Embryo Stem Cell Research: Ten Years of Controversy

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Embryonic stem cell (ESC) research has been a source of ethical, legal, and social controversy since the first successful culturing of human ESCs in the laboratory in 1998. The controversy has slowed the pace of stem cell science and shaped many aspects of its subsequent development. This paper assesses the main issues that have bedeviled stem cell progress and identifies the ethical fault lines that are likely to continue.

The time is appropriate for such an assessment because the field is poised for a period of rapid development. President Obama has removed the Bush administration's restrictions on federal funding. A huge influx of federal research funds is in the offing and presumably a more rapid maturing of the science will take place. Stem cell science is also moving into the clinical realm. In March 2009, the Food and Drug Administration (FDA) approved the first clinical trial with an ESC-derived therapy for spinal cord injuries, an important first step — though by no means a final or a sure one — in moving ESC research out of the laboratory into clinical medicine.[1] Finally, recent work with induced pluripotent stem (IPS) cells suggests that non-embryonic sources of pluripotent stem cells may one day be routinely available. Such a development will lessen the temperature of the ethical debate while raising other issues.

Together these factors show how complicated the trajectory of innovation can be. The scientific challenges are great enough, but they must be overcome in a political and social world of ethical battling and regulatory response. They are another reason why the stem cell experience is so illustrative of how law and policy affect scientific innovation.

I. Why ESCs Are Controversial

ESCs are the first differentiation after fertilization of cells of the embryo proper. They are not totipotent (capable of forming a new embryo), but they are pluripotent (capable of forming all other cells in the body).

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Because they are the earliest stage of all later cell lineages, they offer a research platform for studying how the subsequent development of tissues arise and for fashioning treatments to cure or prevent disease. They were first cultured in mice in 1981, but not in humans until 1998, when James Thomson at Wisconsin and John Gearhardt at Johns Hopkins managed to do so.[2] The ability to culture human ESCs in the laboratory was an important breakthrough because it opened the door to understanding and controlling human development and thus to cell replacement or regenerative therapies in humans.

the neurologic capacity to feel pain and be sentient. To them it is clear enough that unimplanted embryos, which are a collection of undifferentiated cells, lack the physical characteristics to have the attributes which they view as essential for moral status.[6] However, they are willing to acknowledge that embryos have status greater than other tissue because of the chance that they could implant and come to term, and thus deserve special respect. Such special respect for embryos requires good reasons to create, discard, and experiment on them, such as the need to treat infertility or carry out legitimate scientific research.

There is a fervent battle over the ethical acceptability of destroying early embryos to derive pluripotent ESCs, which is necessary to do to obtain ESCs. Stem cell science is thus drawn into the ongoing, highly divisive wars over abortion and the culture of life that have occupied a central stage in American law and politics over the last 30 years.

Knives have been drawn about ESC research from its inception. Few quarrel over the aim of the research to treat illness and disease. Yet there is a fervent battle over the ethical acceptability of destroying early embryos to derive pluripotent ESCs, which is necessary to do to obtain them.[3] Stem cell science is thus drawn into the ongoing, highly divisive wars over abortion and the culture of life that have occupied a central stage in American law and politics over the last 30 years.[4] I will focus on that battle in the United States, but a version of it has played out in many countries. This is a moral divide that has to be managed or accommodated because it is unlikely ever to be completely removed from political and policy discourse.

The embryo status debate has been well-rehearsed in many places, so I address its merits here only briefly. On one side are persons who think that a fertilized egg in the laboratory is a new human being or individual with all the rights and moral and legal status of fully born persons. They see destruction of embryos, like abortion of fetuses, as murder — as a sacrifice of the weakest among us for the interests of others.[5] They oppose destroying embryos to obtain stem cells even if those embryos will be discarded because they are no longer wanted by the couples who produced them to treat infertility.

The other side sees the embryo as too rudimentary in development to have interests or rights, and thus should not be protected at the cost of legitimate and important scientific research. To take this position they need not agree on the point at which fetuses develop

Although the gap between these positions will never be bridged, several things might be said about it. The first is that the right to life position is based on an essentialist argument with a consequentialist tinge about the importance of human DNA and the potential to become a person. Its proponents stress the equality of all human beings and the dangers of treating some differently from others. The fact that the embryo is not conscious and cannot feel pain does not matter nor that it may never acquire those characteristics or even placed in a uterus for the chance to implant. It must be treated as if it were because it is living, has unique human DNA, and if transferred to a uterus might develop those characteristics. This is a religious-type belief, and there is no way to argue around it.

Interestingly, there is also a consequentialist flavor to the embryo-protection argument: bad consequences will happen if we do not respect human life at the earliest preimplantation stages. All persons, they assert, will be at risk for baleful judgments about their worth and status based on mental characteristics. Yet 30 years of experience with abortion and removing life-sustaining treatments for incompetent patients clearly belie that claim.

A second point is to note that many persons who profess to hold pro-life views are not totally consistent. The staunchest adherents do get prizes for consistency in the fervor with which they oppose any action that harms an embryo or fetus. Presumably they would oppose the fertilization and discard practices in

assisted reproduction as well, though they have been less focused on them.[7] But many people who oppose abortion do see the matter differently when embryos involved are going to be discarded anyway, and life-saving research could occur. Senators John McCain and Orrin Hatch have taken this position, as have others who claim right to life credentials. When important research is at stake, they simply do not recognize the early embryo as having the same status as a fetus, though they may be hard-pressed to reconcile the difference. Such views help explain the poll results consistently showing that 60% or more of Americans favor stem cell research.[8]

The support for stem cell research involving embryos that will otherwise be discarded does not necessarily extend to creating embryos solely for research. This marks another fault line in the ethical debate and an apparent inconsistency in some persons on the pro-research side. Persons who have strong right to life views oppose research regardless of how the embryo was created. But some persons who think embryos are too rudimentary to have interests or rights still find it objectionable to create embryos solely for research and then destroy or discard them.[9] If the embryos are at the same stage of development in each case, then how can one set of embryos deserve protection and the other set not? The distinction seems fallacious because those same persons accept fertilizing all the eggs retrieved from a stimulation cycle as part of IVF treatment even though doing so will inevitably lead to some of them being discarded.[10] Despite the lack of a clear difference between the importance of research and reproduction, the purpose for which embryos have been created has become a central part of federal funding policy, even though creating embryos for research by either method is legal in most states. Future battles over this line are likely.

II. Legal and Constitutional Issues

The ESC debate over the last decade has been a debate about funding and ethics, and only to a lesser extent about positive law. True, a few states have banned embryo research and SCNT, but much of the battle has been about funding and administrative policy.[11] Unlike debates over abortion, however, the courts have had a relatively small role in these battles. Still, the Supreme Court's abortion cases hover in the background, leading one to wonder whether constitutional rights could come into play if government tried to prohibit stem cell research on a broader scale or otherwise stop the use of ESC-based therapies.

