

# Regulating Science: Genomic Editing, the Embryo, and the Lives of Our Children\*

By Janet Cohn, J.D.; Yu-fen Chou, Ph.D.; Richard Dees, Ph.D.; and Matthew Kohn, Ph.D.

In April 2015, Chinese scientists announced that they had used a new gene editing technique, CRISPR-Cas9, to alter the genome of defective human embryos,<sup>1,2</sup> moving the prospect of genetic engineering from the world of science fiction to the realm of the possible. If perfected, this technique could allow parents to alter the genes of their potential children, either to eliminate disease or to make selections from a menu of attributes. Like many other biomedical breakthroughs, this one brings with it new ethical, legal, and regulatory challenges. In this article, we draw on lessons learned from our work at NYSTEM, New York State's stem cell science funding program, first, to recount the technical background and regulatory challenges of stem cell research generally; second, to describe the scientific breakthroughs that led to the use of CRISPR-Cas9 on human embryos; and finally, to assess the choices that society must make as research using this powerful technology continues.

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## I. The Stem Cell Revolution

When James Thompson first isolated embryonic stem cells in 1998,<sup>3</sup> it generated excitement and controversy: excitement because the cells offered hope for treating a wide variety of devastating diseases; controversy because they could not be obtained without destroying a human embryo.<sup>4</sup>

Stem cells have two properties that together make them powerful tools: they can renew themselves, and they can differentiate into other types of cells. Self-renewal means a stem cell can replenish its population. When a stem cell divides, each "daughter" cell can either remain a stem cell or can differentiate and become more specialized. The ability to self-renew means scientists can grow large numbers of stem cells, and the ability to differenti-

ate—their "potency"—means scientists can use them to create any cell type in the body. There are different kinds of stem cells, however, and their potency and capacity for self-renewal are not equal. Embryonic stem cells (ESCs) are the only naturally occurring stem cells with virtually complete potency and immortality.

In contrast to much of Europe,<sup>5</sup> Latin America, Africa, Canada and a number of states, there is little federal law specifically applicable to the use of human embryos in medical research. While some other jurisdictions have banned or criminalized certain procedures, the United States has taken a different approach. Rather than prohibit procedures that result in the destruction of an embryo, for example, it prohibits the use of federal funds for such activities. So far, however, individual states and private philanthropies are free to fund this research. As a result, the Food and Drug Administration (FDA), which oversees clinical trials in this country no matter who is paying, may find itself supervising work that its sister federal agencies could not legally support. States with funding programs create their own regulatory structures, while nonbinding guidance has come from the National Academy of Sciences (NAS) and the International Society for Stem Cell Research (ISSCR). Overall, within the United States, New York has been the most progressive.

### A. Somatic Stem Cells

Somatic stem cells—often called "adult" stem cells—occur in humans and animals of every age, and they are normally responsible for tissue maintenance and repair. The potential of somatic stem cells is limited, however, because they can only produce cells of their source tissue, have restricted capacity for self-renewal, and can be difficult to isolate from the body. Nevertheless, therapies using somatic stem cells have a long history. We now know that the "active ingredient" in bone marrow transplants is hematopoietic stem cells, which give rise to blood and immune cells. Many successful therapies have followed since the first bone marrow transplant in 1959, including treatments for certain cancers, sickle cell disease, and severe combined immunodeficiency.<sup>6</sup>

Bone marrow also contains another type of stem cell, mesenchymal stem cells (MSCs), that primarily give rise to bone, cartilage, fat, and connective tissue. To date, a single MSC-based therapeutic has been clinically approved—Prochymal, for the treatment of graft-versus-

host disease<sup>7</sup>—but only in Canada and New Zealand. MSCs have been tested for a number of other applications with mixed results. Several therapies based on other kinds of somatic stem cells are in early phase clinical trials. A notable example is neural stem cells, which are being tested to treat neurodegenerative diseases, spinal cord injury, and stroke. Retinal progenitor cells are being tested for eye diseases. And recently the European Medicines Agency approved Holoclar, which uses stem cells originating from the limbus of the eye, for the treatment of corneal damage.

In the United States, the “practice of medicine” is regulated at the state level by state licensing requirements. Whether the therapeutic use of somatic stem cells in a given situation is the practice of medicine, or whether it is a clinical use subject to FDA regulation, is a somewhat gray area. While treatments marketed here and abroad—so-called “stem cell tourism”—raise safety and efficacy concerns, the use of somatic stem cells in research, because they are generally harvested from adults, has not been controversial. Federal law requires that human subjects research be approved and overseen by an Institutional Review Board (IRB) to ensure that it is conducted with informed consent and proper oversight, and clinical trials must be approved and supervised by the FDA. However, some somatic stem cells—most notably neural stem cells—are harvested from aborted fetuses. These cells can only be obtained with the informed consent of the donor, who must have made the decision to undergo an abortion before the topic of donation can be broached.<sup>8</sup>

## B. Human Embryonic Stem Cells

Still the gold standard, ESCs self-renew indefinitely. Because they are effectively immortal, scientists can easily generate vast numbers. ESCs are also pluripotent—theoretically, they are capable of generating any cell in the human body. ESCs are now being used to develop treatments for many conditions, particularly degenerative diseases like Parkinson’s, multiple sclerosis, age-related macular degeneration (AMD), spinal cord injury, amyotrophic lateral sclerosis (ALS, Lou Gehrig’s disease), liver failure, diabetes, and Alzheimer’s. Scientists think that these therapies will not only stop the progression of these diseases, but will also reverse them by replacing the missing or dysfunctional cells responsible for symptoms. Several trials using ESCs are in progress. The first to receive the green light from the FDA was Geron Corporation’s trial to treat spinal cord injury. Ocata Therapeutics, Inc. (formerly Advanced Cell Technologies or ACT), is testing ESC-derived retinal pigment epithelium (RPE) for the treatment of dry AMD and Stargardt’s macular dystrophy, another degenerative eye disease.

