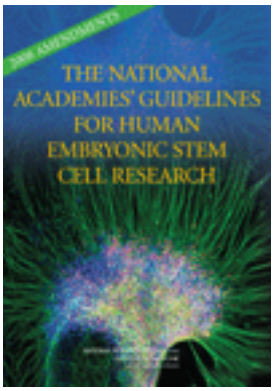

2008 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research

Human Embryonic Stem Cell Research Advisory Committee, National Research Council and Institute of Medicine of the National Academies

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2008 AMENDMENTS

THE NATIONAL ACADEMIES' GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH

Human Embryonic Stem Cell Research Advisory Committee

Board on Life Sciences
Division on Earth and Life Studies

Board on Health Sciences Policy
Institute of Medicine

NATIONAL RESEARCH COUNCIL *AND*
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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Cover: A cluster of motor neurons and neural fibers derived from human embryonic stem cells in the lab of University of Wisconsin–Madison stem cell researcher and neurodevelopmental biologist Su-Chan Zhang. The motor neurons are shown in red, neural fibers appear green, and the blue specks indicate DNA in cell nuclei. These motor neurons were developed from one of James Thomson's original human embryonic stem cell lines. Copyright for the photograph is held by the University of Wisconsin's Board of Regents.

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

George Q. Daley, Children's Hospital Boston and Harvard Medical School
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions

or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Janet Rowley**, University of Chicago Medical Center, and **Floyd Bloom**, Scripps Research Institute (retired). Appointed by the National Research Council, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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2008 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research

INTRODUCTION

The National Academies' report *Guidelines for Human Embryonic Stem Cell Research* (NRC and IOM, 2005) was developed by the Committee on Guidelines for Human Embryonic Stem Cell Research and released in April 2005. The body of the report provided the background and rationale for the choices involved in formulating the Guidelines, which were compiled in its final chapter. Because human embryonic stem (hES) cell research touches on many ethical, legal, scientific, and policy issues, the Guidelines are intended to make explicit how research with hES cells can be pursued most responsibly. The Guidelines are intended to address researchers primarily in the United States, but they may be applicable internationally as well.

The 2005 publication of the Guidelines offered a common set of ethical standards for a field that, because of the absence of comprehensive federal funding, was lacking national standards for research. Although the Guidelines have proved useful since 2005, it was recognized soon after their initial issuance that some aspects of them needed clarification in light of experience and that they must be kept up to date given the rapid pace of scientific developments in the field of stem cell research. The National Academies established the Human Embryonic Stem Cell Research Advisory Committee for that purpose in 2006 with support from the Ellison Medical Foundation, the Greenwall Foundation, and the Howard Hughes Medical Institute. It issued its first set of amendments to the Guidelines in 2007 (NRC and IOM, 2007).

Statement of Task of the Human Embryonic Stem Cell Research Advisory Committee

The Advisory Committee will meet 2 to 3 times per year over a period of 36 months to (1) monitor and review scientific developments and changing ethical, legal, and policy issues related to human embryonic stem cell research, (2) discuss the need for revisions to the Guidelines for Human Embryonic Stem Cell Research, and (3) prepare periodic reports to update the Guidelines as needed. Minimal but necessary changes may be issued as letter reports, but more extensive modifications may necessitate the preparation of traditional reports to fully provide the rationale for the changes.

Sources of information that will be considered by the Advisory Committee will include public symposia organized by the Committee to review developments in stem cell science and how these impact the ethical and policy issues surrounding hES cell research.

The Human Embryonic Stem Cell Research Advisory Committee continues to engage in a number of efforts to gather information about the need, if any, for revision of the Guidelines. For example, the Committee conducted three regional meetings (in southern California, Chicago, and the Boston area) in the first half of 2007 for those involved in institutional Embryonic Stem Cell Research Oversight (ESCRO) committees to hear from people in the field about their experiences in implementing the Guidelines and any problems they have encountered. In addition, the Committee participated in a day-long session on ESCRO committees at the annual meeting of Public Responsibility in Medicine and Research (PRIM&R) in December 2007 to gather more feedback from the community.