The Supreme Court has never ruled on the constitutional status of embryos outside of the body and most states have no law on the matter. But the Court has ruled without a dissenting voice that fetuses are not persons within the meaning of the 14th Amendment, and thus do not have constitutional rights as such. Presumably that ruling would extend to embryos as well. The question left open, however, is whether state or federal government may choose to invest them with rights, for example, making it a crime to create embryos for research and then destroy them. This question, which is at the heart of the constitutional debate over abortion, was settled in *Roe v. Wade*[12] and *Planned Parenthood v. Casey*.[13] The Court has said that the state has a legitimate interest in protecting potential life and may take steps to demonstrate that respect prior to viability only when doing so would not create a substantial obstacle — an undue burden — on a woman's obtaining an abortion. After viability government may ban abortion altogether, except where the mother's life or health is threatened by continuing the pregnancy.

Under this approach a state could argue that it could restrict the use of embryos in research, for example, preventing their destruction for research or banning creating them for research, or perhaps even prohibiting fertilization of more eggs than are needed for a successful pregnancy because of its interest in showing respect for the earliest stages of human life. It might also argue that since the embryos are outside of the body, *Roe v. Wade* and *Planned Parenthood v. Casey*, which strictly speaking concern only abortion, do not apply. Such a law would certainly meet a rational basis test because restricting destruction of embryos is a rational way to show respect for early human life. The question, however, would be whether a more compelling standard must be met because of the importance of embryos to ESC research and to ESC researchers and to the protection of life and health. If so, it is unlikely that a rational basis justification alone would do.

A key distinction here is the purpose or impact of the state restriction. If it is pitched to the creation of embryos for treatment of infertility, such laws would most likely be unconstitutional because they would interfere with a constitutionally protected interest in reproducing. Any restriction on creating, preserving, or discarding embryos that substantially interferes with a decision to have or not have offspring would have to meet a higher standard than that of rational basis.[14] The state's moral concern with demonstrating respect for human life without more would not justify infringing a person's right to engage in IVF or avoid reproduction by discarding unwanted embryos.[15]

Whether direct restrictions on embryo research are constitutional would depend on whether that research is part of a constitutionally protected right to research or is otherwise required as part of a negative right to

obtain needed medical treatment. I have analyzed those issues elsewhere and will not repeat them here in detail.[16] The validity of a First Amendment right to research turns on whether the restriction is aimed at the content of the ideas or knowledge sought in the research and whether it is a content-neutral restriction based on the means used in the research to generate knowledge. If content-based, the First Amendment is implicated and the restriction is most likely invalid. On the other hand, if the restriction is aimed at the methods used without regard to the subject-matter of the research, then there is a greater chance that the restriction is constitutionally valid.

There is a plausible case that restrictions on the use of embryos in research are method-based and not aimed at any particular ideas that would be generated. If so, it may be that only a rational basis for the methods-based restriction is needed, as is the case with research restrictions requiring informed consent or avoiding cruelty to animals. Whether such restrictions are constitutional then will depend on how stringent and demanding the courts will be in applying a rational basis test when important interests such as research and treatment are at stake. If a more demanding test is applied, one more akin to the intermediate scrutiny standard sometimes used in evaluating non-content based restrictions on speech, then state restrictions on embryo research might be struck down.[17]

Another basis for constitutional protection for ESC research could arise from its connection with developing effective treatments for illness and disease. One could argue that there is a fundamental negative right to have and use effective medical treatments as part of a person's due process right to life or liberty. If so, government could not prohibit the use of a safe and effective therapy because it used ESCs or was derived from research based on the destruction of human embryos. Because research with ESCs is necessary to test and develop such therapies, it too must be protected as part of the negative right to receive necessary medical care.

At present such an approach has several problems. One is that the courts have not yet recognized a negative right to receive necessary medical care. A federal appeals court panel so held in the context of terminal patients seeking access to Phase II experimental drugs but that decision was reversed en banc and further review denied by the Supreme Court.[18] Even if there were a negative right to use established therapies, it does not follow that bans on the research necessary to develop those therapies are invalid. If the research ban has independent justification, it may be that the research is too far removed from establishing a safe and effective therapy to be protected. While some very targeted late-stage research might be protected under such a right, earlier stage research might not be.

Despite these difficulties with finding a constitutional right to research or treatment, courts nevertheless might carve out a constitutional role in arbitrating ESC controversies in the future. This would be more likely if ESC therapies were established as safe and effective and a state tried to block their use, or prevented a person from objecting to their use on grounds of conscience. As we have more experience with ESC research and therapy and the Supreme Court is pushed to deal with other issues at the beginning of life, we may see in future years a greater role for judicial scrutiny over ESC research and access to medical care generally.

III. Funding Issues

The main battles of the last decade over ESC research have been about federal funding policy, not restrictions on private investment in ESC research. Federal funding has been the focus of debate because it is necessary for early-stage science, like ESC research, which is too far upstream from marketable products to draw much private investment. Because private investors cannot capture for themselves alone the benefits of such investments, they have no incentive to invest to produce that knowledge. The burden thus falls on the government to do so, as it does with other public goods, such as national defense and highways.

Ethical controversy, however, may plug the federal funding spigot. It did so with regard to fetal tissue transplantation research in the late 1980s. It took the election of Bill Clinton in 1992 to unplug it. A parallel story has unfolded with federal funding of ESC research and George W. Bush's highly restrictive funding policy. The story of federal funding for embryo research has a long history, going back to 1975 and the views of the Ethics Advisory Board (EAB) — the first federal review body in this area — about funding research into IVF.[19] The Reagan and Bush administrations disbanded the EAB, so no IVF or embryo research was ever funded. President Clinton in 1992 asked Harold Varmus, his new head of NIH, to develop guidelines for embryo research. The NIH Human Embryo Research Panel in 1994 recommended several instances in which embryo research should be funded, including some cases in which creating embryos solely for research was justified.[20] In 1994 Congress had become Republican. A rider attached to the 1995 appropriation bill banned the use of federal money to create embryos for research or for destructive embryo research.[21] Known as the Dickey-Wicker amendment, it has been attached to every appropriations bill since.

These developments formed the backdrop for the debate over federal funding of ESC research. The issue arose in 1998 when Thompson and Gearhart reported the first successful culturing of human embryos in the laboratory. A key question was whether the government could fund such research given the Dickey-Wicker ban on funding destructive embryo research. Secretary Donna Shalala of HHS asked Harriet Raab, the General Counsel of HHS, to advise as to the legality of such funding. Raab's legal opinion was that embryonic stem cells were not organisms and thus not embryos within the meaning of Dickey-Wicker. As a result, although ESCs are derived from embryos, they are not themselves embryos, and thus not covered by the federal ban on funding research with embryos.[22] Research opponents argued that funding violated the spirit of the amendment, if not its letter, but Raab's opinion has carried the day, and neither President Bush nor Congress sought to change it.[23]

The NIH then developed guidelines for funding ESC research and was ready to make grants when the new Bush administration in 2001 halted such efforts.[24] Although George W. Bush professed right to life beliefs, it was unclear whether he would find the scientific arguments for proceeding with research more persuasive than the right to life arguments against doing so. His decision was announced in an August 9, 2001 speech nationally televised in those halcyon days before 9/11.[25] It was Bush's first public policy address to the nation and generally won good marks, though it pleased neither side in the stem cell wars.