Critics maintain that because embryos contain all the genetic material needed to create a person, they should be accorded the same moral status as fully developed humans. Proponents counter that the embryos from which ESCs are derived—which are usually less than a week old, never more than two, and cannot develop into humans unless implanted in a uterus—have a lesser moral status, and that given their enormous therapeutic potential, research using them is warranted. In 2001, President George W. Bush responded to this controversy by limiting federal funding to research using only those human ESC lines that were already in existence at that time. Nonetheless, some research proceeded. A handful of states, notably California, Connecticut, Maryland and New York, responded to the restrictions by creating their own programs to fund ESC research. Private philanthropic groups also provided support.

In 2005, the NAS addressed the void in federal regulation by issuing recommendations for the oversight of ESC research. It concluded that any research involving ESCs must be essential to an important scientific goal. In addition to the protections required for any human subjects research,<sup>9</sup> institutions conducting ESC research were advised to form Stem Cell Research Oversight committees (SCROs or ESCROs), which should include at least one ethicist, to insure that proposed research merited the use of human ESCs (hESCs).<sup>10</sup> In 2006 the ISSCR promulgated its own guidelines on hESC research. These too emphasized the need for a strong scientific rationale and enhanced oversight and concluded that when these conditions were met, research involving embryos no older than fourteen days was permissible.<sup>11</sup>

The New York State Stem Cell Science program (NYSTEM)—the second largest state program, at about one fifth the size of the largest, California’s—was created in 2007. It is advised by the Empire State Stem Cell Board (ESSCB), which makes recommendations for research standards, funding mechanisms, and awards. To date, over \$350 million has been committed to funding basic stem cell research, disease modeling using stem cells, preliminary studies to develop therapies, infrastructure, training, and general education. In addition, it has made awards of up to \$15 million each to six consortia to ready stem cell therapies for clinical testing for Parkinson’s disease, AMD, multiple sclerosis, ovarian cancer, sickle cell disease, and other blood malignancies.

In 2009, President Barack Obama lifted the Bush era restrictions on federal funding for hESC research.<sup>12</sup> But because of the Dickey-Wicker amendment, which has been attached to every Health and Human Services (HHS) appropriations bill since 1996, federal funding of research involving human embryos remains significantly limited. The amendment provides:

SEC. 509. (a) None of the funds made available in this Act may be used for—

- (1) the creation of a human embryo or embryos for research purposes; or
- (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero....

It goes on to define “human embryo or embryos” to include

any organism, not protected as a human subject under [the Human Subject Protection regulations]..., that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes (sperm or egg) or human diploid cells (cells that have two sets of chromosomes, such as somatic cells).

After Obama issued his executive order, the National Institutes of Health (NIH) promulgated new guidelines on funding of hESC research, restricting it to research using leftover embryos that had been created for reproductive purposes. The guidelines explicitly noted that federal funding to derive stem cells from human embryos was prohibited by the Dickey-Wicker Amendment. James Sherley, a somatic stem cell researcher, filed a lawsuit challenging the regulations so far as they permitted the funding of hESC research. Ultimately a panel of the D.C. Court of Appeals upheld the NIH regulations, finding that Dickey-Wicker did not prohibit the funding of *research* on hESCs, just their *derivation* by means that could injure or destroy an embryo.<sup>13</sup> The Supreme Court denied certiorari. In compliance with the decision, NIH now maintains a registry of cell lines, derived from leftover IVF embryos obtained with documented consent, which are eligible for federal funding. As the table that accompanies this article demonstrates, however, the effect of the Dickey-Wicker Amendment remains extensive.

### C. SCNT

Since the first isolation of hESCs, two new techniques have been developed to create ESC-like cells: somatic cell nuclear transfer (SCNT) and induced pluripotent stem cell (iPSC) technology. In SCNT, the nucleus of a somatic (non-embryonic) cell, which contains the cell’s genetic material, is transferred into an egg from which the genetic material has been removed. Embryonic stem cells can then be derived from the new “embryo.” This process constitutes the first step of “reproductive cloning,” in which the resulting embryo is implanted into the womb of a surrogate mother; it was used to create Dolly

the sheep in 1996<sup>14</sup> and other non-primate mammalian species since then. Many countries, and individual states in this country, have banned reproductive cloning. New York has not, but NYSTEM funds cannot be used for this purpose.<sup>15</sup>

In a process called “therapeutic cloning,” however, SCNT has the potential to create effective therapies for disease. Instead of transferring the embryo created by SCNT into a uterus, as would occur in reproductive cloning, scientists can extract ESCs from the embryo. These cells would be an immunological match to the somatic cell’s donor. If they were transplanted back into the donor as part of a therapy, the chance of rejection would be greatly reduced. In 2013, a group from Oregon Health Sciences University first succeeded in creating ESCs by SCNT, using fetal cells as a donor source.<sup>16</sup> The result was soon replicated in a lab at the New York Stem Cell Foundation, funded by NYSTEM, which went on to create the first disease-specific SCNT-ESCs from an adult diabetes patient.<sup>17</sup> Disease-specific ESCs, which contain the genetic defect that causes the disease, offer many advantages to researchers. Importantly, disease-specific cells allow researchers both to examine the mechanisms by which a disease arises and to test drugs to identify possible cures.

