

The More Things Change: The New NIH Guidelines on Human Stem Cell Research

ABSTRACT. Many assumed that the Obama administration would usher in a sea change from the previous administration by expanding NIH support for human embryonic stem cell (hESC) research and reducing the patchwork of state and federal regulations that currently governs it. This article examines the extent to which NIH's new Guidelines are likely to accomplish these goals.

During the Bush Administration, federally fundable human embryonic stem cell (hESC) research was limited to certain kinds of research on, at most, 21 existing stem cell lines of dubious quality (Baker 2008). With the election of Barack Obama, hESC advocates hoped that the National Institutes of Health (NIH) would become the “central source of funding” of hESC research, leading to less duplication of effort, more collaboration, quicker progress toward clinical trials, and “federal rules and procedures to clear up the ethical derivation of new embryonic stem cell lines” (Wong 2009). As expected, President Obama signed an executive order revoking the Bush policy (2009a). Most researchers hailed it as “signal[ing] a sea change from the last Administration” (Holden 2009). NIH (2009c) then issued implementing Guidelines for Human Stem Cell Research.

Throughout the process, the administration announced several goals, including to support and conduct legal, “scientifically worthy” research based on sound, depoliticized science and “open inquiry.” It also sought to “expand NIH support” for stem cell research, “ameliorate” the “patchwork” of standards that now govern it, and ensure America’s “economic prosperity” and “global leadership in scientific discoveries” by preventing its “best scientists” from leaving for other countries. Finally, it sought to support “responsible” research on lines derived with the informed con-

sent of the embryo donors, for which there is broad public support (NIH 2009a & c; Obama 2009a & b).

Each goal raises questions that have received considerable attention. There are continuing debates, for example, about whether the Dickey-Wicker Amendment (Consolidated Appropriations Act, 2009), which prohibits federal funding from being used to support research that involves creating or destroying human embryos, should be repealed and whether it permits federal funding of research on hESC lines derived using nonfederal funds. Scientists and others debate the relative merits of adult stem cells, induced pluripotent stem cells, and hESCs, as well as lines derived from spare IVF embryos versus embryos created via somatic cell nuclear transfer (SCNT) or parthenogenesis. There is considerable debate over standards of informed consent; what to do when existing lines fail to meet those standards; whether hESC research is morally exceptional or should be treated like all other human subject research; and whether the scope of federally-funded research should hew closely to broad consensus, reflect the views of the party in office, or be driven solely by scientific considerations.

In this article, we place these complex issues to one side in order to focus on two less contentious questions: the extent to which the Guidelines are in fact likely to achieve two of their stated goals: expanding federal support for hESC research and ameliorating the current patchwork of standards. As President Obama (2009b) has recognized, federal stem cell policy involves a “difficult and delicate balance” of values and goals. Not surprisingly, many of the administration’s goals stand in tension with one another, and the Guidelines reflect a series of tradeoffs. At least if one is a consequentialist, whether the Guidelines strike an ethically satisfactory balance depends in part on the extent to which they succeed in achieving some objectives at the expense of others. Thus, although we do not resolve these normative questions here, we think that our analysis will prove useful to those who seek to do so.

With respect to the goal of expanding federal hESC research, the Guidelines effect only incremental change in the *scope* of eligible research, preserving all the Bush restrictions except the prohibition on funding research on new lines. Although that amendment expands—in theory, infinitely—the *number* of new eligible lines, much research is based on existing lines, and the number of those that will become eligible depends on how strictly NIH applies its detailed informed consent requirements. Finally, the significance of expansions in the *fundability* of hESC research

is meaningful largely to the extent that such research is *funded*, and we predict that, compared to other funders, NIH's funding will only modestly increase.

With respect to the goal of ameliorating the “patchwork” of standards governing U.S. stem cell research, although the Guidelines centralize crucial aspects of federal policy, and may exert influence even over non-NIH-supported researchers and other research funders and regulators, they almost certainly will not substantially reduce the multiple standards for conducting hESC research that exist in the U.S., much less in the world.

EXPANDING STEM CELL RESEARCH?

The NIH's goal of “expanding” stem cell research could refer to one or more of three aspirations: expanding the *quality and scope* of the kinds of federally fundable hESC research; expanding the number of *lines* on which research is eligible for federal funds; and expanding the amount of federal *funding* of hESC research.

Expanding the Quality and Scope of Federally Fundable hESC Research

Under President Bush's policy, hESC research was eligible for federal funding only if four criteria were met: (1) the embryo-destroying process of deriving the stem cell line must have begun before 9 August 2001, 9 p.m. EDT; (2) the line “must have been derived from an embryo that was created for reproductive purposes and was no longer needed;” (3) the donation “must not have involved financial inducements;” and (4) “informed consent must have been obtained” (NIH 2001). President Obama's executive order implicitly repealed the first Bush criterion, allowing federal funding of hESC research on lines created at any time. This change not only expanded the *number* of eligible lines (as discussed below); it also expanded their *quality*. The Bush lines are not genetically diverse, and many were grown on beds of mouse cells, making any resulting human transplant therapies potentially dangerous (Gordon 2009; Wong 2009).

