers have not devoted enough attention to the oversight that would be appropriate for PGM research.

Although federal research policies contain rules and guidance relevant to designing acceptable PGM studies, significant policy gaps exist as well. This inconsistent coverage reflects the limits of federal policies governing gene transfer research, human embryo research, and the protection of human research participants. A second set of policy issues concerns the appropriate interpretation of the current regulations. Review bodies would confront many questions in applying the existing policy provisions to PGM proposals.

Federal Policies Governing Human Genetic Research

National Institutes of Health

Some proposals to study PGM in humans would be subject to federal oversight systems governing gene transfer research. The Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) reviews proposals to conduct gene transfer research in institutions receiving federal funds for any type of recombinant DNA research. Privately funded studies need not be reviewed by the RAC, although officials encourage sponsors to submit such studies for RAC evaluation. Strictly speaking, the RAC lacks the authority to prevent even federally funded gene transfer proposals from being implemented. However, federal officials may require a full RAC review and discussion of proposals raising "important scientific, safety, medical, ethical, or social issues" (Recombinant DNA Advisory Committee 2002, 7). Because the review and discussion are open to the public, investigators and sponsors

disregarding the RAC's recommendations could face severe criticism. The RAC's recommendations are also distributed to NIH officials, who may invoke their funding authority to induce compliance. Finally, RAC materials are available to institutional review boards (IRBs), which can refuse to approve research proposals that disregard the RAC's recommendations for protecting human subjects (King 2002).

Investigators submitting gene transfer research proposals to the RAC must respond to a series of questions in the NIH's Guidelines for Research Involving Recombinant DNA Molecules (NIH 2002). These questions seek general information pertinent to human subjects protection, such as the study intervention's expected risks and benefits, facts to be disclosed to prospective participants, and criteria for subject selection. But the guidelines do not cover other topics relevant to human subjects protection in PGM studies.

This omission is due in part to the RAC's current stance on human studies of germ line modification. The RAC's official position is that it "will not at present entertain proposals for germ line alterations" (NIH 2002, 94). But the RAC's definition of germ line studies would not necessarily encompass PGM research. According to the NIH's guidelines, a germ line alteration "involves a specific attempt to introduce genetic changes into the germ . . . cells with the aim of changing the set of genes passed on to the individual's offspring" (NIH 2002, 94). As noted earlier, supporters today stress PGM's potential benefits for the children who are expected to develop from genetically modified embryos. These researchers see changes in the genes of the direct subjects' offspring as an unavoidable side effect of PGM rather than its aim. Thus, the RAC's refusal to review germ line studies might not apply to PGM proposals whose primary objective is to change the genes in direct subjects. At the same time, the NIH's current guidelines leave the RAC unprepared to conduct a thorough review of PGM proposals.

Recent developments could lead the RAC to revise its policies. In the late 1990s, researchers asked the RAC to consider preliminary protocols for *in utero* gene transfer in humans. They argued that genetic alterations at the fetal stage were needed to mitigate the harm produced by certain mutations. The RAC, however, determined that its approval would be premature, due to inadequate preclinical data regarding the risks and potential benefits to the fetuses (and ultimately the children) who would be the study's subjects. The RAC also expressed concern about possible germ line effects, because the genetic modifications would occur

relatively early in the subjects' development (Recombinant DNA Advisory Committee 2000). Despite this concern, the RAC has said it would be willing to consider future proposals for *in utero* gene transfer research (NIH 2002). If the RAC does review such proposals, it will have to develop a systematic approach to evaluating potential germ line effects in this form of genetic modification research.

In 2001, a second event highlighted the need for the RAC to pay closer attention to potential germ line alterations. At that time, the RAC was shown evidence that foreign DNA was present in the seminal fluid of men participating in a somatic cell gene transfer study. Although there was no indication that the foreign DNA had been incorporated into the men's sperm cells, officials acknowledged that certain somatic cell gene transfer approaches might cause germ line alterations (National Human Genome Research Institute 2002). This incident put pressure on the RAC to scrutinize more carefully the potential germ line effects in somatic cell gene transfer studies.