SCNT has brought with it its own share of ethical and legal challenges. SCNT requires a ready supply of scarce human eggs. Most jurisdictions prohibit the financial compensation of egg donors, beyond their medical expenses, except when donated for *in vitro* fertilization (IVF). Indeed, Governor Jerry Brown of California recently vetoed a bill that would permit compensating donors for the time, burden and discomfort associated with donation in amounts commensurate with IVF donation. The model for the failed bill came from New York State, the only jurisdiction in the country that permits the use of its funds for this purpose.<sup>18</sup> An unsuccessful lawsuit challenging the practice both as coercive and as advancing human cloning made its way through the New York courts and was ultimately rejected by the Appellate Division.<sup>19</sup>

A new controversy has followed the development of a procedure that is based on SCNT: the generation of embryos through mitochondrial DNA replacement therapy (sometimes and perhaps misleadingly called “three-parent embryos”). Mitochondrial DNA replacement therapy, also called mitochondrial donation, may allow women with mitochondrial diseases to have children that are genetically related to them, yet free of the diseases. One method involves removing the nuclear material from the egg of a healthy donor (the “third parent”), leaving her mitochondria intact, and inserting the nuclear material from the future mother’s egg. The resulting egg is fertilized with sperm from the intended father and then

transferred to the womb of the mother-to-be. Less than 1% of the DNA in the modified embryo—all contained within the mitochondria, which have their own separate genome—would come from the mitochondrial donor. The United Kingdom approved allowing clinical trials using mitochondrial transfer in 2015, and U.S. agencies are holding discussions to determine their position on the procedure. Like other debates on procedures that create or modify human embryos, a divergence of strongly held views is expected.

#### D. iPSCs

Despite potential advantages, SCNT is not currently widely pursued. In 2006 and 2007, Shinya Yamanaka discovered a quicker, easier, and less controversial method to generate patient-specific pluripotent cells. He (and James Thomson in his own lab) created “induced pluripotent stem cells” (iPSCs) by inserting four pieces of DNA, or factors, into adult skin cells—first from mice and then from humans—to reprogram them into ES-like cells.<sup>20</sup> Like ESCs, iPSCs are immortal and pluripotent, but they can be generated from the cells of any living person and do not involve the use of embryos. This discovery rapidly changed the stem cell research landscape and in 2012 Yamanaka received the Nobel Prize. The technology is still new, however, and much work remains to determine its full potential and limitations. To date there is only one clinical trial testing an iPSC-based therapeutic: in 2014 a single patient in Japan was transplanted with iPSC-derived RPE generated from her own cells.

## II. Genomic Editing

The latest controversy swirling around the stem cell field concerns the use of genomic editing on human embryos. This technique not only requires research on the embryo but, if it can be performed safely and effectively, poses new questions that are at least as hard to resolve. If modified embryos are implanted in a uterus, the edited genes will be transmitted to the resulting child and its descendants. Is it ever ethical to make changes that will affect future generations, changes to which they cannot consent? Is it ethical if the goal is the elimination of potential disease? The elimination of *certain* disease? What about genomic editing to make the children genetically “superior”—smarter, taller, stronger? Thinner? Blonder?

#### A. Gene Therapy and Recombinant DNA

Gene editing that does not affect the germline (is not passed down to future generations) is already being used by researchers around the world. Efforts to treat disease by genetic intervention began as early as the 1960s, when the American physician Stanfield Rogers and colleagues at Oak Ridge National Laboratory explored the use of viruses to carry and transmit genetic information to

patients. In 1975, the group collaborated with German physician H.G. Terheggen in a study to treat two children suffering from hyperargininemia, a severe metabolic disorder.<sup>21</sup> They administered the Shope papillomavirus into the patients, believing it contained the gene needed to treat them. The study failed. It would take the sequencing of the papillomavirus in the mid-1980s to realize that the needed gene had been absent all along. But the concept of transferring therapeutic genetic information using viral gene therapy was established.

At about the same time, scientists began to manipulate DNA from bacteria, viruses, and mammals into new combinations. In 1972, Paul Berg at Stanford University created the first recombinant (hybrid) DNA molecule, combining a virus that infects monkeys with another virus that infects bacteria, in this case *E. Coli*. Concerns arose that recombinant DNA research could trigger a biodisaster: bacteria carrying a viral cancer gene might escape the lab and cause a pandemic, or recombinant DNA derived from infectious pathogens could cause unforeseen outbreaks or be used in bioterrorism. In 1974, the NIH responded by creating the Recombinant DNA Advisory Committee (RAC), a regulatory oversight committee, to supervise NIH-funded recombinant DNA research projects. In 1975, a group of scientists led by Berg agreed to a voluntary moratorium and gathered in California, at the so-called Asilomar Conference, to debate the dangers of recombinant DNA and the appropriate response. They decided that the research should continue, but only under stringent restrictions.<sup>22</sup> Their recommendations formed the basis of the official NIH guidelines on research involving recombinant DNA, first issued in 1976. Despite early reservations, the first patent on a recombinant DNA technology was granted in 1980 and the FDA approved the use of recombinant human insulin to treat diabetes in 1982. Berg shared the 1980 Nobel Prize in chemistry for his work in this field.

As work on gene therapies developed in the 1990s, the role of the RAC was expanded to work with the FDA to review protocols for human gene therapy trials. Gene therapy entails treating diseases by modifying, deleting, replacing or inserting genes into target cells.<sup>23</sup> In the 1990s, early gene therapy trials produced disappointing results.<sup>24</sup> Then, in 1999, another early trial led to the tragic death of an 18-year-old patient. Jesse Gelsinger had volunteered to participate in a clinical trial that used a virus carrying a specific gene to correct ornithine transcarbamylase (OTC) deficiency, a metabolic disorder of the liver. After receiving a single dose of the virus, Gelsinger suffered a massive inflammatory reaction and died as a result of multi-organ failure.<sup>25</sup> An FDA investigation questioned whether there had been appropriate patient screening and adequate disclosures. Gelsinger’s death rocked the research community and resulted in height-

ened scrutiny for gene therapy oversight by both the RAC and the FDA. Despite these setbacks, a variety of gene therapy approaches are now in early clinical trials testing their safety and efficacy in humans; most target various forms of cancer.<sup>26</sup> Gene therapy is also being tested to treat blood disorders through viral delivery of functional genes into the genome of hematopoietic stem cells.