The order was silent, however, on the remaining three Bush criteria; in his accompanying statement, President Obama (2009b) ruled out only funding research that could “open the door” to reproductive cloning. The Guidelines resolved the issue. Like the Bush standards, the Guidelines require that donors receive “No payments, cash or in kind,” for the embryo. Although many researchers argue that some form of compensation is required to overcome the inhibiting scarcity of embryos (O'Reilly 2008),

and some jurisdictions have begun experimenting with this (Nelson 2009; *New Scientist* 2009), a prohibition on compensation is the predominant policy (NIH 2000; National Research Council 2005; ISSCR 2006). Consequently, NIH's decision was neither surprising nor unusually restrictive. Similarly, the Guidelines retain the requirement that donors give informed consent. Although, as we discuss later, NIH's informed consent standard is in some ways more restrictive than others, the consent requirement itself was hardly surprising or objectionable.

What is surprising, given its departure from prevailing norms (National Research Council 2005; ISSCR 2006)—and is, to many hESC advocates, disappointing (Connolly 2009; NYSCF 2009; *New York Times* 2009; Weissman 2009)—is NIH's decision to continue the Bush policy of only funding research on lines derived from embryos that were created, but no longer needed, for reproductive purposes—i.e., “spare IVF embryos.” Lines derived from all other sources, including parthenogenesis, SCNT, and IVF embryos created for research, remain ineligible.¹ These derivation methods are useful in part because they permit researchers to establish disease-specific lines. Such lines potentially will yield insight into the genetics of disease and better disease models—the most likely hESC-based medical breakthrough in the short term—as well as disease-specific therapies without immunosuppressive problems, a longer term hope. The Guidelines do allow research on lines derived from preimplantation genetic diagnosis (PGD) embryos, but PGD is not available for many diseases, and PGD embryos almost certainly comprise a small fraction of IVF embryos.

NIH explained that its decision “reflect[s] the broad public support for federal funding of research using hESCs created from such embryos based on wide and diverse debate on the topic in Congress and elsewhere.” Other sources, it said, “involve complex ethical and scientific issues on which a similar consensus has not emerged” (NIH 2009b). Indeed, the Guidelines as a whole closely resemble the Stem Cell Research Enhancement Act—a bill passed twice by Congress with bipartisan support before being vetoed by President Bush: like the Guidelines, the Act differs from the Bush policy primarily by permitting funding of new as well as existing lines. The Obama administration's emphasis on national consensus—which does not shift quickly on an issue like hESC research—means that its funding rules are not much different from those of the Bush administration. As Francis Collins, President Obama's nominee for NIH Director, remarked, the Guidelines are “not very radical” compared to the previous regime but instead constitute “a pretty modest but defensible step forward” (Pew 2009).

Expanding the Number of Eligible Lines

Expanding the types of hESC research that enjoy federal funding may not have been NIH's primary goal. According to Story Landis, head of the NIH stem cell task force, "the most important thing [i]s to expand the ability to investigate more lines" (Gordon 2009), and the Guidelines themselves seek to "ensure that the greatest number of responsibly derived hESCs are eligible" for funding (NIH 2009b). The extent to which NIH will accomplish this goal depends on how strictly it applies its informed consent criteria to existing lines.

Unlike the Bush administration's vague requirement that "informed consent must have been obtained," the Guidelines specify precisely what constitutes informed consent in the spare IVF embryo context. In addition to the three Bush requirements that lines were derived using spare IVF embryos provided by donors who gave written informed consent, without payment, the Guidelines establish 12 criteria. Donors must have been informed: of all options available at the health care facility for disposition of the spare embryos; of their right to withdraw consent until the embryos are used or can no longer be traced to them; that the embryos would be used to derive hESCs for research; of what would happen to the embryos during the derivation process; that the resulting hESCs might be kept for many years; that they may not restrict or direct the recipients of any resulting therapy; that they are not intended to directly medically benefit from the research; that they would not receive financial or other benefits from any commercial development of the research; and whether researchers would be able to identify them. In addition, policies must have been in place providing that neither consenting nor refusing to donate would affect the donor's quality of care; consent must have been given at the time of donation; and, unless impracticable, the attending physician treating the prospective donor and the person seeking consent must not have been the same.