Guidelines addressing possible germ line effects in *in utero* and somatic cell gene transfer studies could form the foundation for guidelines addressing such effects in PGM studies. All three forms of research would require attention to similar matters, such as appropriate long-term follow-up procedures for direct subjects and their offspring. But PGM would also raise a distinct set of questions about human subjects. For example, unlike the other two types of research, PGM studies would raise questions about the storage, disposition, and control of genetically modified embryos. Until the RAC completes a focused inquiry into the protection of PGM subjects, it will not be prepared to review proposals to modify genes in embryos expected to develop into children.

Food and Drug Administration

The Food and Drug Administration (FDA) operates a second federal oversight system for human gene transfer studies. The agency requires that human tests of "products containing genetic material . . . to alter the biological properties of living cells" conform to the same standards that govern drug tests (FDA 1984; FDA 1993, 53, 249). Research sponsors must secure an investigational new drug (IND) exemption before testing genetic material in humans. The IND application must describe the investigator's plans for protecting human subjects and include a commitment to submit the study for an IRB evaluation (FDA 2003a). In

contrast to the RAC, the FDA has the authority to block human tests, including industry-sponsored proposals.

Like the RAC, the FDA has not explicitly addressed human subjects protection in germ line modification research. In a guidance statement for industry sponsors, the FDA presents its standards for human testing of interventions involving genetically modified cells. But the document does not cover product tests involving "genetic modification aimed at the modification of germ cells" (FDA 1998, 3). Again, the exclusion of germ line modification would not necessarily apply to PGM tests aimed at modifying the genes of direct subjects. But the FDA's failure to consider human subjects protection in PGM means that the agency is not prepared to evaluate PGM product testing.

Recent developments could generate revisions in the FDA's policy. Because of the possible germ line effects produced by somatic cell gene transfer techniques and by certain interventions aimed at enhancing women's fertility, the FDA is considering policies that address germ line risks in these contexts (FDA 2002). Although this response might signal the beginning of a policy approach to PGM research, an expanded inquiry would be needed to develop a robust oversight system for human PGM (Palmer and Cook-Deegan 2003). The policy would have to address matters unique to PGM, such as the control of genetically modified embryos. For the agency to exercise adequate human subjects oversight, its policies must be more closely tailored to PGM research.

U.S. Policies Governing Human Embryo Research

For the past two decades, policy discussions of human embryo research have focused on laboratory studies that require the destruction of early embryos. But when novel interventions, such as genetic modification, target embryos expected to be transferred for gestation, the interventions could affect the health and welfare of later-born children. As a result, the interventions should be evaluated according to regulatory policies governing research involving human subjects.

Advisory groups have recognized this dimension of embryo research. In 1979, the Ethics Advisory Board of the U.S. Department of Health, Education and Welfare issued a report on research involving human

in vitro fertilization (IVF) and embryo transfer (U.S. DHEW 1979). Department officials had asked the board to consider whether such research was ethically acceptable and could be eligible for federal funding. In its report, the board expressed concern about the safety of IVF and urged researchers and clinicians to collect data that could shed light on the procedure's possible risks to children. But human subjects policies were never established in response to the board's report.

In the early 1990s, the NIH's director asked another group, the Human Embryo Research Panel, to consider the ethics of embryo research. The panel determined that preimplantation embryos should be regarded as human research subjects when investigators intend to transfer them to a woman's uterus. The panel then recommended that research interventions affecting such embryos be permitted only if "there is reasonable confidence that any child born as a result of the procedures has not been harmed by them" (NIH 1994, 41). Again, however, the advisory group's recommendations never became official human subjects policy.

Partly because of the absence of federal oversight, rigorous data on the safety and efficacy of IVF and related interventions are lacking (Schultz and Williams 2002; Sutcliffe 2002). At this point, only one federal law explicitly addresses experimental interventions on embryos expected to become children. This is the provision that prohibits the NIH from funding research that involves the destruction of human embryos (U.S. Congress 1996). The provision also bans NIH funds for research in which embryos are "knowingly subjected to risk of injury or death greater than that allowed" by the regulations of the U.S. Department of Health and Human Services (DHHS) governing research on fetuses *in utero* (discussed later). The provision sets a level of acceptable risk for PGM studies but says nothing about other human subjects issues raised by such studies. Moreover, the law applies solely to studies seeking the NIH's support.