### B. New Technologies for Gene Editing

An ongoing concern of viral gene therapy, however, is that the virus can insert randomly into the genome, disrupting necessary genes or inadvertently activating genes that cause cancer.<sup>27</sup>

To edit the genome more precisely, scientists have developed new technologies, building on earlier work involving recombinant DNA. These technologies act like DNA scissors, cutting the double helix at specific locations for gene addition, correction, and disruption. San-gamo BioSciences received FDA approval in early 2015 to conduct a safety and feasibility clinical trial of one such method, Zinc Finger Nucleases, in patients with HIV-1.<sup>28</sup>

CRISPR-Cas9, the newest technology to be used in this way, is the most efficient and accurate yet and the least expensive by far. The Cas9 enzyme, which acts as the scissors, is accompanied by a *guide RNA*—a small, synthetic RNA strand that directs the Cas9 to cut at a specific genomic site. Cells then repair the cut using a synthetic DNA template with the correct sequence. Theoretically, modifying the sequences in the guide RNAs will cause the system to target any site of interest, allowing it to correct the genetic causes behind many diseases. Major questions remain, however, concerning the specificity and safety of these gene-editing tools, including CRISPR-Cas9, for therapeutic applications.

Into this context came the paper from Liang, *et al.*, in *Protein & Cell*.<sup>29</sup> The researchers reported that they had used CRISPR-Cas9 to modify the genome of human embryos (albeit embryos that were defective and not viable) to target the gene that causes beta-thalassemia, an inherited blood disorder affecting the ability of red blood cells to transport oxygen. The team reported relatively poor results. The genetic modifications were successful in 4 of 54 tested embryos; in those, the gene repair was only partial, and many of the edits were at unintended sites (off-target). The research team concluded that the clinical use of CRISPR-Cas9 was premature.

### C. The Community Response

Nevertheless, the study unleashed a firestorm. It put two contentious issues under the spotlight on the same stage: conducting research on human embryos and manipulating a gene that could be passed on to future gener-

ations. Groups of prominent scientists convened meetings to discuss the appropriate response. They issued papers and statements. Website and blogs posted interviews and debates. Most have urged restraint and called for a self-imposed moratorium.<sup>30</sup> Some have questioned whether such experiments should ever be conducted, now or in the future. A few have responded by stressing the importance of eliminating human suffering over yielding to fear. Others have argued that the ability to perform genetic engineering safely is years away and that research toward that goal should proceed. Eric Lander, the lead author of the paper that published the results of the Human Genome Project, commented: “It has been only about a decade since we first read the human genome. We should exercise great caution before we begin to rewrite it.”<sup>31</sup>

In light of the widespread and easy access to CRISPR-Cas9 technology, and in response to both the technical challenges and the newly pressing concerns about future genetic modifications affecting the germline, the National Academy of Sciences will hold an Asilomar-like conference—by invitation only—to discuss whether limitations should be placed on the research.<sup>32</sup> Francis Collins, Director of the NIH, promptly issued a statement declaring that already existing regulations blocked federal funding of work that had the goal of modifying the germline and that no applications for such funding would be considered at this time.<sup>33</sup>

### D. Current Legal Framework

As the table that accompanies this article shows, the existing legal framework should ease some fears of imminent applications of genomic editing with the intent to create a baby. Federal law blocks such funding on two fronts. First, as the recent research by the Chinese group showed, CRISPR-Cas9 currently poses risks to the embryos it seeks to modify and thus violates the Dickey-Wicker Amendment. Second, because the CRISPR-Cas9 system involves recombinant DNA, its use is regulated by the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)<sup>34</sup> and therefore comes under the authority of the Recombinant DNA Advisory Committee (RAC) at the federal level and the Institutional Biosafety Committees (IBCs) at the institutional level. In Appendix M, the Guidelines provide that:

RAC will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer. The purpose of somatic cell gene transfer is to treat an individual patient, e.g., by inserting a properly functioning gene into the subject’s somatic cells. Germ line alteration involves a specific attempt to introduce genetic changes

into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring.

The Guidelines would also restrict New York research involving genomic editing. Not only are they explicitly applicable to any institution that receives any federal funding for the kind of work the Guidelines regulate (and all but a few of the 35 institutions that NYSTEM has funded receive such funding), but New York State immediately acted independently to require all New York based researchers to adhere to the Guidelines.<sup>35</sup> NYSTEM contracts also require compliance with the Guidelines. But NYSTEM funds, which are not subject to the Dickey-Wicker Amendment, can be used for research involving *in vitro* modification of embryos, so long as approval is obtained from the institution's IRB, SCRO and IBC.

As with reproductive cloning, however, nothing in federal law prevents researchers or clinicians with private funds in private clinics from attempting to edit the genome of an embryo and with it to create a child. A House Appropriations subcommittee responsible for FDA funding released a bill in June 2015 to ban the FDA from using public funds to evaluate applications for clinical trials involving genetically modified human embryos.<sup>36</sup> Other efforts to rein in the perceived risk of this research may follow. The question, then, is whether the new technology requires as strong or even a stronger legal response than research using human ESCs, or human cloning, or any other technique or biotechnology that has come along. Even if it does, could it succeed in stopping such experiments or is germline engineering inevitable?<sup>37</sup>

### E. Ethical Considerations

The current use of CRISPR-Cas9 to create a child is unsafe and, at a minimum, a voluntary and temporary moratorium is appropriate. But the technical obstacles may with time be overcome,<sup>38</sup> and it is not too soon to consider whether genomic editing should ever be permissible. Genomic editing poses unique ethical challenges that fall roughly into two categories. The first, which concerns the use of embryos that could be injured in the process, raises the same or similar issues as hESC research and will not be the focus of this discussion. The second stems from the fact that any germline changes will affect future generations that will not be given an opportunity to consent to the modifications, which may be irreversible.