For the scientists Bush allowed NIH funding to go forward, but only for research with ESC lines that had already been derived.[26] For the embryo protectionists, no federal funding would be available for deriving new lines or for research with ESC lines derived after his August 9 speech. There would thus be no direct federal funding or encouragement of the destruction of additional embryos. While each side had problems with the Solomonic qualities of this position, it did allow research to go forward, albeit in a limited way.[27]

The limitations of the August 2001 cut-off date quickly became apparent. Only a few of the lines were easily available, they provided little genetic diversity, and had been cultured with mouse feeder cells, which raised the risk of infection and contamination. Many additional lines would be needed for the field to progress. Banning federal funding for new privately derived lines would greatly slow the field, in part because of the hoops it required of institutions and investigators who received federal funding for other projects to jump through.[28] Institutions could not get involved with hESCs unless they were in a position to physically separate laboratories receiving federal and non-federal funds. Even Bush's own head of NIH eventually agreed that the limits on federal funding had hampered ESC research.[29]

The conclusion of the funding saga is that federal funding will inject new resources and energy into stem cell science. No funding is available for the destruction of human embryos or for research with lines derived from embryos created for research purposes, but it may be provided for research on the hundreds of ESC lines created from leftover embryos since 2001 and which will be created in the future.

Several states jumped into the breach, most notably California with the $3 billion commitment it made in 2004 with passage of Proposition 71.[30] Pressure mounted in Congress to loosen the screws on federal funding. A bipartisan bill, Castle/DeGrette, passed the House in 2004. Stem cell funding was an issue in the 2004 presidential race and again in 2008, with the question debated by the candidates in nationally televised presidential debates each year. A bipartisan bill to lift the federal ban on new lines passed both houses of Congress 2005, but was vetoed by the president. The 2006 Congress re-enacted it, only to have it vetoed again.[31]

The 2008 election of Barack Obama has radically shifted the federal funding situation. In March 2009, President Obama ordered the lifting of the moratorium on funding of ESC research with new lines. In his statement accompanying the lifting of the funding moratorium, President Obama said:

> When it comes to stem cell research…our government has forced…a false choice between sound science and moral values. In this case…the two are not inconsistent. As a person of faith, I believe we are called to care for each other and work to ease

> human suffering. I believe we have been given the capacity and will to pursue this research and the humanity and conscience to do so responsibly...
>
> The majority of Americans — from across the political spectrum, and of all backgrounds and beliefs — have come to a consensus that we should pursue this research. That the potential it offers is great, and with proper guidelines and strict oversight, the perils can be avoided.[32]

The Obama policy did not, however, do away with all limits on federal funding. There would be no funding of derivation of cells or of ESCs derived from embryos created for research purposes, by nuclear transfer or parthenogenesis, and no funding of research in which ESCs or induced pluripotent cells are introduced into non-human primate blastocysts or involving animals in which ESCs may have contributed to the germ line. In addition, federally funded research must comply with regulations to assure donor voluntariness and understanding.

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IV. Regulatory Issues

Although federal funding of ESC research has been controversial, no controversy exists over the need for regulation of ESC research. The federal common rule applies to all institutions that receive federal research funds, even if a particular research project occurring there has not been federally funded. But research on ESCs may not itself qualify as research with "a human subject," even though interactions with persons who provide the gametes or embryos may still require IRB review.[34] Also, IRBs may not be well-situated or have the expertise to handle the special ethical issues that arise in ESC research.

A set of guidelines specifically for ESC research has emerged during this period. The Bush funding guidelines took main elements from those drafted by Clinton's NIH, which reappear now in the Obama rules. California developed its own set of rules for research carried out under grants from the California Institute of Regenerative Medicine (CIRM), which share many of those features, as do the rules adopted in other states that have independently funded ESC research. Scientific organizations such as the National Academy of Sciences (NAS) and the International Society for Stem Cell Research (ISSCR) have played an important role, and professional groups of doctors involved with IVF, such as the American Society of Reproductive Medicine and the American College of Obstetrics and Gynecology, have issued guidelines for some aspects of ESC donation.

Because some regulation is needed to guide scientists and reassure the public at large that science is not out of control, it often falls to scientists themselves to develop those rules.[35] Indeed, professionals who see a looming threat of government regulation are usually quick to preempt outside regulation with their own guidelines. Professional efforts are of course self-serving, and for that reason may require close scrutiny. However, they may also provide some degree of normative certainty and signal to the public and lawmakers that scientists are acting responsibly as they seek to go forward, even as funding and other issues are fought out.

The United States in 2003 was faced with a regulatory vacuum that could stifle the ESC science even further than the lack of federal funds. The National Academy of Sciences stepped into this breach with a committee to develop guidelines so that the field could move forward despite the lack of federal support.[36] That committee operated publicly, was not dominated by scientists, took input from many affected actors, and found a consensus on what was ethically acceptable at that time and for the foreseeable future.

Such a move was important for the field to move forward. First, it assured the public and scientists that there was an ethically acceptable framework for ESC research, with attention to the rights of those donating embryos and oversight of practices that were more controversial. Second, it provided scientists, institutions, states, and other countries a model to follow in the research they conducted or sponsored. Third, it provided a sound basis both for private funding and for donation by families of embryos and gametes for ESC research. As a result, the NAS guidelines became the "industry standard" for both institutions and stem cell scientists.[37] Of course, some may disagree with particular portions, and other stem cell organizations may develop competing versions.[38] Particular details become less important than the guidelines and oversight that an authoritative set of professionally derived guidelines provide. The NAS now has a standing com-

mittee on ESC research to monitor the field and recommend changes in guidelines.[39]

There is a wide degree of consensus about the main substantive elements of a regulatory approach. The cardinal principle here is the autonomy of the gamete and embryo donor. No gametes or embryos should be donated for ESC research unless the person is fully aware of all relevant aspects of the donation and makes the donation free of untoward influence or unacceptable inducement. With regard to informed consent, for example, the donor must sign a written consent form that states the following: that the donation is voluntary; that the donor has been informed of alternative uses of embryos; what will happen to the embryos in derivation of ESCs; that the ESCs might be maintained for years; that there is not restriction on who might benefit from the donation; that there will be no direct medical benefit to the donor; that the research results may have commercial value in which the donor will not share; and that information might be retained that could identify the donor's identity.[40] In cases where donor sperm or egg has been used to create the embryo donated to research, Bernard Lo and others have argued that gamete donors should be informed that their gamete donation could lead to destructive ESC research.[41]

To guard couples going through IVF against intrusion or pressure from their doctor, someone other than the doctor treating them must ask for consent "whenever practicable." No more stimulation should be imposed or eggs retrieved than they would want for their own treatment. Also, they must make the decision to donate at the time they remove their embryos for storage, and cannot do so by advance directive. Nor may any "inducements" be offered for the donation.