At this time, the federal regulations governing research involving human subjects do not explicitly cover investigational interventions in human embryos expected to be transferred for further development. The Federal Policy for the Protection of Human Subjects (also known as the Common Rule) defines a "human subject" as "a living individual" (Federal Policy 1991, 28,013). Although the language is sufficiently general to encompass preimplantation embryos when the intent is to transfer for gestation, it has not been interpreted in this way. The DHHS

regulations governing research involving fetuses apply only after embryo implantation.

A new group, the DHHS Secretary's Advisory Committee on Human Research Protections, could possibly respond to this policy problem. The committee was directed to "provide advice on the responsible conduct of research involving human subjects," including "pregnant women, embryos, and fetuses" (U.S. DHHS 2002b, 1). It remains to be seen whether committee members will propose policies for studies involving interventions in embryos expected to develop into children.

Federal Policies Governing Research Involving Human Subjects

Federal policies to protect human subjects would apply to PGM studies after modified embryos were transferred to a woman's uterus. The basic federal policy is contained in the Common Rule, which governs proposals supported by or performed at institutions funded by the NIH and most other federal agencies. The Common Rule requires investigators to submit human study proposals to multidisciplinary IRBs, which determine whether the proposals meet the regulatory demands for a reasonable balance of risks and anticipated benefits. Institutional review boards also evaluate the research team's plans for explaining the study to prospective participants and for ensuring that a study's potential burdens and benefits will be equitably distributed (Federal Policy 1991).

Studies conducted by employees of institutions receiving funds from the NIH and other DHHS agencies must also comply with regulations governing vulnerable populations that would be included in PGM research. These regulations include Subpart B: Additional DHHS Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (U.S. DHHS 2001), and Subpart D: Additional DHHS Protections for Children Involved as Subjects in Research (U.S. DHHS 2002a). The regulations require IRBs and investigators to pay special attention to the complexities of decision making when pregnant women and couples consider enrolling in studies that will affect an expected or existing child. The regulations also limit the acceptable research risks to fetuses and children and give sufficiently mature children a role in deciding whether to enter or remain in a study.

Certain human subjects protections would also apply to PGM studies in private settings not explicitly covered by the Common Rule. The Food and Drug Administration's regulations cover the investigational uses of new biological products in humans, requiring such proposals to be reviewed by an IRB applying the Common Rule's substantive provisions on acceptable risk-expected benefit ratios, informed decision making, and subject selection (FDA 2003b). Since 2001, the FDA has applied the DHHS's pediatric research rules to privately sponsored research that the agency regulates (FDA 2001), but it has not adopted the DHHS's provisions governing research involving pregnant women and fetuses.

Although the federal regulations governing human subjects research offer guidance on the appropriate conduct of PGM studies, the guidance is incomplete. The existing policies offer a framework for protecting many of the rights and interests of prospective parents participating in research but leave later-born children vulnerable to harm. Both the DHHS and the FDA lack policies explicitly addressing situations in which investigational modifications in the genome of an embryo could have health consequences for a later-born child. As noted earlier, the federal embryo research statute limits the permissible risk in such situations, but it does not address parental decision making and other ethical considerations relevant to this form of investigational intervention. Moreover, the federal embryo research statute applies solely to NIH-funded studies.

These gaps in federal oversight leave human subjects without adequate protection in certain settings. Some fertility specialists, particularly those working in clinics not affiliated with academic medical centers, are unaccustomed to submitting study proposals for FDA and IRB review (Frankel and Chapman 2001). In 2001, for example, infertility specialists published the results of a study using a technique called *ooplasm transfer*, which produces embryos with a mixture of mitochondrial DNA from two women (Parens and Juengst 2001). The infertility researchers had not obtained an investigational new drug (IND) exemption for this work. After the results were published, FDA officials notified researchers that an IND exemption would be required. But this was four years after the first pregnancy involving an ooplasm transfer. Meanwhile, FDA officials expressed concern about the procedure's safety (FDA 2002). To prevent similar unauthorized investigations, clear human subjects rules are needed governing novel interventions in embryos expected to be transferred for gestation.