Proponents of genomic editing to create a child fall into two overlapping camps. The first points to the many genetic diseases that could be prevented, like Huntington's and sickle cell disease,<sup>39</sup> curing not only the child,

but also the child's descendants. The second camp points to the possibility of improving the human species, and by extension the world we live in, by engineering children with genes for traits such as superior intelligence, greater creativity, and heightened empathy.<sup>40</sup>

Critics contend that neither of these benefits outweighs the moral costs. First, they argue that the medical case for genomic editing is not strong. Promising research that does not include genomic editing is underway to cure many genetic diseases, although without genomic intervention the cure cannot be passed down to future generations. Many heritable diseases can already be prevented by preimplantation genetic diagnosis (PGD),<sup>41</sup> which uses IVF to create embryos, from which cells are removed and analyzed for genetic defects. But PGD, like IVF, requires the creation of more embryos than are needed and, as with all assisted reproductive technologies, there is evidence from animal models that *in vitro* manipulations can affect the offspring. Those who object to genomic editing because of the use of embryos will not view PGD as an ethical substitute, and it too is outlawed in some jurisdictions and highly regulated in others. Nonetheless, thousands of couples have benefited from PGD, although there will still be some couples who cannot produce an embryo free of disease.<sup>42</sup> For these couples there is currently no known way to give birth to a genetically related disease-free baby. Those who object to genomic editing argue that these benefits are too small and that such couples have other options not including medical intervention, which better serve society as a whole.

Some opponents of the technology for the purpose of improving human beings think that genetic enhancements come at too high a moral cost; others believe that even attempting to genetically engineer future generations is unethical. Some of the first group's objections are based on principles of distributive justice, that permitting the wealthy to make genetic selections for their children will give them even greater advantages over those who cannot, creating an unalterable two-class society that will finally lay to rest the American Dream. Supporters of genetic engineering answer that societal inequalities existed before the availability of these new technologies, are not a product of these technologies, and should be addressed directly.<sup>43</sup> Some have even suggested government subsidies for those who cannot pay for the technology themselves.

The concerns of the second group, which believes that genetic engineering is itself immoral, are harder to express and harder to answer. The argument is that choosing children's traits without their consent undermines their dignity and autonomy by commodifying them. Planning a child would become more like ordering up a

new car. Would society put limits on acceptable modifications? Would there be a limit on the extent to which a parent could impose their preferences and biases on another human being? Should we allow the prejudices of today to mold the genomes of future generations? Those who oppose genetic engineering also argue that designing the genome of children endows a degree of power over those children that may forever alter the human family. Michael Sandel argues that children would be a product of our will rather than a gift we receive, beings we control rather than cherish.<sup>44</sup> Supporters argue that parents have always tried to mold their children—with math tutors and piano lessons, compulsory church attendance and private schools. What makes genetic modification different?

Finally, the critics claim, genomic editing faces an insuperable problem: the people affected can never consent to the use being made of them; they face the risks of genetic engineering, but have no say about whether they want to participate.<sup>45</sup> On reflection, however, this worry too may be misplaced. Louise Brown did not consent to be the first “test tube baby,” nor was there consent from any child created by IVF. But while IVF has its detractors, few think that IVF should be banned for that reason. No child consents to being created, yet many will face great hardships. What matters morally is whether they are subjected to undue risk. If genomic editing can be done safely, then the fact that its subjects cannot consent may not be determinative.<sup>46</sup>

These are difficult ethical questions. At this time it is almost impossible to separate them from the safety concerns. In the continuing conversations, and as the technology advances, they must be reassessed regularly.<sup>47</sup>

### III. Going Forward

The central question is no longer whether there should be a voluntary moratorium on genomic editing to create a child. Even though the NAS has not yet held its meeting, the majority of scientists and bioethicists who have spoken out have already declared a moratorium, although one limited to germline modification. It is important to remember that the proposed moratorium would not preclude the work done by the Liang team in China, which never intended to implant the altered embryos. While there have been calls for a moratorium on all gene editing of embryos, whether to produce a child or for *in vitro* experiments in the lab, the consensus seems to be that *in vitro* research should continue. The ISSCR, the largest and most recognized international association of stem cell scientists, has called only “for a moratorium on attempts to apply nuclear genome editing of the human germ line in clinical practice.”<sup>48</sup>

The fact of the self-imposed moratorium does not mean that all the issues have been resolved. Credible arguments have been made on both sides. Commentators have pointed out that a moratorium, in addition to giving needed time to debate the ethics, would also generate good will. It would demonstrate to the public that the scientific community is proceeding responsibly, and it may forestall congressional involvement. To fully achieve these potential benefits, however, more time is needed to hear from dissenters—both those who favor a broader moratorium and those who favor none.

The central question now is whether there is a need for a more restrictive response than a self-imposed moratorium. Is there a way to create a more effective deterrent? A moratorium will already deter those who view themselves as members of the scientific community and hope to have their work recognized by it someday. Are there others who do not care about community approbation, but who have the necessary skills and means to carry out such work? Should society’s prohibitions be geared to the most egregious and unpredictable offenders?

George Daley, one of the researchers who sounded the alarm on genomic editing, told the *New York Times* that a deranged desire for world acclaim sometimes prompts people to attempt forbidden acts, acts like human reproductive cloning or implanting a modified embryo in a uterus.<sup>49</sup> Henry Greely, a professor at Stanford Law School, commented that only the criminally insane would attempt such an act at this time in light of the obvious dangers. If they are right, can society deter such actors?