The Committee also met in March and August 2007 and in February 2008 to hear from invited speakers who addressed issues that the Committee has taken under consideration for potential further amendments to the Guidelines. Finally, the Committee is planning a second symposium (its first was held in November 2006) for November 2008 to hear invited speakers review the latest scientific developments, describe how the developments might affect analyses of associated ethical issues, and identify possible effects on the workability or justifiability of the current Guidelines. The meeting will

focus in part on recent developments in moving toward clinical translation of stem cell therapeutics. The Committee has also established an electronic mailing list for ESCRO committee members and staff to communicate and share questions and answers, and members of the Committee have been actively soliciting input from their colleagues and receiving comments via a Web site[1] established for the purpose.

As it did in 2007, the Committee identified issues that appeared to warrant consideration of revisions of the Guidelines. The present report addresses those issues in a second brief set of amendments. Most important, the Committee is issuing this second set of amendments to address new scientific developments in reprogramming of somatic cells to pluripotency by adding a new section (Section 7) and revising other relevant sections of the Guidelines. It is also issuing several other minor amendments to

- Clarify the obligations of investigators to notify and obtain approval from their institutions' ESCRO committees before initiating any hES cell experiments and to provide for the possibility of "expedited review" of some hES cell experimental protocols—Section 1.3(a)[2], Section 6.1, and Section 6.2.

- Clarify what is included in "direct expenses" for allowable reimbursements to women donating oocytes—Section 3.4(b).

- Further enumerate the registration and auditing responsibilities of institutions conducting hES cell research to improve public access to information and ensure that ESCRO committees are carrying out their responsibilities appropriately—Section 2.0.

In addition, inconsistencies in the original numbering of the Guidelines have led to some confusion. Various sections of the Guidelines, particularly within Section 1, have been renumbered in these amendments for greater clarity.

Future deliberations of the Committee will address items for which additional information-gathering and more extensive debate and discussion may be necessary. For example, based on the National Institutes of Health (NIH) determination that the pre-2001 "presidential" lines were derived from embryos donated with informed consent and without financial induce-

[1]http://www.nationalacademies.org/stemcells

[2]Formerly Section 1.2(a). As explained below, several sections of the Guidelines, particularly within Section 1, are being renumbered in these amendments for greater clarity.

ment (NIH, 2001), the 2007 Guidelines deemed those lines to have been acceptably derived (see Sections 1.4 and 1.5 and associated discussion in NRC and IOM, 2007). In light of questions raised when the present report was already near completion about the derivation or use of some of those lines (Streiffer, 2008), and as per its charge, the Committee will monitor developments as to the ethics and policy regarding the lines in question in order to consider whether any future changes in the Guidelines are warranted. Stem cell research oversight committees are, of course, free to set their own policies about the use of these lines according to the principles outlined in Section 1.6 of the Guidelines (as renumbered in this document). The Committee is also aware that the scientific and oversight communities desire additional guidance on how to evaluate research that requires the development of chimeras. In response, the Committee has added some text in the new Section 7.3(c) [as well as 1.3(b)] and also plans to address research involving chimeras at the meeting it is organizing for November 2008.

These amended Guidelines supersede those issued in 2005 and 2007 by the Committee on Guidelines for Human Embryonic Stem Cell Research and the Human Embryonic Stem Cell Research Advisory Committee, respectively. It is important that the clarifications and amendments presented here be interpreted in the context of the complete set of amended Guidelines, which is included at the end of this report (Appendix A). In addition, the glossary included in the 2005 *Guidelines for Human Embryonic Stem Cell Research* (NRC and IOM, 2005) has been amended by adding definitions for the terms *hPS cells* and *multipotent*, and the entire glossary is reprinted as Appendix B.

APPLICABILITY OF THE GUIDELINES TO NON-EMBRYONIC HUMAN PLURIPOTENT STEM CELLS

The original Guidelines released in 2005 were addressed specifically to research with hES cell lines, although institutions and investigators conducting research on human adult stem cells or fetal stem cells were encouraged to "consider which individual provisions of these guidelines are relevant to their research." Because the Guidelines were developed primarily for research with hES cells, however, it was not made explicit which provisions of the Guidelines might apply to other types of stem cells.