Uncertainties in Interpreting Current Human Research Rules

The existing human subjects policies cover investigational interventions involving adults, children, and fetuses *in utero*. Researchers and reviewers, however, would encounter numerous questions when applying the Common Rule and DHHS requirements to PGM studies. The following is a survey of the major issues that they would encounter.

The Common Rule

The Common Rule establishes three basic requirements for human studies. First, the risks to the subjects must be minimized, and any remaining risks must be "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (Federal Policy 1991, 28,015). For PGM studies, the reasonableness of risks to the subjects depends largely on the seriousness of the target condition, the available alternatives to PGM, and the social value of the anticipated research data.

Whether PGM studies present reasonable risks could be a point of contention. Studies aimed at avoiding genetic diseases in children could provoke disagreement because of the available alternatives to PGM. In most cases, for instance, preimplantation genetic diagnosis (PGD) offers prospective parents a better chance of having a healthy child. In this technique, early embryos are genetically tested, and those testing positive for disease are not transferred for gestation (Botkin 1998). The PGD technique raises ethical concerns because it results in discarding embryos. But because PGM also would result in discarding embryos (experts expect that some embryos would be damaged or the mutations would not be corrected), it would not be a morally preferable alternative to PGD. The PGD alternative is not available in the relatively rare case in which both members of a couple have two copies of recessive disease genes or one member has two copies of a dominant disease gene. Yet even these couples have other reproductive options, such as adoption or the use of donor gametes. Because PGD and other alternatives present fewer risks to later-born children, reviewers could find that PGM studies presented unreasonable risks to subjects. It could also be difficult to enroll enough subjects in a PGM study to produce generalizable knowledge, which would reduce the study's value to society.

Studies to improve normal characteristics would present an additional source of controversy. Some members of society may see the benefits of genetic interventions for enhancement as sufficiently important to justify the risks. As Buchanan and his colleagues observed, "If individuals—or groups of individuals—value some enhancements very highly, they may well be willing to take significant risks to produce it . . . in their children" (2000, 195). The question is whether the Common Rule's demand for reasonable research risks permits studies exposing to harm embryos expected to develop into healthy children in exchange for the uncertain possibility of physical or mental enhancement.

Investigators and review groups must also develop a principled approach to evaluating PGM's potential consequences to future generations. In some medical and research contexts, individuals are exposed to radiation, chemotherapy, and other interventions that may cause mutations in germ line cells (Blaese 2003). In these situations, the benefits to the recipients are regarded as sufficiently valuable and probable to justify potential harms to their offspring. In the context of PGM research, however, the potential benefits to direct subjects would not be as clear. Evaluating PGM's possible consequences to descendants would be further complicated by the need to rely initially on nonhuman and other preclinical data. Review groups would also have to consider the possibility that future techniques could prevent the transmission of germ line changes or reduce adverse effects in descendants (Resnik 2002).

Fulfilling the Common Rule's second basic directive could be challenging, too. This directive requires investigators to help prospective participants or their representatives make informed and voluntary decisions about enrolling and remaining in research. The duration of PGM studies would introduce a special complexity. Because genetic alterations could affect the subjects later in life, as well as their offspring, many years of data collection would presumably be necessary. Thus, research discussions would begin with the prospective parents considering PGM and would occur later with the parents of the genetically modified children. Eventually, investigators would have to discuss the research with child subjects mature enough to understand basic study information. When these children turned eighteen, they would be free to decide whether to participate in the research. Those subjects who bore children would also be responsible for deciding whether to allow their offspring to be followed. Research teams would have to ensure that prospective subjects

in each of these groups were given an opportunity to choose both to begin and to continue participating in the study.

The Common Rule's third major requirement mandates equitable subject selection. This provision is designed to ensure that the harms and benefits of the research are fairly distributed among groups and individuals. Although pregnant women would participate in PGM studies, the subjects at greatest risk would be their later-born children. In the early phase of PGM studies, a vulnerable population would be exposed to relatively high risk, primarily to advance knowledge that could benefit others. Review groups would have to decide whether PGM's potential benefits justified exposing vulnerable subjects to this level of risk.