These requirements differ from NIH's 2000 guidelines, and from the informed consent requirements of other bodies, including the National Academy of Sciences (National Research Council 2005) and the International Society for Stem Cell Research (ISSCR 2006). In some ways, the Guidelines are more lenient. For example, although NAS and ISSCR require that donors be informed that the embryos will be "destroyed" during the derivation process, NIH requires, more vaguely, only that donors be told "what would happen to the embryo." And although they require consent by gamete donors, NIH only requires consent by the "individuals who sought reproductive treatment." Unlike NAS, NIH does

not require that donors be informed that their cells might be genetically manipulated, used to make human/nonhuman chimeras, or used in human transplantation research. Where lines are traceable, NAS requires that donors be given the option of being recontacted to receive general research results, and suggests that they be given the option of consenting to some research uses and not others. And, unlike NIH, NAS requires a statement of risks. Although ISSCR requires that donors be told about the alternatives to donating their embryos to research, NIH requires only that donors be told about alternatives that happen to be available at that particular facility. NIH requires donors to be told that cell lines “may be kept for many years,” while ISSCR requires that donors understand the relevance of this, which is that donors are consenting to have their lines used in future studies whose nature is unpredictable. And unlike ISSCR, NIH does not require donors to be told that resulting cell lines may be genetically matched to them.

But in other ways described later, the Guidelines are stricter. In the draft Guidelines, NIH made its informed consent criteria retroactive (NIH 2009a). Scientists panicked, predicting that many—perhaps most—existing lines would be excluded (Keim 2009; Stein 2009; Taylor 2009). Some urged NIH to “grandfather in” existing lines categorically, or at least the Bush lines, or NAS- or ISSCR-compliant lines. The Final Guidelines strike a compromise. They are not fully retroactive. But they also explicitly reject the option of grandfathering *any* lines—a marked contrast to how NAS has handled the problem of retroactivity (National Research Center 2007).²

Instead, the Guidelines create two eligibility standards. Lines derived from embryos donated on or after 7 July 2009, whether inside or outside³ the U.S., must meet the informed consent requirements outlined above. Those wishing to use lines from embryos donated before that date, whether inside or outside the U.S., may instead submit materials regarding the derivation process to an NIH Working Group, which will make a recommendation about eligibility. The NIH Director will make the final determination.

The Working Group will apply the following standard in its case-by-case review of existing lines:

The materials submitted must demonstrate that the hESCs were derived from human embryos: (1) that were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose; and (2) that were donated by donor(s) who gave voluntary written consent for the human embryos to be used for research purposes.

The Working Group will review submitted materials . . . taking into account the principles articulated in [the Guidelines applicable to new lines], [the Common Rule], and the following additional points to consider. That is, during the consent process, including written or oral communications, whether the donor(s) were: (1) informed of other available options pertaining to the use of the embryos; (2) offered any inducements for the donation of the embryos; and (3) informed about what would happen to the embryos after the donation for research. (NIH 2009b).

These three “additional points” are in fact taken from the Guidelines criteria for new lines (in some cases slightly reworded), which the Working Group has already been directed to consider. In its preamble, the Guidelines note that the Working Group will advise “on whether the core ethical principles and procedures used in the process for obtaining informed consent . . . were such that the cell line should be eligible.” The reiteration of these three criteria suggests that NIH views them as “the core ethical principles” of informed consent, and will give them additional weight.

As we read the Guidelines, then, the standard for eligibility of existing lines is best described as consisting of 15 criteria divided into three tiers: First, such lines *must* (1) have been derived from spare IVF embryos, from (2) donors who gave voluntary written consent. Second, the Working Group likely will give extra weight to three of the post-7 July Guidelines criteria: whether donors were (3) informed of other options available in the facility; (4) offered any inducements; and (5) informed about what would happen to the embryos after donation. Third, the Working Group will “take into account” the remaining 10 post-7 July Guidelines criteria.

A comparison of these criteria to some prevailing standards suggests that some lines that are fully compliant with one of these standards may nevertheless now be ineligible for federal funding. Most obviously, NAS and ISSCR permit lines to be derived from the full panoply of sources rather than merely from spare IVF embryos. Presumably, this will eliminate some existing lines. As for the second mandatory criterion, NAS nowhere explicitly requires informed consent to be in written form, although probably most NAS-compliant protocols will have done so. Turning to the three “core” criteria NIH appears to consider central to informed consent, neither the 2000 NIH nor the NAS guidelines require donors to be informed of alternatives to donation, and ISSCR, although discouraging *undue* inducements to donate, permits oversight committees to authorize inducements. As for the remaining criteria the Working Group will “take into account,” the 2000 NIH guidelines are silent about whether institu-

tions must have a policy to ensure that neither agreement nor refusal to donate would affect a patient's care. ISSCR, although generally requiring contemporaneous consent, permits oversight committees to deem prior consent sufficient where obtaining contemporaneous consent would prove "prohibitively difficult," and by requiring donors to be informed *whether or not* they will receive benefits from any commercialization of stem lines, ISSCR implicitly permits donors to be promised a share of any profits resulting from the donation, which the Working Group could see as an inappropriate inducement.