There have been several recent reports on reprogramming of somatic cells to pluripotency (for definitions see glossary, Appendix B). In light of the production of so-called induced pluripotent stem (iPS) cell lines derived

by introducing sets of genes into, first, murine somatic cells (Takahashi and Yamanaka, 2006) and, later, human somatic cells (Takahashi et al., 2007; Yu et al., 2007; Park et al., 2008), it seems prudent to consider more explicitly which provisions of the Guidelines should apply also to stem cells of types other than hES cells. This is not to suggest that the need for research with hES cells is supplanted by the availability of other pluripotent stem cells. It is far from clear at this point which cell types will prove to be the most useful for regenerative medicine, and it is likely that each will have some utility. Such iPS cells are currently derived by introduction of retroviruses that carry the inducing genes. This derivation procedure raises serious issues about their potential for use in therapy, inasmuch as it is known that inserted retroviruses can cause cancer, and research will be necessary to develop alternative means to derive iPS cells or to circumvent the potential tumorigenicity. Furthermore, the demonstration that iPS cells are indeed pluripotent relies on careful comparisons with hES cells; for either cell type to be used therapeutically in regenerative medicine, methods need to be developed to promote their differentiation into specialized cell types and to evaluate the safety of introducing cell populations that may contain some pluripotent cells into patients. Much further research will be required on both hES and iPS cells to develop the required procedures, including drawing appropriate comparisons between them. Understanding of the potential for differentiation of hES cells, iPS cells, or, indeed, adult multipotent (capable of differentiation into a limited spectrum of differentiated cell types)[3] stem cells will require testing in animals and screening for potential tumorigenicity. Therefore, issues arising from such human-animal chimera experiments pertain to all these cell types.

For those reasons and in response to inquiries from the scientific community, the Human Embryonic Stem Cell Research Advisory Committee has consulted with experts and carefully considered potential modifications of the Guidelines to cover other pluripotent and multipotent stem cells, which the Committee presents herein. The intention is not to extend unnecessarily the oversight of stem cell research where it is already adequately monitored under existing regulations and guidelines. For example, derivation of human pluripotent stem cell lines from sources other than embryos does not involve ethical or policy issues beyond those normally encountered in sampling any tissue from human subjects, although *use* of such cells may raise issues similar to those for embryonically derived cells. Derivation of iPS cells and

[3]A multipotent stem cell can give rise to other types of cells but it is limited in its ability to differentiate. An example is found in the multipotent stem cells in bone marrow that give rise to all blood cells but not other cell types.

of other non-embryonic human pluripotent stem cells (hereafter referred to as hPS cells) does not require special stem cell expertise and is adequately covered by current Institutional Review Board (IRB) regulations. It does not require additional review by an ESCRO committee. The Committee notes in particular that under federal regulations, even IRBs would not be required to review the generation of hPS cells from existing anonymized somatic cells from surgical waste, tissue banks, or commercial entities that provide tissue for research, nor would they be required to review the generation of hPS cells from cadaveric tissue, whether or not it is anonymized. Similarly, with few exceptions, purely *in vitro* experiments with hPS cells do not raise ethical concerns beyond those encountered with any human cell line and also do not require ESCRO committee review.

However, as mentioned above, introduction of any hPS cells and introduction of some multipotent stem cells (such as neural stem cells) into animals raises issues similar to those pertaining to hES cells. The earlier versions of the Guidelines placed responsibility for review of such experiments with hES cells in the hands of ESCRO committees and Institutional Animal Care and Use Committees (IACUCs), and it is logical to do the same for hPS cells and for stem cells with more limited potential for differentiation. The revisions presented in this document provide guidance on the levels of review for various categories of experiments with iPS and other hPS cells and on categories of research for which such review is not necessary. Most of the changes appear in a new Section 7, "Recommendations for Research on Non-Embryo-Derived Human Pluripotent Stem Cells (hPS Cells)", although some provisions of Sections 1, 3, 4, and 5 are also affected, as follows (new or revised wording is underlined, and deleted text appears in ~~strikeout~~ form):

From Section 1

1.1 What These Guidelines Cover

1.1(a) These guidelines cover all derivation of hES cell lines and all research that uses hES cells derived from

(i) blastocysts made for reproductive purposes and later obtained for research from *in vitro* fertilization (IVF) clinics,
(ii) blastocysts made specifically for research using IVF,
(iii) somatic cell nuclear transfer (NT) into oocytes.

1.1(b) ~~Many, but not all,~~ Some of the ~~guidelines and~~ concerns addressed in this report are common to other ~~areas~~ types of human stem cell research; as such, certain of these Guidelines should also apply to those other types of research. For example, ~~such as~~

(i) research that uses human adult stem cells.