DHHS Policies Governing Research Involving Vulnerable Populations

The DHHS provisions governing research involving vulnerable populations would raise more questions for groups considering PGM proposals. These provisions, and the ethical principles they incorporate, would raise serious questions about the acceptability of initial human studies. Initial human tests of drugs and biological products are designed mainly to obtain information about dosage and toxicity. Such studies also seek, "if possible, to gain early evidence on effectiveness" (FDA 2003c, 62). A crucial regulatory issue would be whether the reviewers classified the initial PGM studies as offering a potential benefit to later-born child subjects. Their decision would turn on whether the data from animal and other preclinical investigations furnished a reasonable basis for predicting a direct benefit to child subjects.

The DHHS's regulations restrict the level of permissible risk when study interventions do not offer subjects the prospect of a direct benefit. In this situation, Subpart B permits only minimal risk to fetuses (U.S. DHHS 2001). According to the Common Rule, minimal risk "means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (Federal Policy 1991, 28,013-4).

Although federal regulations do not include a specific definition of minimal risk to fetuses, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research considered this matter extensively (1974). The commission members concluded that

minimal research risks are those that are similar to the risks of normal fetal development and routine obstetric tests. They also concluded that the pregnant woman's ability to terminate her pregnancy should not affect the level of fetal risk permitted in research. Congress incorporated this latter conclusion into the law governing federally funded research involving fetuses (U.S. Congress 2003).

In a similar approach, Subpart D limits the risks to children from research interventions that do not offer a direct benefit. Institutional review boards may approve a study intervention offering child subjects no direct benefit if the intervention presents no more than minimal risk. Alternatively, such interventions may be approved if they present "a minor increase over minimal risk," involve "experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical . . . situations," and are "likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance" (U.S. DHHS 2002a, 121).

It is unclear whether initial human PGM studies could be approved under the regulations governing research interventions that present no prospect of direct benefit. To support their approval, compelling animal and other preclinical data demonstrating the probable safety for humans would be necessary. A related issue is whether the concepts of "minimal risk" and "minor increase over minimal risk" should be evaluated against the usual risks faced by healthy children or by children with the genetic condition being studied. The latter approach could permit certain higher-risk research procedures to be classified as minimal risk, because the usual risks faced by children with serious genetic diseases are much higher than those faced by healthy children (Kopelman 2000).

Different issues would be raised if the initial PGM studies were classified as offering fetuses and children the prospect of a direct benefit. The federal regulations permit fetuses and children to be exposed to research interventions presenting greater than minimal risk if the interventions also offer them the prospect of a direct benefit. The pediatric research regulations deem as acceptable those interventions offering a direct benefit if the "relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches" (U.S. DHHS 2002a, 121). Investigators seeking to perform PGM to avoid genetic disease thus would have to show that existing therapies offered a similar or less satisfactory balance of risks and potential benefits. Investigators proposing PGM to produce disease resistance

or other enhancements would need to establish that the possible benefits were significant enough to justify the risks to healthy children, taking into account the available alternatives to achieving such enhancements.

It is possible that federal officials would permit PGM studies that do not conform to these DHHS requirements. The regulations governing research involving pregnant women and fetuses establish a national review process for permitting research not otherwise approvable. In this process, the local IRB, the DHHS secretary, and a national panel of experts must determine that the research offers "a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women [or] fetuses." The secretary and national panel must also conclude (following a public meeting and an opportunity for public comment) that the study will be consistent with "sound ethical principles" and satisfy the usual requirements for informed choice (U.S. DHHS 2001, 56,780). The pediatric research regulations establish a similar process (U.S. DHHS 2002a). Although the requirements for a national review would ensure that such proposals received public scrutiny, the policies' substantive standards are sufficiently vague that PGM interventions might qualify for approval through this process.

Conclusion

This examination shows that U.S. policies offer limited protection to human subjects in research involving the genetic modification of embryos expected to develop into children. The inadequacies of current policies mean that officials are not fully prepared to respond to future proposals for human PGM research and to the harmful consequences of any objectionable PGM experiments that might be performed. Certain policy shortcomings are relevant not only to PGM research but also to cloning and other investigational interventions affecting preimplantation embryos expected to be transferred for gestation (Dresser 2003).