Clearly, no law will deter everyone. It is unlikely that a renegade scientist will be more effectively deterred by the laws of general society than by the laws of the relevant professional community. Furthermore, does it make sense for Congress to legislate the practice of scientific investigation? In our highly politicized and ideologically driven system, can Congress be relied on to get it right?

The strength of our current regulatory system, cumbersome and sometimes random as it is, is that it should allow the flexibility needed to respond to scientific advancement. American laws, however, are notoriously difficult to change. If open discussion and debate is the best way to resolve the ethical challenges of an evolving field, nothing will stop that faster than a legislative prohibition. Despite the alarm generated by the first report of an *in vitro* attempt to modify the genome of embryos, and given the potential dangers of *in vivo* experiments, the response so far has been rational, appropriate and considered. We should allow it to continue.

## SPECIAL EDITION: LEGAL ISSUES IN BIOTECHNOLOGY

<b>Creating Human Embryos and Using Embryonic Stem Cells for Research</b>				
TECHNOLOGY	FUNDING SOURCE	PERMISSIBILITY PER LAW/ REGULATIONS/ CONTRACT	OVERSIGHT REQUIRED	VOLUNTARY GUIDELINES (regardless of \$ source)
Research using embryonic stem cells	Federal	Ok, if listed in NIH human ESC registry	IRB FDA*	NAS and ISSCR—limited oversight by [E]SCRO and IRB
	NYSTEM	Ok	IRB / SCRO FDA* & OP	
Derivation of new embryonic stem cell lines for use in research	Federal	No per D-W		NAS and ISSCR—Full [E]SCRO review
	NYSTEM	Ok, by whatever means derived	IRB / SCRO FDA* & OP	
Creating embryos by IVF for use in research** ±	Federal	No per D-W		NAS and ISSCR:
	NYSTEM	Ok	IRB / SCRO FDA* & OP	OK up to lesser of 14 days or primitive streak (earliest development of nervous system)
Creating embryos by SCNT for use in research (therapeutic cloning)	Federal	No per D-W—no creating embryos		NAS and ISSCR:
	NYSTEM	Ok	IRB / SCRO	Ok up to lesser of 14 days or primitive streak
Donation of oocytes to research for embryo creation (IVF or SCNT)	Federal	No per D-W—no creating embryos		NAS: compensation only for direct expenses incurred as result of procedure
	NYSTEM	Ok, and ok to compensate donors with state funds for costs plus for associated time and burden	IRB / SCRO	ISSCR: With SCRO, additional comp ok but NOT for number or quality of eggs; should not constitute undue inducement  ASRM: comp for time and burden, regardless of successful retrieval or number of eggs
SCNT for reproduction (reproductive cloning)	Federal	No per D-W but no across-the-board ban		NAS: should not be conducted at this time.
	NYSTEM	No—  Use of NYSTEM funds prohibited. PHL § 265-a (2).  Willful violation of any provision of PHL is misdemeanor  PHL § 12-b. Penalties up to 1 year imprisonment and \$2,000		ISSCR: given current scientific and medical safety concerns, reproductive cloning should be prohibited



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Modifying Human Embryos				
TECHNOLOGY	FUNDING SOURCE	PERMISSIBILITY PER LAW/ REGULATIONS/ CONTRACT	OVERSIGHT REQUIRED	VOLUNTARY GUIDELINES
Mitochondrial donation / transfer ≠	Federal	Under study by IOM and FDA ≠ D-W prohibits—risk to embryo		ISSCR—YES, with SCRO NAS—under review
	NYSTEM	Ok	IRB / SCRO FDA	
Editing genome of embryos in vitro (solely for research)	Federal	No per D-W		ISSCR—June 2015 draft Guidelines for Stem Cell Science and Clinical Translation support such research, with proper oversight
	NYSTEM	Ok	IRB / SCRO / IBC	
Editing genome of embryos for implantation	Federal	No per D-W and NIH Guidelines on Recombinant DNA	These entities would have oversight if such work planned or attempted:  IRB / SCRO / IBC / RAC FDA* & OP	June 2015 draft Guidelines prohibit and call for broad public and international dialogue on genome-editing technologies and rigorous deliberation on ethical, legal and societal implications of modifying human germ line  NAS—supports moratorium and organized discussions
	NYSTEM	Probably not at this time  NIH guidelines apply to any institution receiving federal funds for research using recombinant DNA  NYS PHL § 3222 requires certification and adherence to NIH guidelines for recombinant DNA work. Willful violation of PHL § 3222 would constitute misdemeanor		

\* for use in clinical trials.

± Canada—criminal penalties apply.

\*\* IVF for individual reproductive purposes is legal both federally and in NYS and is regulated as a medical procedure.

≠ UK—approved February 24 2015. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015; [www.legislation.gov.uk/uksi/2015/572/contents/made](http://www.legislation.gov.uk/uksi/2015/572/contents/made) (effective 29 October 2015).

≠≠ U.S. Food and Drug Administration, Cellular, Tissue and Gene Therapies Advisory Committee Meeting: Announcement, [www.fda.gov/AdvisoryCommittees/Calendar/ucm380042.htm](http://www.fda.gov/AdvisoryCommittees/Calendar/ucm380042.htm); [www.iom.edu/activities/research/mitoethics.aspx](http://www.iom.edu/activities/research/mitoethics.aspx).