Moreover, even assuming that the Working Group deems the NAS and ISSCR guidelines adequate, they are voluntary. Further, many existing lines were established before they were even available. As a result, it is anyone's guess what the informed consent protocols of many existing lines looked like. A recent study found that 77 percent of requests for Bush-era lines, which involved lines derived from embryos donated between 1997 and 2001, were for one of just two lines (Scott, McCormick, and Owen-Smith 2009). The five most requested lines—comprising 92 percent of requests—were all derived by the Wisconsin Alumni Research Fund (WARF). WARF's protocol differs in relevant ways from the Guidelines. Most significantly, it did not require that donors be informed of alternatives to donation to hESC research—one of NIH's "core" criteria. In addition, it did not require donors to be informed that they would not be able to restrict or direct any resulting therapies, and its communications to donors regarding what would happen to the embryo during research and what the research would involve, including potential human transplantation, was "ambiguous" (Streiffer 2008).

What effect these differences will have on the Guidelines' ability to expand the number of federally-fundable lines will depend on how strictly the Working Group applies its three-tier standard to existing lines. By committing only to "taking into account" all but two of the Guidelines criteria, NIH has left itself ample room to be more or less strict. As NIH decides how strict to be, however, it may find itself on the horns of a dilemma. In August 2008, evidence emerged suggesting that as many as five of the 21 NIH-approved Bush-era lines may have been derived without proper informed consent (Streiffer 2008). The report received widespread press coverage and prompted other institutions to reconsider their positions toward the Bush lines. This episode likely had some influence on the Obama administration's repeated commitment to develop and "rigorously enforce" "strict guidelines" (Obama 2009b). Yet insider accounts sug-

gest that NIH's lapsed ethics standards in 2001 were the result of intense political pressure to deem eligible as many lines as possible (Weiss 2008). This highlights the pressure administrations may feel to promote research touted as potentially life-saving. NAS faced a similar dilemma. Its decision to grandfather in the Bush lines was based largely on an assumption of valid informed consent, but NAS chose not to confirm this by conducting its own review of the documentation. In defending this decision, NAS explained that a thorough review of the 21 lines would have taken several months (Baker 2008).

The Working Group—which as of this writing has not yet been formed—can be expected to take at least as long to review the 700 lines now estimated to exist, although in light of recent findings, it might profitably focus its initial efforts on the most widely-used WARF lines. Given the labor-intensive nature of this process, NIH's decision to conduct a case-by-case review may reflect a strong desire to avoid a similar scandal and a judgment that if federal support of already-controversial hESC research is to succeed, it must not undermine public confidence in that endeavor by proceeding irresponsibly. As NIH adds existing lines to its registry, it can expect similar investigations into the origins of those lines, and so has a strong incentive to rigorously apply its criteria to existing lines. Indeed, Richard M. Doerflinger of the U.S. Conference of Catholic Bishops already has warned that “Accepting these lines, obtained in ways that do not comply with the new guidelines, would render meaningless any claim that NIH is setting and enforcing strict ‘ethical’ requirements” (Stein 2009). On the other hand, the scientific, biotechnology, and patient advocacy communities might be expected to object strenuously if it appears that large numbers of existing lines, or the few lines on which research has been centered, will be deemed unfundable. How NIH will resolve these tensions remains to be seen.

Expanding the Amount of Federal Funding of hESC Research

To say that a kind of hESC research or a particular line is federally fundable is not to say that it will be funded. Although NIH has noted that it “expect[s] to be spending more on stem cell research in the future” (NIH 2009c), there has been no clear indication of the precise amount of funding hESC researchers can expect. Current annual NIH spending on hESC research is below \$100 million—small by NIH standards (NIH 2009d). Although NIH received a large increase in funding (\$10 billion, or close to 30 percent) via the stimulus package for spending over the

next two years, it is unclear that increased budgets for NIH as a whole will translate into equally large increases in hESC funding.

In the short term, the Working Group's lengthy review process may serve as an administrative drag on committing large amounts of money to hESC research. The Working Group might reduce this lag substantially by reviewing first the mere handful of lines used in most ongoing research (Scott, McCormick, and Owen-Smith 2009), but resulting conflicts over the informed consent procedures for these lines could equally prolong the grant award process. Although money can be obligated before lines are approved (applicants are now being asked to state simply that they plan to use an NIH registry line), the large amounts of "beaker ready" research in other fields may limit the amount of money NIH is willing to set aside for hESC research if the lag between obligation and actual disbursement of funds is long. Although the funding outlook is difficult to gauge, it nevertheless seems more reasonable in the short run to expect smaller rather than larger increases, at least until NIH can approve enough stem cell lines to justify more funding.

Even in the longer term, a significant increase in total expenditures on hESC research—one large enough to make NIH a dominant funder compared to states and private entities—would provoke opposition by the same groups that historically have opposed this research. In addition, NIH budgets have remained flat for the last several years, and grant approval rates have declined to as low as 10 percent in some areas. Other scientists who are having trouble supporting their research may object if their stem cell colleagues, who have been receiving funds from states and private foundations, begin to receive considerable additional support from NIH. NIH officials may instead steer the bulk of new funding toward uncontroversial areas of research that lack substantial state or private support.