(ii) research that uses fetal stem cells or embryonic germ cells derived from fetal tissue; such research is covered by federal statutory restrictions at 42 USC 289g-2(a) and federal regulations at 45 CFR 46.210.

(iii) research that uses human pluripotent stem (hPS) cells derived from non-embryonic sources, such as spermatogonial stem cells and "induced pluripotent" stem cells derived from somatic cells by introduction of genes or otherwise (so-called iPS cells), and other pluripotent cells yet to be developed.

Recommendations as to which guidelines apply to other hPS cells are collected in Section 7 below. Institutions and investigators conducting research ~~using such materials~~ with adult and fetal stem cells should also consider which individual provisions of these guidelines are relevant to their research.

1.1(c) The guidelines do not cover research that uses nonhuman stem cells.

From Section 3

3.1 An IRB, as described in federal regulations at 45 CFR 46.107, should review all new procurements of all gametes, blastocysts, or somatic cells for the purpose of generating new hES or hPS cell lines. This includes the procurement of blastocysts in excess of clinical need from infertility clinics; blastocysts made through IVF specifically for research purposes; ~~and~~ oocytes, sperm, and somatic cells donated for development of hES cell lines derived

through NT or by parthenogenesis or androgenesis; and hPS cells derived by any means and that require human subjects review.

3.6 In the context of donation of gametes, blastocysts, or somatic cells for hES cell research, or for hPS cell research that requires human subjects review, the informed-consent process should, at a minimum, provide the following information:

(a) A statement that the blastocysts, gametes, or somatic cells will be used to derive hES or hPS cells for research that may include research on human transplantation.
(b) A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation.
(c) A statement as to whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hES or hPS cell lines.
(d) If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines.
(e) An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells. (Traceable information, however, must be secured to ensure confidentiality.)
(f) A statement that derived hES or hPS cells and/or cell lines might be kept for many years.
(g) A statement that the hES or hPS cells and/or cell lines might be used in research involving genetic manipulation of the cells or mixing of human and nonhuman cells in animal models.
(h) Disclosure of the possibility that the results of study of the hES or hPS cells may have commercial potential and a statement that the donor will not receive financial or any other benefits from any future commercial development.
(i) A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.

(j) A statement that embryos will be destroyed in the process of deriving hES cells.
(k) A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.
(l) A statement of the risks involved to donors.

In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others. For example, donors might agree to have their materials used for deriving new hES cell lines but not want their materials used, for example, for NT. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored. Investigators and stem cell banks are, of course, free to choose which cell lines to accept, and are not obligated to accept cell lines for which maintaining information about specific research use prohibitions would be unduly burdensome.

New derivations of stem cell lines from banked tissues obtained prior to the adoption of these guidelines are permissible provided that the original donations were made in accordance with the legal requirements in force at the place and time of donation. This includes gametes, blastocysts, adult stem cells, somatic cells, or other tissue. In the event that these banked tissues retain identifiers linked to living individuals, human subjects protections may apply.

From Section 4

4.6 Investigators must document how they will characterize, validate, store, and distribute any new hES cell lines and how they will maintain the confidentiality of any coded or identifiable information associated with the lines (see Section 5.0 below). Investigators are encouraged to apply the same procedures and standards for characterization, validation, storage, and distribution to hPS cell lines.

From Section 5

5.0 BANKING AND DISTRIBUTION OF hES CELL LINES

There are several models for the banking of human biological materials, including hES cells. The most relevant is the U.K. Stem Cell Bank. The guidelines developed by this and other groups generally adhere to key ethical principles that focus on the need for consent of donors and a system for monitoring adherence to ethical, legal, and scientific requirements. As hES cell research advances, it will be increasingly important for institutions that are obtaining, storing, and using cell lines to have confidence in the value of stored cells—that is, that they were obtained ethically and with the informed consent of donors, that they are well characterized and screened for safety, and that the conditions under which they are maintained and stored meet the highest scientific standards. Institutions engaged in hES research should seek mechanisms for establishing central repositories for hES cell lines—through partnerships or augmentation of existing quality research cell line repositories—and should adhere to high ethical, legal, and scientific standards. At a minimum, an institutional registry of stem cell lines should be maintained. Institutions are encouraged to consider the use of the same procedures for banking and distribution of hPS cell lines.