### Abbreviations

ASRM	American Society for Reproductive Medicine
D-W	Dickey Wicker Amendment
ESC	Embryonic Stem Cell
ESCRO	Embryonic Stem Cell Research Oversight
FDA	Food and Drug Administration
IBC	Institutional Biosafety Committee
IOM	Institute of Medicine
IRB	Institutional Review Board
ISSCR	International Society for Stem Cell Research
IVF	in vitro fertilization
NAS	National Academy of Sciences
NIH	National Institutes of Health
OP	NYSTEM's Independent Oversight Panels, applicable to NYSTEM Consortia awardees
PHL	New York State Public Health Law
RAC	Recombinant DNA Advisory Committee (NIH)
SCNT	Somatic Cell Nuclear Transfer
SCRO	Stem Cell Research Oversight

Endnotes

1. Puping Liang, et al., *CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes*, *PROTEIN & CELL* 6 (May 2015): 363-72.
2. We use the term genomic editing to mean editing the genome that affects the germline.
3. James Thomson, et al., *Embryonic stem cell lines derived from human blastocysts*, *SCIENCE* 282 (1998): 1145-7.
4. Typically, embryos used for derivation of embryonic stem cells are created by *in vitro* fertilization and are in excess of clinical need, i.e., the patients no longer need or want them for reproductive purposes.
5. See <http://www.eurostemcell.org/stem-cell-regulations>.
6. Severe combined immunodeficiency (SCID), or “bubble boy disease,” is a disorder that renders the immune system unable to fight off infection. The term “bubble boy disease” refers to David Vetter, a boy with SCID who lived for over a decade in a plastic bubble that protected him from germs.
7. Graft-versus-host disease (GVHD) occurs after bone marrow or stem cell transplants when the newly reconstituted immune cells mount an attack on the patient’s body.
8. 42 U.S.C. § 298g-1(b)(2)(A)(i).
9. Public Health Services Act, Title 42 United States Code, Chapter 6A.
10. National Academy of Sciences, *Guidelines for Human Embryonic Stem Cell Research* (NAS Press, 2005), chapter 2.
11. ISSCR, *Guidelines for the Conduct of Human Embryonic Stem Cell Research*, <http://www.isscr.org/docs/default-source/hesc-guidelines/isscrhescguidelines2006.pdf>.
12. Executive Order 13505, Removing Barriers to Responsible Scientific Research Involving Human Stem Cells, <http://www.gpo.gov/fdsys/pkg/FR-2009-03-11/pdf/E9-5441.pdf>.
13. *Sherley v. Sebelius*, (“*Sherley VI*”), 689 F.3d 776, 785 (D.C. Cir. 2012), *aff’g* 776 F. Supp. 2d 1 (D.D.C. 2011).
14. Ian Wilmut, et al., *Viable offspring derived from fetal and adult mammalian cells*, *NATURE* 385 (1997): 810-13.
15. Public Health Law § 265-a(2).
16. Masahito Tachibana, et al., *Human embryonic stem cells derived by somatic cell nuclear transfer*, *CELL* 153 (2013): 1228-38.
17. Mitsutoshi Yamada, et al., *Human oocytes reprogram adult somatic nuclei of a type 1 diabetic to diploid pluripotent stem cells*, *NATURE* 510 (2014): 533-36.
18. Empire State Stem Cell Board, Resolution of the Funding Committee Regarding Recommended Standards For the Compensation of Women Donating Oocytes Solely for Research Purposes, June 11, 2009, <http://stemcell.ny.gov/node/226>. See also Beth Roxland, *New York State’s landmark policies on oversight and compensation for egg donation to stem cell research*, *Regen. Med.* (2012) 7(3) 397-408.
19. *Feminists Choosing Life of New York, Inc. v. Empire State Stem Cell Board*, 87 A.D.3d 47, 926 N.Y.S.2d 671 (3d Dept.), leave denied, 18 N.Y.3d 801, 938 N.Y.S.2d 858 (2011).
20. Kazutoshi Takahashi and Shinya Yamanaka, *Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors*, *CELL* 126 (2006): 663-76; Kazutoshi Takahashi, et al., *Induction of pluripotent stem cells from adult human fibroblasts by defined factors*, *CELL* 131 (2007): 861-72; Junying Yu, et al., *Induced pluripotent stem cell lines derived from human somatic cells*, *SCIENCE* 318 (2007): 1917-20.
21. Theodore Friedmann, *Stanfield Rogers: insights into virus vectors and failure of an early gene therapy model*, *MOLECULAR THERAPY* 4 (2001): 285-8; Cormac Sheridan, *Gene therapy finds its niche*, *NATURE BIOTECHNOLOGY* 29 (2011): 121-8; Gerhard Bauer and Joseph S. Anderson, *Gene Therapy for HIV* (Springer-Verlag New York, 2014), chapter 2: *History of Gene Therapy*.
22. Paul Berg, *Meetings that changed the world: Asilomar 1975: DNA modification secured*, *NATURE* 455 (2008): 290-1.
23. Magid H. Amer, *Gene therapy for cancer: present status and future perspective*, *MOLECULAR AND CELLULAR THERAPIES* 2 (2014): 27.
24. *Revolution in Progress: Human Genetics and Medical Research*, <http://history.nih.gov/exhibits/genetics/sect4.htm>, Gene Therapy.
25. Sheryl Gay Stolberg, *The Biotech Death of Jesse Gelsinger*, *NEW YORK TIMES*, Nov. 28, 1999.
26. Of current trials in gene therapy most are in phase I clinical trials (60%), followed by phase II clinical trials (35%), and only a very small fraction are in phase III clinical trials (5%). About 65% concern cancer. Brendan Lee and Beverly L. Davidson, *Gene therapy grows into young adulthood: special review issue*, *HUMAN MOLECULAR GENETICS*, 20(2011): R1.
27. Steven J. Howe, et al., *Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients*, *THE JOURNAL OF CLINICAL INVESTIGATION*, 118 (2008): 3143-50.
28. [ClinicalTrials.gov](http://ClinicalTrials.gov), Identifier:NCT02500849.
29. See note 1, *supra*.
30. David Baltimore, et al., *A prudent path forward for genomic engineering and germline gene modification*, *SCIENCE* 348 (2015): 36-38.
31. Eric Lander, *Brave new genome*, *NEW ENGLAND JOURNAL OF MEDICINE* B 373 (2015): 7.
32. The NAS announced that the meeting will be held the first week of December 2015, in Washington, D.C., and will be co-hosted by the Royal Society (the science academy of the U.K.) and the Chinese Academy of Sciences.
33. *Statement on NIH funding of research using gene-editing technologies in human embryos*, [http://www.nih.gov/about/director/04292015\\_statement\\_gene\\_editing\\_technologies.htm](http://www.nih.gov/about/director/04292015_statement_gene_editing_technologies.htm).
34. [http://osp.od.nih.gov/sites/default/files/NIH\\_Guidelines\\_0.pdf](http://osp.od.nih.gov/sites/default/files/NIH_Guidelines_0.pdf).
35. New York PHL Article 32-A, NYCRR part 61.
36. House Fiscal Year 2016 FDA Appropriations Bill (H.R. 3049) & Report (H. Rept. 114-205), <https://www.congress.gov/bill/114th-congress/house-bill/3049> and <https://www.congress.gov/114/crpt/hrpt205/CRPT-114hrpt205.pdf>.
37. See Katrin S. Bosley, et al., *CRISPR germline engineering—the community speaks*, *NATURE BIOTECHNOLOGY*, 33 (2015): 478-86.
38. Rebecca Dressler argues that germline modification can never be safely done because no preliminary study could show that the first experiments in humans could be done safely. See Dresser, *Designing babies: Human research issues*, *IRB* 26.5 (2004): 1-8.
39. Ronald Munson and Lawrence David, *Germ-line gene therapy and the medical imperative*, *KENNEDY INSTITUTE OF ETHICS JOURNAL* 2 (1992): 137-58. See also Henry Miller, *Germline gene therapy: We’re ready*, *SCIENCE* 348 (2015): 1325.
40. See Julian Savulescu, *New breeds of humans: The moral obligation to enhance*, *ETHICS, LAW, AND MORAL PHILOSOPHY OF REPRODUCTIVE BIOMEDICINE* 1 (2005): 36-39; Ingmar Persson and Julian Savulescu, *Unfit for the Future: The Need for Moral Enhancements* (Oxford: Oxford University Press, 2012).
41. Lander, *supra* note 31 at 27. See also John Robertson, *Extending preimplantation genetic diagnosis: The ethical debate*, *HUMAN REPRODUCTION* 18 (2003): 465-71.
42. A couple cannot produce a disease-free embryo if one parent has two copies of an autosomal dominant disease gene or if both parents have an autosomal recessive disease.