AN END TO THE PATCHWORK?

The minimal federal funding of hESC research during the Bush administration led stem cell advocates to develop alternative, multi-billion-dollar funding mechanisms centered around state and private funding sources (Fossett, forthcoming). Those funders developed regulations that, collectively, run the policy gamut, particularly around such controversial issues as payment of gamete or embryo donors and the use of SCNT or other research embryos (Lomax and Steyn 2008). As a consequence, "guidelines on hESC research have been issued by a number of different organizations

and governments, and different practices have arisen around the country and worldwide, resulting in a patchwork of standards” (NIH 2009b).

Whatever its potential merits, a clear drawback of a diversity of standards is that it hinders collaboration among researchers at different institutions. A second goal of the current NIH Guidelines is to “ameliorate” this patchwork. We consider here the likelihood that the Guidelines will improve consistency in ethical-legal standards among *institutions* involved in federally-funded hESC research, as well as consistency among federal and other *funders* and *regulators* of hESC research. In each case, in some ways the Guidelines may promote consistency of standards, thereby ameliorating the patchwork. But in other ways the patchwork will almost certainly remain.

*Consistency Among Institutions Involved in
Federally-Funded hESC Research*

The most straightforward way in which the Guidelines will promote consistency among institutions involved in federally-funded hESC research is by delegating the task of determining the eligibility of lines to NIH. This structure avoids the administrative inefficiency and inconsistency that likely would have resulted from instead delegating this task to local IRBs, as urged by many (NIH 2009b).

Under the IRB alternative, each IRB’s to-do list of lines to review would have been limited to those of interest to researchers within their jurisdiction. Centralizing the process, by contrast, risks creating a bottleneck as the Working Group takes on the task of reviewing some 700 lines. On the other hand, multiple IRBs would have to determine the eligibility of the same lines, thereby inefficiently duplicating efforts. More problematically, IRBs of equal competence and good intent can and do reach conflicting conclusions about the same protocol. As NIH ultimately concluded, delegating the eligibility task to IRBs would have created uncertainty within the scientific community about whether a given stem cell line was eligible or not and would have made it difficult for researchers at different institutions to collaborate, since the eligibility of a given line would in some cases depend on which IRB was asked (NIH 2009b).

However, centralizing the determination of line eligibility does not constitute a change from the Bush administration, which also delegated this task to NIH. Strictly speaking, then, this feature of the Guidelines does not so much ameliorate the patchwork as simply avoid worsening it.

More importantly, providing one uniform answer to which lines *NIH* is willing to fund does not preclude other facilitators and regulators of federally-fundable hESC research—such as IRBs, university administrators, and state governments—from setting more restrictive standards that bind researchers under their jurisdiction. Several states prohibit the use of state funds or facilities to conduct some or all hESC research, and others criminalize some or all of this research. These policies contribute to the regulatory thicket through which researchers must wade, especially when collaborating across institutional or state lines, and they show no signs of going away. Even entities that permit hESC research may draw the same ethical line as President Bush. For instance, the president of Nebraska University, under pressure from pro-life groups, announced that university researchers may conduct no research under the new Guidelines until the university's Board of Regents decides to adopt them; in the interim, only research that complies with the Bush regime will be permitted (Ruggles 2009). Similarly, in the wake of a report that the provenance of five of the Bush lines was ethically problematic, for example, Stanford's stem cell ethics committee recommended that Stanford researchers be limited to the remaining 16. Other universities and state stem cell agencies initiated similar investigations (Weiss 2008). Given that some bioethicists already have argued that portions of the Guidelines are too lenient, we may see more examples of these bodies resisting plenary adoption of the Guidelines.

Finally, the Guidelines say little about the ethical *uses* of hESC lines, such as how to conduct those kinds of chimera research that are eligible for funding and whether to induce gametes from pluripotent stem cells. Nor do the Guidelines require any local or national oversight regarding these issues, except to note that where donors are identifiable, research is subject to IRB approval. These omissions in federal hESC policy produce a vacuum that other funders and regulators will continue to fill.

Consistency Among Funders and Regulators of hESC Research

That the Guidelines will exert “influence” on NIH grantees is fairly obvious. It should also be clear that the Guidelines will *not* supplant the patchwork of standards governing research that they declare ineligible for federal funding. The state and private funders that have been supporting most of this research presumably will retain the standards they have developed or adopted—with one caveat. Some of the Guidelines' informed consent provisions are applicable to this other research, and it

might behoove funders to incorporate them into their standards in case NIH later decides to expand funding to these areas.