Persons might debate the need for particular elements of this regulatory regime, for example, why consent to embryo donation for ESC research should not occur at the time one creates the embryos or has them frozen.[42] The most significant area of disagreement, however, is whether a ban on inducements is justified in the case of women who donate eggs for research. Eggs are a scarce resource and a limit on the creation of new ESC lines, whether by SCNT or for research generally. Women who donate eggs undergo significant bodily intrusion and deserve to be paid for their efforts. Indeed, there is a well-developed system for paying egg donors for infertility services. Logically, it should be extended to paying donors for eggs to be used in research as well, yet there is great resistance to doing so.[43] The NAS in 2005 took a cautious position and recommended against any payments beyond transportation expenses without argument or analysis of why that position was chosen. But it did state that the issue should be revisited with experience, which in some states may not be easy to do. California and Massachusetts, two pro-ESC research states, also included bans in payment to egg donors for research in their enabling legislation.

The result of such a politically driven position is the anomaly that human subjects in research generally are paid as are egg donors to infertile couples, but not egg donors for research. This ban has created a barrier to obtaining eggs for SCNT and creating embryos for research, and may need to be changed for the field to progress. The ethics committees of the two main professional organizations of physicians involved in stimulating ovaries and removing eggs have come out in favor of payment for donation for research on the same terms as paying for infertility donation. The ISSCR guidelines leave it up to the law of the particular jurisdiction. The New York state board responsible for regulating this area has now concluded that payments of up to $10,000 may be made to egg donors for research, which is comparable to the going rate in New York for infertility donors.[44] It is likely that other states will follow suit, and that payment to egg donors for research will eventually be permitted on a wider basis than now occurs.

The emerging consensus about ESC regulation has also found common ground over the need for a special review body beyond IRBs to review individual ESC projects because of the specialized nature of the scientific and ethical questions posed by ESC research. The NAS guidelines were a key step in this direction. It called for the creation of a new institutional structure that gave a more expert and specialized review than the familiar institutional review boards (IRBs) in place to review human subjects research.[45] The ESCs themselves were not persons, and the research was not being done on the persons who provided the gametes or embryos. Yet they would have ethical and legal interests that needed protection that IRBS could not provide.

To have the field adequately guided, some entity in addition to IRBS would be needed. This new entity body was called an Embryonic Stem Cells Research Organizations (ESCROs).[46] In addition to any required IRB review, an ESC researcher would also need ESCRO approval to proceed with ESC research. While some persons have argued that another layer of review in addition to an IRB is costly and delaying, the argument for them was the need to assure that there was adequate expertise about the ESC research and the special ethical problems which it posed, which an IRB might lack. It would also assure the public that careful review of ESC research was occurring. The idea quickly caught on in most places doing ESC research and in the

state and professional guidelines, e.g., ISSCR. Surprisingly, the Obama regulations for ESC research do not require it. However, most institutions receiving federal ESC research funds may still require it.

A final area of regulatory concern has been the creation of human-nonhuman chimeras to test the safety of ESC differentiation and proliferation. Neurologic researchers have been prominent in using such models because of the difficulty of testing in patients the safety of ESC-derived progenitor cells for treating spinal cord injuries, Parkinson's disease, and other central nervous system disorders in humans. While objections against any interspecies mixing are easily overcome (think pig sources for insulin and heart valves), the more nagging question is the fear that nonhuman animals will have human brains and related mental capacities ordinarily found in humans, thus raising knotty questions about their moral status. Do they then deserve the rights and respect accorded human subjects? How many cells must be infused to give them some human standing? How can one measure the presence of the characteristics that confer moral status? The NAS took the position that infusing hESCs into nonhumans at any stage of development requires ESCRO and animal care committee review. They specifically prohibit the transfer of hESCs to nonhuman primate blastocysts, but they do not prohibit transferring them into primate fetuses or primates at later stages of development or into other large mammals at the embryonic stage.[47] In addition they prohibit any breeding of animals into which hESCs have been introduced. Later revisions of the guidelines cure some of these problems, but there is still room for improvement.[48] Working out the rules for human-nonhuman chimeric research will require more debate than has yet occurred.

The 10-year battle over ESC research has thus yielded a wide consensus on the need to protect the interests and autonomy of those being asked to contribute gametes or embryos for ESC research. Special committees to oversee the protection of donor interest and the need for the research add an additional layer of protection. The consensus about regulation is a further sign of the ethical and legal infrastructure that is now in place for further developments in ESC science. A remaining problem, however, is the lack of one central regulatory body. With so many jurisdictions and advisory bodies having weighed in on the topic, there is a risk of redundancy and confusion, with some ESC research receiving multiple reviews. For example, ESC lines established in one jurisdiction may have to undergo another ethical review if those lines are used in an institution in another jurisdiction. Ways to minimize the multiplicity of review will have to be devised.

V. Translation into the Clinic

The ESC research field has been marked by often extravagant claims about the likely curative power of ESC research (also by claims by opponents about the curative power of adult stem cells, which are not as pluripotent as ESCs). Theoretically, ESC research could lead to treatment or cures for diabetes, cancer, heart disease, spinal cord injuries, macular degeneration, and neurodegenerative diseases such as Parkinson's and Alzheimer's. But we are a long way from doing so. Getting there will require "translation" of ESC research into clinical research and eventually clinical medicine. The translation process poses its own set of ethical and regulatory issues.