Section 7

7.0 RECOMMENDATIONS FOR RESEARCH ON NON-EMBRYO-DERIVED HUMAN PLURIPOTENT STEM CELLS (hPS CELLS)

7.1 Derivation

Because non-embryo-derived hPS cells are derived from human material, their derivation is covered by existing IRB regulations concerning review and informed consent. No ESCRO committee review is necessary, although the IRB may always seek the advice of an ESCRO committee if it seems desirable. The IRB review

should consider proper consent for use of the derived hPS cells. Some of the recommendations for informed consent that apply to hES cells also apply to hPS cells (see Section 3.6), including informed consent to genetic manipulation of resulting pluripotent stem cells and their use for transplantation into animals and humans and, potentially, in future commercial development.

7.2 Use in *in Vitro* Experiments

Use of hPS cells in purely *in vitro* experiments need not be subject to any review beyond that necessary for any human cell line except that any experiments designed or expected to yield gametes (oocytes or sperm) should be subject to ESCRO committee review.

7.3 Use in Experiments Involving Transplantation of hPS Cells into Animals at Any Stage of Development or Maturity

7.3(a) Research involving transplantation of pluripotent human cells derived from non-embryonic sources into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by ESCRO committees and IACUCs, as are similar experiments that use hES cells.

7.3(b) ESCRO committees should review the provenance of hPS cells as they review the provenance of hES cells (see Section 1.6) to ensure that the cell lines were derived according to ethical procedures of informed consent as monitored by an IRB or equivalent oversight body.

7.3(c) Proposals for the use of hPS cells in animals should be considered in one of the following categories:

(i) Permissible after currently mandated reviews and proper documentation [see Section 1.3(a)]: experiments that are exempt from full ESCRO committee review but not IACUC review (experiments that involve only transplantation into postnatal animals with no likelihood of contributing to the central nervous system or germ line).

(ii) Permissible after additional review by an ESCRO committee, as described in Section 2.0 of the Guidelines [see Section 1.3(b)]: experiments in which there is a significant possibility that the implanted hPS cells could give rise to neural or gametic cells and tissues. Such experiments need full ESCRO committee and IACUC review and would include generation of all preimplantation chimeras and neural transplantation into embryos or perinatal animals. Particular attention should be paid to at least three factors: the extent to which the implanted cells colonize and integrate into the animal tissue; the degree of differentiation of the implanted cells; and the possible effects of the implanted cells on the function of the animal tissue.

(iii) Should not be conducted at this time [see Section 1.3(c)]:

(1) Experiments that involve transplantation of hPS cells into human blastocysts.

(2) Research in which hPS cells are introduced into nonhuman primate embryos, pending further research that will clarify the potential of such introduced cells to contribute to neural tissue or to the germ line.

7.4 Multipotent Neural Stem Cells

It is also relevant to note that neural[4] stem cells, although not pluripotent, are multipotent and may have the potential to contribute to neural tissue in chimeric animals. ESCRO committees should decide whether they wish to review and monitor such experiments with neural stem cells in a similar fashion.

7.5 Prohibition on Breeding

No animal into which hPS cells have been introduced such that they could contribute to the germ line should be allowed to breed.

[4]Referring to cells of the nervous system that give rise to both neurons and glia.

7.6 Guidance for Banking and Distribution

Institutions should consider the value of banking and distributing hPS cells using the guidance and rules that are already in place for hES cells and the value of including hPS cell lines in their registries.

CLARIFICATION OF THE MEANING OF "PROPER NOTIFICATION"

Section 1.3 (formerly Section 1.2) of the Guidelines specifies research that is "permissible after currently mandated review and *proper notification* of the relevant research institution" (emphasis added). Section 1.3(a) clarifies which documentation is required for determining the provenance of the cell lines, but it does not address what "proper notification" entails. Similarly, Sections 6.1 and 6.2 concerning research use of hES cell lines refer to "notification" and "notice" but do not specify what notification entails.

Use of the word "notification" has led some ESCRO committee representatives to ask whether the Guidelines intend that investigators fulfill this requirement by merely informing ESCRO committees that the research would be occurring (that is, the investigator would determine and inform, but the ESCRO committee would have no role). That is not what was intended. The discussion in the 2005 report states that the "ESCRO committee should ensure that the procurement process has been appropriate by requiring documentation that it was approved by an IRB and adhered to basic principles of ethically responsible procurement" (NRC and IOM, 2005, pp. 54-55). Thus, the ESCRO committee—not the investigator—must decide whether the proposed research is purely *in vitro* research with existing hES cell lines that meet appropriate standards for procurement.