Perhaps less obviously, it is possible that the Guidelines will exert influence on researchers *not* currently funded by NIH as well as by alternative funders and regulators of hESC research. Prior to the release of the Guidelines, some had predicted that any new federal guidelines “would likely be adopted across granting agencies by default” (Wong 2009). We think this overstates things. The degree of indirect influence of the Guidelines is likely to be strongly related to the amount of funding NIH contributes to hESC research. Currently, funding of hESC research is decentralized, spread across multiple state and private entities with a corresponding multiplicity of standards. If NIH expends ample new money on hESC research and becomes the dominant funder, researchers’ and even other regulators’ behavior is likely to conform to the Guidelines. Researchers may amend their protocols and choice of cell lines, and institutions may reconfigure their informed consent procedures and other policies, to ensure eligibility for federal funding. If, on the other hand, NIH provides only modest increases in federal funding, or if stimulus funding is not renewed when it expires, one might expect less behavioral change and more resistance to federal policy. As discussed previously, we think it unlikely, in the short run, that the amount of NIH funding will even approach the several billions of dollars provided by state and private sources.

Not only does NIH have reasons to increase hESC funding only moderately, but state and private funders also retain many of the motives that led them to become central players in hESC research. For example, “disease foundations” and other philanthropic organizations will remain motivated to find cures. Some for-profit companies and venture capitalists see hESC research as a sound investment and, if anything, appear to have accelerated their investment as a result of the change in administration (Butkus 2009).

Some states saw themselves as filling the gap left by the Bush policy by providing basic research grants. NIH’s new willingness to fund basic hESC research, combined with severe state budget difficulties, may lead some states to reduce the scope of their commitment to hESC research. But states have had multiple motivations in supporting hESC research. Elected officials, particularly governors, see their electoral futures as tied to state economic growth and may feel obliged to devise strategies for stimulating investment and employment growth. Much of the public rhetoric supporting state funding for hESC research focuses on the need for

states to remain “competitive” by establishing policies that will attract or retain scientific talent. Available evidence suggests that these efforts have, in fact, been successful (Levine 2008). Despite state budget difficulties and diminished endowments, then, we expect most state and private funders to remain in the hESC research field.

The question thus becomes whether these funders will adopt the Guidelines or retain their own standards. Where hESC research is permitted or funded, governments and oversight bodies typically have expended considerable resources developing and implementing ethical standards. They may be reluctant to relinquish policy control, especially where they continue to fund the research. And of course funders or regulators will not adopt the Guidelines if doing so would be antithetical to their goals or values. For instance, they might have a conscientious disagreement over best practices in obtaining informed consent, or they might conclude that the Guidelines’ strictness inhibits research. To foster collaboration, states may permit fundees to demonstrate compliance with the Guidelines as an alternative to their own rules, as some do now with the NAS standards, but it seems unlikely that they require such compliance.

Nevertheless, there are plausible scenarios under which the Guidelines might have significant influence, even without NIH becoming the dominant funder of hESC research. For instance, state stem cell initiatives increasingly involve complex financial arrangements with private companies to fund “translational” research designed to produce products that can be brought to market quickly. This shift may reduce the overall amount of money state and private funders spend on basic research. If so, and assuming that NIH is in a position to expand its stem cell funding significantly, it may have an opportunity to expand its regulatory reach and dominance as a basic research funder. Similarly, researchers who hope ultimately to develop products subject to FDA regulation may find it prudent to comply with NIH guidelines, since the FDA requires assurance that cells were derived according to ethically accepted standards.

Researchers not currently funded by NIH may voluntarily conform their protocols to the Guidelines. Federal standards often have considerable visibility. Researchers also may feel pressure to seek federal funding because of the substantial overhead institutions receive, and both researchers and their institutional employers may see federal grants as more prestigious than the alternatives. In the short term, if the NIH review process stalls or seems onerous, or if NIH commits little additional money to hESC research, researchers may pursue other funding. But hESC research agendas

span years, and NIH budgets and policies wax and wane. Researchers who want to avoid closing the door to future funding opportunities will have an incentive to create or choose a line that adheres to the most rigorous informed consent standard, so long as it does not impede her work. Because some elements of the Guidelines' informed consent standard are more rigorous than those of other standards, while other elements are less rigorous, the strictest set of ethical standards, in many cases, will be a combination of the Guidelines and some other prominent standard, such as the NAS guidelines or those of a researcher's home state. Perhaps in order to relieve researchers of the burden of parsing multiple sets of standards and to promote collaboration, funders and regulators themselves may amend their standards to adhere to the Guidelines.

CONCLUSION

Although there are significant uncertainties around the ultimate impact of the Guidelines, there can be little doubt that their intent was to produce incremental, rather than sweeping, change in federal hESC policy. The Guidelines clearly enable new, better-quality lines to receive funding. But they retain the other Bush-era restrictions on the *kinds* of eligible lines, and the number of eligible *existing* lines on which much ongoing research depends is unclear. The Guidelines centralize the determination of whether lines are eligible for federal funding. But providing a uniform standard for which lines NIH will fund does not preclude other entities from insisting on narrower or broader standards. Nor, by definition, can the Guidelines dominate policy in areas of hESC research that it does not cover. Although the Guidelines may exert some influence over researchers and other funders and regulators, the extent of this influence will depend significantly on NIH's level of funding relative to state and private funding, and it is unlikely that NIH's slice of this funding pie will increase dramatically. Multiple funders and regulators, and so multiple sets of rules, will continue to exist, with none clearly dominant. Our best guess for the short-term future of U.S. stem cell policy in the aftermath of the Guidelines, then, is that—for better or worse—it will look very much like the recent past.