As with other regulatory issues for ESC research, much work has been done by ethicists on the ethical principles that should guide translational research. In some respects the ethical challenge is no different than with other new therapies. It is essential that randomized clinical trials be held so that the safety and efficacy of treatments can be established. Clear outcome measures of improvement, such as survival, disease-free survival, or improvements in objective measures of disease-related function, are needed to determine whether there is evidence to change prevailing medical practice, as well as justify the imposition of the risks on research subjects. In some cases, such as Parkinson's and other neurologic diseases, defining and testing for benefit may be difficult.[49]

Generally, participants in a clinical trial should receive all interventions that are known to be safe, effective, and commonly prescribed by physicians.[50] Yet trials should also be designed in a way that will provide reliable information from the study. Usually this will mean some form of a randomized trial, often with the placebo as a control for the new therapy. To ensure that patients get established therapy, the investigational agent can be given as an "add on," with half of subjects getting the new therapy in addition to the old and half getting a placebo.[51]

Doing clinical research with ESCs poses additional safety challenges because ESCs are cellular products which are more difficult to manufacture and purify in a standard way than the small molecule drugs produced by pharmaceutical companies. As an ethics advisory group at Johns Hopkins noted:

> [T]he manufacture of a drug or device and the generation, growth, and maintenance of a cell line are quite different processes. While new drugs used in U.S. clinical trials must meet rigorous FDA standards for production, the process of deriving cell lines does not map neatly to concepts of good manufacturing practices. For example, hESCs

are derived following fertilization (involving cells of varying genetic make-up), manipulation and destruction of the blastocyst, and subsequent cell culture, all of which have less predictability than combining precise quantities of known chemical products.[52]

Stem cells pose additional risks because they are often grown in culture for some time before differentiated to produce the progenitor cells that may then be infused into a patient in a clinical trial. As the Hopkins group noted, "The longer cells are grown in culture, the more likely they are to acquire genetic and epigenetic changes, such that later passages may not be genetically identical to earlier passages."[53] Some stem cell preparations may lack immunogenicity while others not. Systematic assessment of integrity and potency of cell products is essential for minimizing risks to patients, but it is unclear what tests will serve this purpose (e.g., DNA sequencing, expression analysis) and provide meaningful data about risks to researchers, human subjects, and review committees.[54] The risk of transferring the cell donor's own genetic disease must also be considered.

Rigorous preclinical testing in animal models whenever possible is especially important because stem cells can act through multiple mechanisms. Yet animal models may not exist for many diseases sought to be treated with ESCs or may not be comparable in important ways. Take central nervous system disorders — from spinal cord injuries to Parkinson's disease and Alzheimer's. Pharmacologic agents that have shown promise in nonhuman animal models of stroke, for example, have not been successful in humans. The predictive utility of animal models for human diseases is often unknown even when risks, such as tumorgenicity and the need for immunosuppression, can be evaluated in nonhuman animal models.

These limitations on animal studies show the importance of expertly qualified oversight bodies for assessing preclinical data. The ISSCR has emphasized the need for individuals with stem-cell-specific expertise to be involved at each step along the translational research process. Other commentators, such as Bernard Lo, stress the importance of integrated scientific and ethics review. This will require coordination among the several oversight bodies that have some say in whether research should go forward — IRBs, SCROs, the FDA, and national level review bodies. Since SCROs have been constituted primarily to review the ethical issues peculiar to stem cell research, such as the derivation of ESCs and donation of gametes and embryos, they may not have the scientific expertise to review the scientific and design aspects of clinical trials. Lo suggests that an integrated scientific and ethical review such as that conducted by the Recombinant DNA Advisory Committee (RAC) for gene transfer research be followed here as well.[55]

A major problem for researchers, IRBs, and other oversight bodies in translational research is to ensure voluntary informed consent. Patients who desperately want a cure or improvement may jump at the chance to take part in a new study, especially one with the sexy cachet of "stem cell." The problems here are familiar ones, but the political and scientific stakes are likely to be higher because of the great interest in stem cells generally.

A major problem for researchers, IRBs, and other oversight bodies in translational research is to ensure voluntary informed consent. Patients who desperately want a cure or improvement may jump at the chance to take part in a new study, especially one with the sexy cachet of "stem cell."[56] The problems here are familiar ones, but the political and scientific stakes are likely to be higher because of the great interest in stem cells generally. The science is complex, the risk of therapeutic misconception is high, and the patient's condition, especially in neurologic research may be grave. Consider what must be done to make sure that the subject understands that the risks "include sensitivities surrounding the source of cellular products, tumor formation, immunological reactions, unexpected behavior of the cells, and unknown long-term health effects."[57] Subjects must also be educated about the realistic potential for therapeutic benefit so that they may have recourse to reasonable therapeutic alternatives. If there are not alternatives, they may harbor misconceptions about the potential for therapeutic effect ("the therapeutic misconception").[58] Given the complex issues involved, formalized methods of assessing understanding, such as interviews, questionnaires, or

consent monitors, may be needed.[59] A long and time-consuming consent process seems inevitable.

The selection of subjects for early stem cell trials must also be ethically defensible. It is now standard to use the sickest patients for Phase I safety studies because they are not as likely to be harmed as less sick patients. Yet they are more likely to be prey to the therapeutic misconception and least able to give a valid informed consent. On the other hand, they may not be as appropriate for Phase II studies because they are the least likely to benefit, which could lead to the false conclusion that the intervention provides no benefit when it might work in healthier patients. Oversight bodies must also consider when it is acceptable to include children in early human trials.

Risks to research participants should be further minimized through careful patient-subject monitoring and timely adverse event reporting. Subjects' health is of utmost importance and should be carefully monitored throughout the clinical trial. A data monitoring plan with aggregate updates to peer review committees should be required. A commitment to publication of both positive and negative results and adverse events is needed to prevent others from being subjected to unnecessary risk in future clinical research and to ensure the development of clinically effective stem-cell based therapies.[60]

Questions will also arise about providing innovative therapy outside of the context of a formal clinical trial.[61] The ISSCR guidelines recognize that there may be exceptional circumstances that allow clinicians to attempt medically innovative care in a very small number of seriously ill patients, subject to the stringent oversight of others. These criteria include independent peer review of the proposed innovative procedure and its scientific rationale, institutional accountability, rigorous informed consent and close patient monitoring, transparency, timely adverse-event reporting, and a commitment to move to a formal clinical trial after experience with at most a few patients. Many clinics that tout stem cell therapies for a profit in Eastern Europe and Asia would not meet those standards.

While the general principles for ethical translational research are known, the specifics can be resolved only in specific clinical contexts, which include the underlying disease, alternatives therapies for it, the site where stem cells are injected, the amount and purity of cells, and the intended function of the transplanted cells. The resolution of these issues for Parkinson's disease will differ from other neurologic conditions, which will differ in turn from treatments for macular degeneration, diabetes, heart disease, and the many other conditions for which stem cell interventions may be tried. As translation issues come to the fore, the ethical steam of the debate should lessen. The problems facing researchers and clinicians will then be the standard ones of context-driven risks, benefits, alternatives, and showing whether new interventions work or not.

VI. Future Issues

This survey of the ethical, legal, funding, regulatory, and translational landscape shows that we have made great progress during the last decade in coming to terms with the issues that this novel research platform raises. Despite the ethical debate and controversies that have roiled the field, the science has made much progress, though it undoubtedly has been slowed by the reluctance in the United States to fund research with new cell lines. With the ethical and legal landscape now well defined, the field is poised to move forward at a more rapid pace. The hard work will be doing the science so that the nature of stem cells and their differentiation is better understood and the clinical safety and efficacy of treatments derived from them is established.