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43. See Nick Bostrom, *In defense of posthuman dignity*, *BIOETHICS* 19 (2005): 202-14. For a longer discussion of the limits of the arguments against enhancements, see Richard H. Dees, *Better brains, better selves?: The ethics of neuroenhancements*, *KENNEDY INSTITUTE OF ETHICS JOURNAL* 17 (2007): 375-99.
44. Michael Sandel, *The case against perfection*, *ATLANTIC* 293 (April 2004): 50-62.
45. See Francis Collins, Statement on NIH funding of research using gene-editing technologies in human embryos, [http://www.nih.gov/about/director/04292015\\_statement\\_gene\\_editing\\_technologies.htm](http://www.nih.gov/about/director/04292015_statement_gene_editing_technologies.htm).
46. For a related discussion, see John Fletcher, *Moral problems and ethical issues in prospective human gene therapy*, *VIRGINIA LAW REVIEW* 69 (1983): 515-46 at 542-45.
47. See note 30, *supra*.
48. The ISSCR Statement on Human Germline Genome Modification, 19 March, 2015.
49. Gina Kolata, *Chinese Scientists Edit Genes of Human Embryos, Raising Concerns*, *NEW YORK TIMES*, April 23, 2015.

Janet Cohn, J.D. is Executive Director and Yu-fen Chou, Ph.D. and Matthew Kohn, Ph.D. are science officers at the New York State Stem Cell Science Program (NYSTEM). Richard H. Dees, Ph.D., is an associate professor of philosophy and bioethics at the University of Rochester and a member of the Ethics Committee of the Empire State Stem Cell Board (ESSCB).

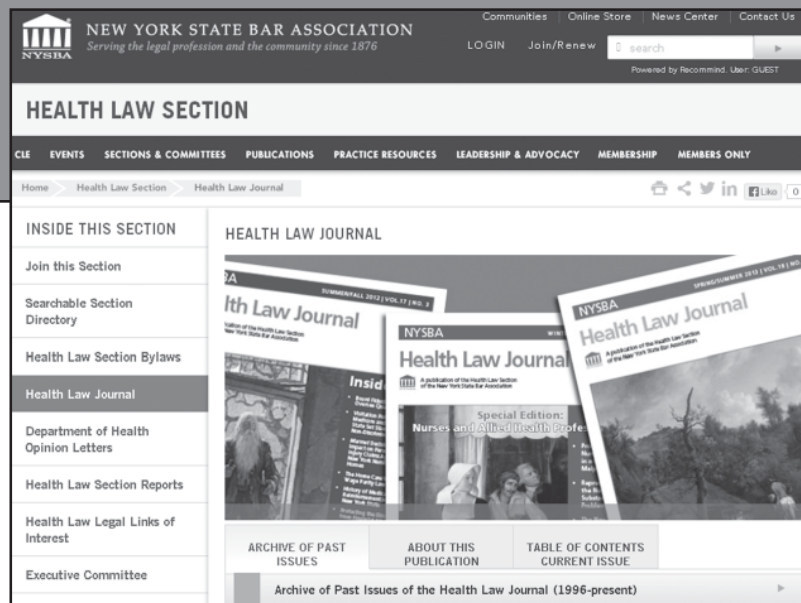
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