We thank two anonymous reviews for helpful comments on an earlier draft of this article. Michelle Meyer also gratefully acknowledges funding from The Greenwall Foundation.

NOTES

1. The Guidelines also deem ineligible two kinds of research involving chimeras or hybrids—research that would introduce human stem cells into nonhuman primate blastocysts and research involving animal breeding where the introduction of hESCs or human iPSCs might contribute to the germ line—but appear to permit other kinds of chimera research.
2. In 2007, “to avoid precluding hES cell research that would otherwise be rendered difficult or impossible,” NAS amended its guidelines to grandfather in Bush-era lines of uncertain provenance, determining that NIH’s requirements of informed consent, lack of inducements, and IRB approval were sufficient. Similarly, NAS permits the importation of non-NAS compliant lines, whenever and wherever derived, if an oversight committee determines that the alternative rules “afford protections consistent with” NAS guidelines. NAS has explained that this “deference facilitates collaboration among institutions and shows proper respect for the diversity of authority” in the area of hESC research (National Research Council 2007).
3. Applicants wishing to use a line derived from an embryo donated outside the U.S. must submit either an assurance that the line complies with the post-7 July criteria or materials showing that it was derived under alternative standards that “provide protections at least equivalent to” those criteria. In the latter case, the Working Group will determine if such equivalency exists.

REFERENCES

- Baker, Monya. 2008. When the Past Catches Up with the Present. *Nature Reports Stem Cells* (14 August). Available at <http://www.nature.com/stem-cells/2008/0808/080814/full/stemcells.2008.116.html>, accessed 10 August 2009.
- Butkus, Ben. 2009. Pfizer Licensing Deal with WARF Allows Firm to Develop hESC-Based Therapies, Discovery Tools. *Biotech Transfer Week* (13 May). Available at <http://www.genomeweb.com/biotechtransferweek/pfizer-licensing-deal-warf-allows-firm-develop-hesc-based-therapies-discovery-to>, accessed 10 August 2009.
- Connolly, Ceci. 2009. Compromise Rules Issued on Embryonic Stem Cells. *Washington Post* (18 April). Available at <http://www.washingtonpost.com/wp-dyn/content/article/2009/04/17/AR2009041701880.html?sub=AR>, accessed 10 August 2009.
- Consolidated Appropriations Act, 2009. Pub. L. 110–161, 11 March (Dickey-Wicker Amendment); 2009 Omnibus Appropriations Act (Public Law 111–8, Division F, Title V, § 509).

- Fossett, James W. Forthcoming 2009. Beyond the Low Hanging Fruit: Stem Cell Research in an Obama Administration. *Yale Journal of Health Policy, Law, and Ethics* 9.
- Gordon, Serena. 2009. Stem Cell Decision Opens New Doors, May Spur More Research. *HealthDay* (15 July). Available at <http://health.usnews.com/articles/health/healthday/2009/07/15/stem-cell-decision-opens-new-doors-may-spur-more.html>, accessed 10 August 2009.
- Holden, Constance. 2009. A First Step in Relaxing Restrictions on Stem Cell Research. *Science* 323: 1412–13.
- ISSCR. International Society for Stem Cell Research. 2006. Guidelines for the Conduct of Human Embryonic Stem Cell Research. (21 December). Available at <http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf>, accessed 10 August 2009.
- Keim, Brandon. 2009. Obama's Stem Cell Guidelines Threaten Research. *Wired Science* (14 May). Available at <http://www.wired.com/wiredscience/2009/05/escguideline/>, accessed 10 August 2009.
- Levine, Aaron. 2008. Policy Considerations for States Supporting Stem Cell Research: Evidence from a Survey of Stem Cell Scientists. *Public Administration Review* 68: 681–94.
- Lomax, Geoffrey, and Stayn, Susan. 2008. Similarities and Differences among Stem Cell Research Policies: Opportunities for Policymakers, Patients, and Researchers. *Medical Research Law and Policy Report* 7: 695–98.
- NIH. National Institutes of Health. 2000. Guidelines for Research Using Human Pluripotent Stem Cells. 65 *Federal Register* 51975 (25 August). Available at <http://stemcells.nih.gov/staticresources/news/newsArchives/fr25au00-136.asp>, accessed 10 August 2009.
- . 2001. NOT-OD-01-058, NIH Funding of Research Using Specified Existing Human Embryonic Stem Cells. 27 August. Available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-059.html>, accessed 10 August 2009.
- . 2009a. Draft National Institutes of Health Guidelines for Human Stem Cell Research. 74 *Federal Register* 18578 (23 April). Available at <http://frwebgate6.access.gpo.gov/cgi-bin/PDFgate.cgi?WAISdocID=21650969431+0+2+0&WAIAction=retrieve>, accessed 10 August 2009.
- . 2009b. National Institutes of Health Guidelines for Human Stem Cell Research. 74 *Federal Register* 32170 (7 July). Available at <http://frwebgate6.access.gpo.gov/cgi-bin/PDFgate.cgi?WAISdocID=21650969431+3+2+0&WAIAction=retrieve>, accessed 10 August 2009.