New challenges will arise as ESC-based treatments are tested on a wider basis and come to be accepted as safe and effective treatments for many medical situations. A major challenge will be to ensure that they are available to patients of all means. This is a question of the payment system for health care. Persons with means may be able to obtain experimental treatments before others. But if ESC-based treatments are shown to be safe and effective, then they will be part of ordinary care and covered to the same extent and with the same limitations as are other treatments. There will be nothing here to distinguish ESC therapies from other treatments. Indeed, for many indications, they may have significant cost advantages. They will be available to persons who have health insurance or who qualify for Medicare or Medicaid or other public health programs to the extent that they are seen as standard therapy for particular conditions.[62]

Another issue will be to respect the views of persons who morally object to destroying embryos in research or using them in treatment. Strict right-to-lifers may object to receiving treatments using ESCs or their derivatives. ESC-derived treatments should be labeled as such so that persons with conscientious objections to their use may decline them for themselves. It would not follow, however, that they should have a legal right to decline them for minor children or incompetent persons over whom they have decisional authority because the best interests of those patients would take priority. Limits will also need to be set on the right of doctors, nurses, and other health care providers to refuse to deliver or participate in treatments because they involve ESCs or have been derived from them. Some treatments may be so far removed from direct use of

stem cells that their right of refusal does not come into play. In other cases the obligations as doctors, nurses, and health care providers must give way to the needs of patients dependent on their services. This conflict is not unique to stem cells. Rules developed for objection to participation in abortion will have to be adapted to deal with objections to use of stem cells as well.[63]

Finally, we should consider the issues that will arise if non-embryonic sources of pluripotent cells become available. The experience to date with induced pluripotent stem cells (iPS) is very promising. Shinya Yamanaka and then Thomson have discovered ways to reprogram somatic cells to a primordial state and then redifferentiate them to tissues of choice.[64] Initally done with viral vectors that carry their own risks, progress has been made in using non-viral factors to recreate stemness. Much work is needed to show that they have the same characteristics as embryonic sources of pluripotent cells and will work as well in therapy. Because of the need to compare them to ESCs, they will not supplant them for some time, if they ever do. But if they do become as safe and effective, it will remove a major source of conflict from cell reprogramming and regeneration therapies.

It is important to note, as Yamanaka does, that though iPS technology has enormous potential, it is still at its infancy, and certainly does not do away with the need for ESCs.[65] Patient or disease-specific iPS cells should provide unprecedented cell sources for better understanding the pathogenesis of diseases and for developing safer and more effective drugs, and may even one day make it possible to perform cell transplantation therapies for a wide variety of diseases and injuries, while circumventing ethical issues and immune rejection. But that day is not yet here. To realize the clinical applications, he emphasizes the need

> to achieve complete and uniform reprogramming in iPS cells. Failure to do this would result in resistance to differentiation and increase the risk of teratoma formation. The stochastic model predicts that iPS cells can be generated from a variety of somatic cells with a variety of methods. We have to evaluate different original cells and induction methods to determine the best combination to allow us to generate the safest iPS cells for clinical application.[66]

iPS cells will raise their own unique ethical issues. Of particular concern would be the ability to derive human gametes from them, as appears possible with human ESCs.[67] Such a feat might lead to easy production of the eggs needed to carry out some important forms of ESC research, such as SCNT or tailoring the stem cell line sought to a particular genotype. If so, this would lessen the need for female donors and the controversy over paying women to produce eggs for research. The ethical concern is that pluripotent cell-derived gametes would then be used for in vitro reproduction, either with male or female gametes provided by one's partner or or with both sets of gametes derived from the somatic cells used to derive germ cells. Persons who lack gametes due to chemotherapy, disease, or trauma might welcome the availability of gametes derived from their own somatic tissue. In addition to significant concerns about the health of resulting children, such a practice would raise kinship and family issues as daunting as any that have arisen in assisted reproduction.[68] Somatic cell donors would be the biologic parent of such offspring, and in some cases could be the genetic father and mother of the child. These questions take us outside of stem cell research and therapy into the outer reaches of human reproduction. They are a vivid preview of issues to come from progress in perfecting the ability to induce gametes from induced pluripotent stem cells or from ESCs themselves.

VII. Ethical Conflict and the Pace of Innovation

This survey of the main ethical conflicts that have shaped the field of ESC research show that ethics and law can have a major impact on the pace of a science. Science does not happen in a vacuum, but is embedded in the soil of the societies in which it occurs. The ESC experience shows how important law and ethics are at early stages of a science, and how they can encourage, facilitate, or retard the development of new science and technology. In some cases, ethical roadblocks can lead to "inventing" around them, a frequent practice when existing patents block a firm's forward path. Opponents of ESC research have argued that the Bush restrictions on federal research funding led directly to the emergence of iPS cells and the opportunities which they offer.

After 10 years of debate and controversy with ESCs, the ethical issues have now been thoroughly aired and the path is open to rapid development. Ethical issues will remain, but they are the issues that arise in bringing any new discovery out of the lab into clinical research and then clinical use. Differing perceptions of the moral status of the early embryo will still be important, but they appear no longer to be the major stumbling block that they have been. One can be more optimistic than earlier that the long-awaited payoffs from ESC discoveries may eventually come to pass.