The original Guidelines Committee intended that notification involve the ESCRO committee but allow expedited review procedures, such as those used in the context of IRBs. The federal regulations for IRBs outline the procedure as follows (45 CFR 46.110[5]):

> Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may ex-

[5]http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.110.

> ercise all of the authorities of the IRB except that the reviewers may not disapprove the research. . . .
>
> (c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

ESCRO committees are therefore called on to establish procedures for reviewing purely *in vitro* research that uses previously and appropriately derived hES cell lines; these reviews may be expedited at the discretion of an ESCRO committee. The former Section 1.2(a) [renumbered as 1.3(a)] of the Guidelines is therefore revised to clarify this point.

1.3(a) hES cell research permissible after currently mandated reviews

Purely *in vitro* hES cell research that uses previously derived hES cell lines is permissible provided that the ESCRO committee or equivalent body designated by the investigator's institution (see Section 2.0) receives documentation of the provenance of the cell lines, including (i) documentation of the use of an acceptable informed-consent process that was approved by an Institutional Review Board (IRB) or foreign equivalent for their derivation (consistent with Section 3.6) and (ii) documentation of compliance with any additional required review by an Institutional Animal Care and Use Committee (IACUC), Institutional Biosafety Committee (IBC), or other institutionally mandated review. To determine whether the proposed research meets the requirements of this section, the ESCRO committee may choose to conduct an *expedited review* of such research proposals. In this context, "expedited review" means that the ESCRO committee chair or others designated by the committee chair can act on behalf of the committee to determine that the hES cells have been acceptably derived (see Section 1.6) and report to the entire committee.

In addition, Sections 6.1 and 6.2 are revised to be consistent with the changes in the newly revised and renumbered 1.3(a):

6.1 Institutions should require documentation of the provenance of all hES cell lines, whether the cells were imported into the institution or generated locally. ~~Notice to~~ The institution should obtain ~~include~~ evidence of IRB approval of the procurement process and of adherence to basic ethical and legal principles of procurement as described in Sections 1.3(a) and 1.6. In the case of lines imported from another institution, documentation that these criteria were met at the time of derivation will suffice.

6.2 *In vitro* experiments involving the use of already derived and coded hES cell lines will not need review beyond the ~~notification required~~ review described in Sections 1.3(a) and ~~in Section~~ 6.1.

PUBLIC OPENNESS AND ESCRO COMMITTEE AUDITS

Research that uses hES cells remains controversial in the United States and is still subject to intense political scrutiny. Therefore, it is important to sustain public confidence in the integrity of the institutions and researchers conducting hES cell research; this is one of the reasons that the Guidelines were developed. The Human Embryonic Stem Cell Research Advisory Committee continues to believe that it is in the interests of researchers and their institutions to ensure that the Guidelines of the National Academies or other relevant bodies (such as state regulations and guidelines of the International Society for Stem Cell Research) are being appropriately implemented to ensure that both the public and policy-makers may have a high level of confidence that institutions and their researchers are conducting the research responsibly. As part of this assurance, the public should have reasonable access to information on the types of hES cell research being conducted at an institution and evidence that the research conforms to the requirements of the guidelines being followed by that institution.

For those reasons, the committee is amending the Guidelines in two ways. First, Section 2.0 calls for registries of hES cell research to be maintained by institutional ESCRO committees. Although the original intent was that the information in a registry be available to the public, this intent was not explicit in the Guidelines. The committee is therefore amending the wording of Section 2.0 to make that clear. Second, although the committee cannot impose legally enforceable requirements, it is adding a strong suggestion that institutions at which hES cell research is being conducted carry out pe-

riodic audits (for example, every 3-5 years) of their ESCRO committees to ensure that these groups are performing their duties as intended as a good management practice. The emphasis of the audits should be on documenting decisions regarding the acceptability of research proposals and on verifying that cell lines in use at the institution were acceptably derived. Institutions should also make at least the general findings and preferably the details of the audits available to the public. The amended wording (underlined) of Section 2.0 is as follows:

2.0 ESTABLISHMENT OF AN INSTITUTIONAL EMBRYONIC STEM CELL RESEARCH OVERSIGHT COMMITTEE

To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution should have activities involving hES cells overseen by an Embryonic Stem Cell Research Oversight (ESCRO) committee. This committee could be internal to a single institution or established jointly with one or more other institutions. Alternatively, an institution may have its proposals reviewed by an ESCRO committee of another institution, or by an independent ESCRO committee. An ESCRO committee should include independent representatives of the lay public as well as persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research. It must have suitable scientific, medical, and ethical expertise to conduct its own review and should have the resources needed to coordinate the management of the various other reviews required for a particular protocol. A pre-existing committee could serve the functions of the ESCRO committee provided that it has the ~~recommended~~ expertise recommended here and representation to perform the various roles described in this report. For example, an institution might elect to constitute an ESCRO committee from among some members of an IRB. But the ESCRO committee should not be a subcommittee of the IRB, as its responsibilities extend beyond human subject protections. Furthermore, much hES cell research does not require IRB review. The ESCRO committee should

(a) Provide oversight over all issues related to derivation and use of hES cell lines.
(b) Review and approve the scientific merit of research protocols.
(c) Review compliance of all in-house hES cell research with all relevant regulations and these guidelines.
(d) Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators. An institution conducting stem cell research should make information from the registries (including, but not necessarily limited to, project abstracts and sources of funding) available to the public and the media through the institution's Web site.
(e) Facilitate education of investigators involved in hES cell research.

An institution that maintains its own ESCRO committee should conduct periodic audits of the committee to verify that it is carrying out its responsibilities appropriately. Auditable records include documentation of decisions regarding the acceptability of research proposals and verification that cell lines in use at the institution were acceptably derived (see Section 1.6). Institutions should make the results of the audits available to the public.

An institution that uses an external ESCRO committee should nevertheless ensure that the registry and educational functions of an internal ESCRO committee are carried out by the external ESCRO committee on its behalf or internally by other administrative units. Those institutions that use external ESCRO committees are also responsible for ensuring that these committees are likewise carrying out their responsibilities appropriately.

CLARIFICATION OF POLICY REGARDING REIMBURSEMENT OF OOCYTE DONORS

It was pointed out in the report *Guidelines for Human Embryonic Stem Cell Research* (NRC and IOM, 2005) that although there is widespread consensus that donors should not be paid for blastocysts donated for research,

there is less of a consensus about inducements for women to donate oocytes or for men to donate sperm for research purposes. Oocyte donation solely for research purposes is the issue of most concern because of its invasiveness, its inconvenience, and the risks posed by the procedure (reviewed in IOM and NRC, 2007). If the need for oocytes in hES cell research increases, however, it is possible that donations from clinical procedures or for nonfinancial motives may prove insufficient to meet the demand. In such cases, investigators might want to recruit oocyte donors, and it is from this circumstance that the issue of whether such donors should be paid arises.

Guidelines for Human Embryonic Stem Cell Research contained a long discussion (Chapter 5) of the arguments for and against payment of oocyte donors, which will not be repeated here. In short, one side argues for fair and just remuneration of participants in research, in which inducements are commonly provided for competent adult research subjects provided that the research risks are reasonable in relation to the potential research benefits. Furthermore, because payment is legal and widely practiced for egg donation for reproductive purposes, many find the forbidding of payment in the research context difficult to justify. Others, however, oppose any payment, whether for research or reproduction. Typically, they caution against any form of payment that may create an "undue inducement" that could compromise a prospective donor's evaluation of the risks posed by donation or the voluntariness of her choices. Furthermore, opponents of payment often embed their objections in a larger set of concerns about the "commodification of life," which also apply to payment for human tissue of any sort and to the patenting of genes and other issues. Complicating these principled debates are more pragmatic concerns: whether (and how much) payment is needed to ensure a sufficient supply of oocytes for nuclear transfer and other forms of specialized stem cell research, and the interchangeability of cell lines, material transfers, and the future of collaborative stem cell research if various state and national jurisdictions have different rules regarding reimbursement and compensation for oocyte donors.