- . 2009c. President Directs NIH to Issue Stem Cell Research Guidelines within 120 Days. *NIH Record* 61: 1 (3 April). Available at http://nihrecord.od.nih.gov/newsletters/2009/04_03_2009/story1.htm, accessed 10 August 2009.
- . 2009d. Research Portfolio Online Reporting Tool. Available at <http://report.nih.gov/rcdc/categories/Default.aspx>, accessed 10 August 2009.
- National Research Council and Institute of Medicine. 2005. *Guidelines for Human Embryonic Stem Cell Research*. Washington, DC: National Academies Press. Available at http://books.nap.edu/catalog.php?record_id=11278#toc, accessed 10 August 2009.
- . 2007. *2007 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research*. Washington, DC: National Academies Press. Available at http://books.nap.edu/catalog.php?record_id=11871, accessed 10 August 2009.
- Nelson, Libby. 2009. New York State Allows Payment for Egg Donation for Research. *New York Times* (June 26): A20.
- New Scientist*. 2009. IVF Discounts Beat Cash Rewards for Research Eggs (12 July). Available at <http://www.newscientist.com/article/mg20327163.200-ivf-discounts-beat-cash-rewards-for-research-eggs.html>, accessed 10 August 2009.
- NYSCF. New York Stem Cell Foundation. 2009. Press Release, The New York Stem Cell Foundation Supports Final NIH Guidelines On Stem Cell Research (6 July). Available at http://www.nyscf.org/nyscf_speaks/nyscf_supports_final_nih_stem_cell_guidelines.html, accessed 10 August 2009. *New York Times*. 2009. New Stem Cell Rules (7 July): A24.
- Obama, Barak. 2009a. Executive Order 13505, Removing Barriers to Responsible Scientific Research Involving Human Stem Cells, signed 9 March 2009. 74 *Federal Register* 10667-68 (11 March). Available at <http://edocket.access.gpo.gov/2009/pdf/E9-5441.pdf>, accessed 10 August 2009.
- . 2009b. Remarks of President Barack Obama—As Prepared for Delivery. Signing of Stem Cell Executive Order and Scientific Integrity Presidential Memorandum. 9 March. Available at http://www.whitehouse.gov/the_press_office/Remarks-of-the-President-As-Prepared-for-Delivery-Signing-of-Stem-Cell-Executive-Order-and-Scientific-Integrity-Presidential-Memorandum/, accessed 10 August 2009.
- O'Reilly, Kevin B. 2008. Researchers Urge Pay for Egg Donors. *American Medical News* (15 September). Available at <http://www.ama-assn.org/amed-news/2008/09/15/prsa0915.htm>, accessed 10 August 2009.

- Pew. The Pew Forum on Religion & Public Life. 2009. Event Transcript: Religion and Science: Conflict or Harmony? 4 May. Available at <http://pewforum.org/events/?EventID=217>, accessed 10 August 2009.
- Ruggles, Rick. 2009. NU To Wait on Stem Cells. *Omaha World-Herald* (8 July). Available at <http://www.omaha.com/article/20090708/NEWS01/707089928-1/FRONTPAGE>, accessed 10 August 2009.
- Scott, Christopher Thomas; McCormick, Jennifer B.; and Owen-Smith, Jason. 2009. And Then There Were Two: Use of hESC Lines. *Nature Biotechnology* 27: 696–97.
- Stein, Rob. 2009. New Rules on Stem Cells Threaten Current Research. *Washington Post* (25 May). Available at <http://www.washingtonpost.com/wp-dyn/content/article/2009/05/24/AR2009052402141.html>, accessed 10 August 2009.
- Streiffer, Robert. 2008. Informed Consent and Federal Funding for Stem Cell Research. *Hastings Center Report* 38 (3): 40–47.
- Taylor, Patrick L. 2009. Retroactive Ethics in Rapidly Developing Scientific Fields. *Cell Stem Cell* 4: 479–82.
- Weiss, Rick. 2008. Ethically Challenged. *Science Progress* (25 July). Available at <http://www.scienceprogress.org/2008/07/ethically-challenged/>, accessed 10 August 2009.
- Weissman, Irving. 2009. The ISSCR: Who Are We and Where Are We Going? *Cell Stem Cell* 5: 151–53.
- Wong, Kathleen M. 2009. New Administration Likely to Bring Change to Stem Cell Research. *Cell Stem Cell* 4: 111–12.