References

1. The FDA has also approved Phase I stem cell clinical trials for Batten Disease and Pelizaeus-Merzbacher Disease, which are much rarer than spinal cord injury. B. Lo, "Case-Based Reasoning in Stem Cell Clinical Trials: The Case of Parkinson's Disease," *Journal of Law Medicine & Ethics* 38, no. 2 (2010). Since approving Geron's clinical trial, the FDA has put the study on hold pending more data on cyst formation and immunosuppression in the animal studies used to support Geron's application. P. F. Dimond, "Special Report, Geron's Setback with Testing Its hESC Therapy in Humans Points to FDA's Continued Cautionary Stance," August 28, 2009, *available at* <http://www.genengnews.com/specialreports/sritem.aspx?oid=61364204> (last visited April 7, 2010).
2. J. A. Thomson et al., "Embryonic Stem Cell Lines Derived from Human Blastocysts," *Science* 282, no. 5391 (1998): 1145-1147; M. J. Shamblott et al., "Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells," *Proceedings of the National Academy of Sciences of the United States of America* 95, no. 23 (1998): 13726-13731.
3. This is a conflict over the methods used to obtain the cells used in research. Concerns about research methods, however, can arise at any stage of a science. Research methods can be directly harmful, as with the release of toxic agents or microbes into the biosphere. Or they could use animals in cruel ways or human subjects without consent. The creation of chimeras may also be contentious. See *infra* note 47.
4. Debates over embryo status and ESC research are complicated further by their connection with cloning, assisted reproduction, and other technologies at the beginning of life. The announcement of lab culture of human ESCs came a year after Ian Wilmut's announcement of nuclear transfer cloning of a sheep had roiled the world with the possibility of reproductive cloning and genetic control over progeny. Somatic cell nuclear transfer (SCNT) cloning has been thought necessary to generate ESCs with particular genomes to model disease and to produce histocompatible replacement tissue, and has played a central role in ESC policy debates.
5. R. P. George and C. Tollefsen, *Embryo: A Defense of Human Life* (New York: Doubleday, 2008).
6. For an analysis of this issue, See D. W. Brock, "Creating Embryos for Use in Stem Cell Research," *Journal of Law, Medicine & Ethics* 38, no. 2 (2010).
7. Efforts at state constitutional amendments or legislation protecting all fertilized eggs and embryos have usually failed. In Colorado such an amendment made it to the ballot but failed. See Amendment 48 (2008), *available at* <http://www.leg.state.co.us/lcs/initrefr/0708initrefr.nsf/89fb842d0401c52087256cbc00650696/16f403e0c19126f98725744b0050fd4d/$file/amendment%2048.pdf> (last visited April 8, 2010).
8. Gallup Poll, "Six in 10 Americans Favor Easing Restrictions on Stem Cell Research," 2007, *available at* <http://www.gallup.com/poll/27898/Six-Americans-Favor-Easing-Restrictions-Stem-Cell-Research.aspx> (last visited April 8, 2010).
9. Sometimes they distinguish research embryos created by fertilization from those created by SCNT. In Massachusetts and Missouri, for example, it is illegal to create embryos for research by fertilization but not by SCNT.
10. I have argued that the difference is a symbolic one – the line is a place to symbolize or mark a person's firm commitment to respect for human life. The benefits of that symbolic position, however, should be weighed against the loss in knowledge that results by not having this method of obtaining embryos for research available. J. A. Robertson, "Symbolic Issues in Embryo Research," *Hastings Center Report* 25, no. 1 (1995): 37-38.
11. J. A. Robertson, "Embryo Culture and the Culture of Life: Constitutional Issues in the Embryonic Stem Cell Debate," *University of Chicago Legal Forum* 2006 (2006): 1-40.
12. 410 U.S. 113 (1973).
13. 505 U.S. 833 (1992).
14. J. A. Robertson, "Assisting Reproduction, Choosing Genes, and the Scope of Reproductive Freedom," *George Washington Law Review* 76, no. 6 (2008): 1490-1513.
15. *Id.*
16. J. A. Robertson, "Embryo Culture and the Culture of Life: Constitutional Issues in the Embryonic Stem Cell Debate," *University of Chicago Legal Forum* 2006 (2006): 1-40, at 31-38.
17. *Id.* A relevant case here is *Turner Broadcasting, Inc. v. FCC*, 512 U.S. 662 (1994) (more than minimal rational basis required for First Amendment restriction).
18. *Abigail Alliance for Better Access to Developmental Drugs and Washington Legal Foundation v. Eschenbach*, 445 F.3rd 470 (D.C. Cir. 2006); reversed en banc, 495 F.3d 695 (C.A.D.C. 2007); cert. den. 128 S. Ct. 1069 (2008).
19. The EAB recommended that IVF research go forward and then no embryo research occur without EAB approval. R. M. Green, Political Interventions in U.S. Human Embryo Research: An Ethical Assessment," *Journal of Law, Medicine & Ethicis* 38, no. 2 (2010).
20. President Clinton immediately said he would not permit funding of research embryos. See Green, *id.*
21. The first version of it was Pub. L. No. 104-99, 110 Stat. 26 (1996). For later cites, see President's Bioethics Council, *Monitoring Stem Cell Research*, 2004, at note 8, page 49.
22. See H. Raab, Memorandum to Harold Varmus, M.D., Director, NIH, Federal Funding for Research Involving Human Pluripotent Stem Cells, January 15, 1999.
23. L. Guenin has argued that ESC research is research in which embryos are destroyed because it is necessary to destroy them to get the ESCs, but has failed to convince lawmakers of his position. L. M. Guenin, *The Morality of Embryo Use* (New York: Cambridge University Press, 2008); L. M. Guenin, "A Proposed Stem Cell Research Policy," *Stem Cells* 23, no. 8 (2005): 1023-1027. If the Dickey-Wicker rider had said "research involving embryos," there might have been a different outcome.
24. National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells, *Federal Register* 65 (August 25, 2000): 51975-51981. The National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research* (Rockville, MD: U.S. Government Printing Office, 1999).
25. Remarks by President George W. Bush on Stem Cell Research, August 9, 2001, reprinted in President's Bioethics Council, *Monitoring Stem Cell Research*, Appendix B, 181-185, 2004.
26. His administration claimed that more than 60 lines fit that bill, but in time only between 15-20 lines were available. Some could not be verified. Some had onerous licensing restrictions, and some sources were not set up to become suppliers throughout the world. Interestingly, it is cells from a Bush-approved line at the University of Wisconsin that led to the first clinical trial with ESC therapy.
27. Germany also used a cut-off time. ESC lines cannot be legally derived in Germany, but German researchers could import lines that had been derived legally in other countries before January 1, 2002. See J. A. Robertson, "Assisted Reproduction in Germany and the United States: An Essay in Comparative Bioethics," *Columbia Journal of Transnational Law* 43, no. 1 (2004): 189-227, at 212. See also J. A. Robertson, "Causative vs. Beneficial Complicity in the Embryonic Stem Cell Debate," *Connecticut Law Review* 36, no. 4 (2004): 1099-1113 (arguing that Bush's complicity standard would also support federal funding of those lines that had been derived in the private sector after the Bush announcement).
28. This required separate equipment, accounting, and even buildings for use of cell lines outside the Bush cut-off. If frozen embryos being stored for use to derive new lines in a separate facility had a freezer shutdown, they could not switch them to the federally funded freezer without disqualifying any embryos there stored.
29. The Director of the NIH actually testified before Congress that the Bush administration funding policy was hurting the progress of ESC science. R. Weiss, "Stem Cell Policy Hampering Research, NIH Official Reports," *Washington Post*, January 20, 2007.