Three policy actions would go a long way to remedying this situation. First, the RAC or another qualified interdisciplinary body should begin work on a human subjects policy specifically for PGM studies. Officials from both the NIH and the FDA should help to formulate the policy. Second, federal agencies should develop a human subjects policy to protect later-born children who might be affected by PGM and other investigational interventions in preimplantation embryos. Third, the

FDA should apply the DHHS's regulations protecting pregnant women and fetuses to privately funded studies of the products it regulates.

In addition, scholars and other analysts should respond to the policies' inadequacies. Experts in relevant fields should develop ethically defensible policies to guide PGM and related studies, and they should also develop defensible applications of existing policy provisions to PGM research. Without such efforts, the nation will remain unready to protect human subjects in this emerging research area.

References

Blaese, R.M. 2003. Germ Line Modification in Clinical Medicine: Is There a Case for Intentional or Unintended Germ Line Changes? In *Designing Our Descendants: The Promise and Perils of Genetic Modification*, edited by A.R. Chapman and M.S. Frankel, 68–76. Baltimore: Johns Hopkins University Press.

Botkin, J. 1998. Ethical Issues and Practical Problems in Preimplantation Genetic Diagnosis. *Journal of Law, Medicine & Ethics* 26:17–28.

Buchanan, A., D.W. Brock, N. Daniels, and D. Wikler. 2000. *From Chance to Choice: Genetics and Justice*. Cambridge, England: Cambridge University Press.

Capecchi, M. 2000. Human Germline Gene Therapy: How and Why. In *Engineering the Human Germline*, edited by G. Stock and J. Campbell, 31–42. New York: Oxford University Press.

Dresser, R. 2003. Human Cloning and the FDA. *Hastings Center Report* 33(3):7–8.

Federal Policy for the Protection of Human Subjects. 1991. *Federal Register* 56:28,013–8.

Food and Drug Administration (FDA). 1984. Statement of Policy for Regulatory Biotechnology Products. *Federal Register* 49:50, 878–80.

Food and Drug Administration (FDA). 1993. Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products. *Federal Register* 58:53, 248–51.

Food and Drug Administration (FDA). 1998. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. Available at http://www.fda.gov/cber/gdlins/somgene.pdf (accessed June 10, 2003).

Food and Drug Administration (FDA). 2000. Human Gene Therapy and the Role of the Food and Drug Administration. Available at http://www.fda.gov/cber/infosheets/genezn.htm (accessed June 6, 2003).

Food and Drug Administration (FDA). 2001. Additional Protections for Children in Clinical Investigations of FDA-Related Products. *Federal Register* 66:20, 589–600.

Food and Drug Administration (FDA). 2002. Meeting Documents, Biological Response Modifiers Advisory Committee (May 9–10). Available at http://www.fda.gov/ohrms/dockets/ac/cber02.htm (accessed July 18, 2003).

Food and Drug Administration (FDA). 2003a. IND Content and Format. *Code of Federal Regulations* 21:§312.23.

Food and Drug Administration (FDA). 2003b. Institutional Review Boards. *Code of Federal Regulations* 21:§56.

Food and Drug Administration (FDA). 2003c. Phases of an Investigation. *Code of Federal Regulations* 21:§312.21.

Frankel, M.S., and A.R. Chapman. 2000. *Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues*. American Association for the Advancement of Science Working Group. Available at http://www.aaas.org/spp/dspp/sfrl/germ line/main.htm (accessed April 24, 2003).

Frankel, M.S., and A.R. Chapman. 2001. Facing Inheritable Genetic Modification. *Science* 292:1303.

Friedmann, T. 2003. Approaches to Gene Transfer to the Mammalian Germ Line. In *Designing Our Descendants: The Promise and Perils of Genetic Modification*, edited by A.R. Chapman and M.S. Frankel, 39–54. Baltimore: Johns Hopkins University Press.

King, N. 2002. RAC Oversight of Gene Transfer Research: A Model Worth Extending? *Journal of Law, Medicine & Ethics* 30:381–9.