30. See note 31 for an account of Prop 71. New Jersey, Illinois, Wisconsin, Maryland, and New York also made significant commitments, though none as great at that of California.
31. R. Korobkin, "Embryonic Histrionics: A Critical Evaluation of the Bush Stem Cell Funding Policy and the Congressional Alternative," *Jurimetrics* 47, no. 1 (2006): 1-29.
32. President Barack Obama, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," Executive Order No. 13,505, *Federal Register* 74 (March 11, 2009): 10667-10668.
33. Those lines will still have to meet the strict standards for consent of donors, including their consent to use in the particular kind of research in which they will be used. While this will disqualify some lines from federal funding, enough other lines have been created to meet the needs of researchers. See *Federal Register* 74 (July 7, 2009): 32170-32175; Editorial, "Consent Issue Dogs Stem Cell Approval," *Nature* 462, no. 7275 (December 17, 2009): 837 (embryos donated for diabetes research may not be used for other purposes).
34. 45 CFR 46.101 et seq.
35. This was the classic case with the Berg letter that led to Asilomar and the NIH's Recombinant DNA rules. P. Berg et al., Letter, "Potential Biohazards of Recombinant DNA Molecules," *Science* 185, no. 4148 (1974): 303.
36. National Research Council, "Guidelines for Human Embryonic Stem Cell Research," 2005, *available at* <http://www.nap.edu/catalog.php?record_id=11278> (last visited April 8, 2010) [hereinafter "NAS Guidelines"].
37. Critics may question whether such guidelines have enough bite to get the job done. Sometimes professionally developed guidelines are window-dressing. But this does not appear to be the case with the NAS stem cell rules. With the ESC field so eager to move forward and the source so authoritative (the NAS is not merely another professional interest group), they have earned widespread respect and support.
38. The guidelines of the International Society of Stem Cell Researchers (ISSCR) overlap substantially with those of the NAS, but there are differences. Some ISSCR members have pointed out that the NAS guidelines were drafted without international representation: "To hold that the U.S. guidelines can simply be lifted and imported to other international settings ignores the differing political, cultural, and religious perspectives that shape research policy." I. Hyun, P. Taylor, and G. Q. Daley, "Letter," *San Jose Mercury News*, February 8, 2007.
39. Human Embryonic Stem Cell Research Advisory Committee, National Research Council, *2007 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research*, 2007. The changes to the guidelines involved clarifying the phrase "provenance of the cell lines" (changes to Section 1.2); use of the hESCs approved for use in federally funded research (addition to Section 1.4); importation of hESC lines into an institution or jurisdiction (addition of Section 1.5); and allowing ESCRO committees to serve multiple institutions (changes to Section 2.0 and addition of Section 2.1). *Id*., at 3-4.
40. Department of Health and Human Services, "National Institutes of Health Guidelines for Human Stem Cell Research," *Federal Register* 74, no. 128 (July 7, 2009): 321470.
41. B. Lo, L. Parham, and M. Cedars et al., "NIH Guidelines for Stem Cell Research and Gamete Donors," *Science* 327, no. 5968 (February 19, 2010): 962-963.
42. C. B. Cohen and M. A. Majumder, "Future Directions for Oversight of Stem Cell Research in the United States," *Kennedy Institute of Ethics Journal* 19, no. 1 (2009): 79-103.
43. J. A. Robertson, "Compensation and Egg Donation for Research," *Fertility and Sterility* 86, no. 6 (2006): 1573-1575.
44. Statement of the Empire State Stem Cell Board on the Compensation of Oocyte Donors, June 11, 2009. L. Nelson, "New York State Allows Compensation in Egg Donations for Research," *New York Times*, June 26, 2009, at A18.
45. Strictly speaking the research occurring was not "research with a human subject" under the HHS guidelines. 45 CFR 46.101 et seq. See also M. Cho and D. Magnus, "Issues in Oocyte Donation for Stem Cell Research," *Science* 308, no. 5729 (2005): 1747-1748.
46. See NAS Guidelines, *supra* note 36, at 100.
47. See Cohen and Majumder, *supra* note 42, at 91.
48. *Id*. The Obama guidelines also deny funding for such research. See *Federal Register* 74 (2009): 32170-32175, at 32175 ("Chimera ban").
49. See Lo, *supra* note 1; B. Lo, A. Kriegstein, and D. Grady, "Clinical Trials in Stem Cell Transplantation: Guidelines for Scientific and Ethical Review," *Clinical Trials* 5, no. 5 (2008): 517-522.
50. *Id.* (Lo).
51. Special problems may arise here that require sham surgery, so that all patients will think that they are getting the new therapy. See Lo, *supra* note 49.
52. D. J. H. Mathews et al., "Cell-Based Interventions for Neurologic Conditions," *Neurology* 71, no. 4 (2008): 288-293.
53. *Id*.
54. ISSCR 608 commentary.
55. See Lo, *supra* note 49.
56. The willingness to travel abroad to uncertified clinics for untested but highly touted and expensive treatments is an example of the ease with which consent can be obtained. See Hyun, *infra* note 61.
57. International Society for Stem Cell Research, *Guidelines for the Clinical Translation of Stem Cells*, December 3, 2008.
58. See discussion of therapeutic misconception in D. Magnus, "Translating Stem Cell Research: Challenges at the Research Frontier," *Journal of Law, Medicine & Ethics* 38, no. 2 (2010).
59. The Johns Hopkins group argues that researcher and oversight bodies should ensure that the consent process is above reproach, and that it provides few opportunities for even misguided criticism because of the sensitivity and political ramifications of ESC research. See Mathews et al., *supra* note 51, at 291.
60. Bernard Lo and Jeremy Sugarman also make these points. See Lo, *supra* note 49 and J. Sugarman, "Reflections on Governance Models for the Clinical Translation of Stem Cells," *Journal of Law, Medicine & Ethics* 38, no. 2 (2010).
61. Several papers in this symposium address the issue of innovative therapy. See I. Hyun, "Allowing Innovative Stem Cell-Based Therapies Outside of Clinical Trials: Ethical and Policy Challenges," *Journal of Law, Medicine & Ethics* 38, no. 2 (2010) (page numbers coming); P. L. Taylor, "Overseeing Innovative Therapy Without Mistaking It for Research: A Function-Based Model Based on Old Truths, New Capacities, and Lessons from Stem Cells," *Journal of Law, Medicine & Ethics* 38, no. 2 (2010).
62. I do not mean to underestimate the problems that even people with insurance have in getting standard care. Some of those same problems could prevent access to stem cell therapies just as they do to other treatments.
63. Department of Health and Human Services, "Ensuring that Department of Health and Human Services Funds Do Not Support Coercive or Discriminatory Policies or Practices in Violation of Federal Law; Final Rule," *Federal Register* 73, no. 425 (December 19, 2008): 78072-78101, CFR version at 45 CFR 88.
64. K. Takahashi and S. Yamanaka, "Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors," *Cell* 126, no. 4 (2006): 663-676; J. Gearhardt, E. Pashos, and M. Prasad, "Pluripotentcy Redux – Advances in Stem-Cell Research," *New England Journal of Medicine* 357, no. 15 (2007): 69-72; J. Shaw, "Tools and Tests: The Evolution of Stem-Cell Research," *Harvard Magazine* 112, no. 3 (January-February 2010): 24-29.
65. S. Yamanaka, "Elite and Stochastic Models for Induced Pluripotent Stem Cell Generation," *Nature* 460, no. 7251 (2009): 49-52.
66. *Id*., at 51.
67. See references listed in Cohen and Majumder, *supra* note 42, at 94-95.
68. *Id.*