Kopelman, L. 2000. Moral Problems in Assessing Research Risk. *IRB: Ethics and Human Research* 22(5):3–6.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1974. *Research on the Fetus: Deliberations and Conclusions*. Reprinted in *Villanova Law Review* 22(1976–77):300–14.

National Human Genome Research Institute. 2002. Workshop Summary (July 22). Available at http://www.genome.gov/10004761 (accessed July 17, 2003).

National Institutes of Health (NIH). 1994. *Final Report of the Human Embryo Research Panel*. Bethesda, Md.

National Institutes of Health (NIH). 2002. Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Participants (April). In *Guidelines for Research Involving DNA Molecules*. Available at http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html (accessed April 25, 2003).

Palmer, J.G., and R. Cook-Deegan. 2003. National Policies to Oversee Inheritable Genetic Modification Research. In *Designing Our Descendants: The Promise and Perils of Genetic Modification*, edited by A.R. Chapman and M.S. Frankel, 275–95. Baltimore: Johns Hopkins University Press.

Parens, E., and E. Juengst. 2001. Inadvertently Crossing the Germline. *Science* 292:397.

Recombinant DNA Advisory Committee. 2000. *Prenatal Gene Transfer: Scientific, Medical and Ethical Issues*. Available at http://www.4od.nih.gov/oba/rac/gtpcreport.pdf (accessed April 25, 2003).

Recombinant DNA Advisory Committee. 2002. Frequently Asked Questions: Recombinant DNA and Gene Transfer. Available at http://www4.od.nih.gov/oba/RAC_FAQs.htm (accessed June 6, 2003).

Resnik, D.B. 2002. Bioethics of Gene Therapy. In *Encyclopedia of Life Sciences*, 166–73. London: Nature, Macmillan.

Resnik, D.B., H.B. Steinkraus, and P.J. Langer. 1999. *Human Germline Gene Therapy: Scientific, Moral and Political Issues*. Austin, Tex.: R.G. Landes.

Schultz, R.M., and C.J. Williams. 2002. The Science of ART. *Science* 296:2188–90.

Stock, G., and J. Campbell. 1998. *Summary Report: Engineering the Human Germline Symposium*. Available at http://research.mednet.ucla.edu/pmts/germcont.htm (accessed April 24, 2003).

Stock, G., and J. Campbell. 2000a. Other Voices. In *Engineering the Human Germline*, edited by G. Stock and J. Campbell, 97–8. New York: Oxford University Press.

Stock, G., and J. Campbell. 2000b. The Road Ahead: A Panel Discussion. In *Engineering the Human Germline*, edited by G. Stock and J. Campbell, 73–95. New York: Oxford University Press.

Sutcliffe, A. 2002. Health Risks in Babies Born after Assisted Reproduction. *BMJ* 325:117–8.

U.S. Congress. 1996. Public Law 104–99:§128 (January 26).

U.S. Congress. 2003. Fetal Research. *United States Code Annotated* 42:§289g(b).

U.S. Department of Health, Education and Welfare (U.S. DHEW). 1979. Report of the Ethics Advisory Board. *Federal Register* 44:35,033–58.

U.S. Department of Health and Human Services (U.S. DHHS). 2001. Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research. *Federal Register* 66:56,778–80.

U.S. Department of Health and Human Services (U.S. DHHS). 2002a. Additional DHHS Protections for Children Involved as Subjects in Research. *Code of Federal Regulations* 45:§§46.401–9.

U.S. Department of Health and Human Services (U.S. DHHS). 2002b. Secretary's Advisory Committee on Human Research Protections Charter. Available at http://ohrp.osophs.dhhs.gov/sachrp/charter.pdf (accessed July 16, 2003).

Walters, L., and J.G. Palmer. 1997. *The Ethics of Human Gene Therapy*. New York: Oxford University Press.

Willard, H.F. 2000. Artificial Chromosomes Coming to Life. *Science* 290:1308–9.

Acknowledgments: My research was supported by the National Human Genome Research Institute. I am grateful to Joel Frader, Mark Frankel, Nancy King, and Sue Levi-Pearl for their helpful comments on an earlier version of this article.