The recommendation made by the Committee on Guidelines for Human Embryonic Stem Cell Research in 2005 was that women who undergo hormonal induction to generate oocytes specifically for research purposes should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an Institutional Review Board. Thus, the National Academies' Guidelines prohibit cash or in-kind payments for donating oocytes for research purposes. As pointed out in the earlier report (NRC and IOM,

2005) that position was based in part on the recognition that payments to oocyte donors raise concerns that might undermine public confidence in the responsible management of hES cell research. The report also noted that the recommendation was intended to ensure consistency between procurement practices in the United States and in other countries that have major hES cell research programs and with the limitations enacted in specific states, facilitating collaboration among investigators in the United States and abroad. Since that time, however, California has provided a useful model in its finalized regulations (Title 17 CA Code of Regulations, Section 100020) that allows reimbursement of oocyte donors for "permissible expenses," which are clearly defined to include "actual lost wages." The state of Massachusetts has a similar policy. Although the original National Academies' Guidelines did not specifically mention lost wages as a reimbursable category of direct expenses, institutions and states that perform or support hES cell research should view the National Academies' Guidelines as open to the interpretation that "lost wages" is a legitimate category of reimbursable expenses. To make that explicit, the wording of Section 3.4(b) is modified as follows (new wording underlined):

> 3.4(b) Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for NT) should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB. Direct expenses may include costs associated with travel, housing, child care, medical care, health insurance, and actual lost wages. No payments beyond reimbursements, cash or in-kind, should be provided for donating oocytes for research purposes. Similarly, no payments beyond reimbursements should be made for donations of sperm for research purposes or of somatic cells for use in NT.

The committee does not find persuasive the argument that this change has the effect of assigning differing values to the oocytes of different women based on their relative salaries. Reimbursement for lost wages is not a "price" being paid for oocytes. The intent is to leave all donors no better off, but also no worse off.

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Appendix A

National Academies' Guidelines for Human Embryonic Stem Cell Research Amended as of September 2008[1]

1.0 INTRODUCTION

In this chapter we collect all the recommendations made throughout the report and translate them into a series of formal guidelines. These guidelines focus on the derivation, procurement, banking, and use of human embryonic stem (hES) cell lines. They provide an oversight process that will help to ensure that research with hES cells is conducted in a responsible and ethically sensitive manner and in compliance with all regulatory requirements pertaining to biomedical research in general. The National Academies are issuing

[1]New or modified wording is indicated by underlining, deleted text by ~~strikeout~~.

these guidelines for the use of the scientific community, including researchers in university, industry, or other private-sector research organizations.

1.1 What These Guidelines Cover

1.1(a) These guidelines cover all derivation of hES cell lines and all research that uses hES cells derived from

(i) blastocysts made for reproductive purposes and later obtained for research from *in vitro* fertilization (IVF) clinics,
(ii) blastocysts made specifically for research using IVF,
(iii) somatic cell nuclear transfer (NT) into oocytes.

1.1(b) Some of the ~~guidelines and~~ concerns addressed in this report are common to other ~~areas~~ types of human stem cell research; as such, certain of these Guidelines should also apply to those other types of research. For example, ~~such as~~

(i) research that uses human adult stem cells,

(ii) research that uses fetal stem cells or embryonic germ cells derived from fetal tissue; such research is covered by federal statutory restrictions at 42 U.S.C. 289g-2(a) and federal regulations at 45 CFR 46.210,

(iii) research using human pluripotent stem (hPS) cells derived from non-embryonic sources, such as spermatogonial stem cells and "induced pluripotent" stem cells derived from somatic cells by introduction of genes or otherwise (so-called iPS cells), as well as other pluripotent cells yet to be developed.

Recommendations as to which guidelines apply to other hPS cells are collected in Section 7 below. Institutions and investigators conducting research ~~using such materials~~ with adult and fetal stem cells should also consider which individual provisions of these guidelines are relevant to their research.

1.1(c) The guidelines do not cover research that uses nonhuman stem cells.

1.2 Reproductive Uses of NT

These guidelines also do not apply to reproductive uses of nuclear transfer (NT), which are addressed in the 2002 report *Scientific and Medical Aspects of Human Reproductive Cloning*, in which the National Academies recommended that "Human reproductive cloning should not now be practiced. It is dangerous and likely to fail." Although these guidelines do not specifically address human reproductive cloning, it continues to be the view of the National Academies that research aimed at the reproductive cloning of a human being should not be conducted at this time.

1.3 Categories of hES Cell Research

These guidelines specify categories of research that:

- Are permissible after currently mandated reviews and proper notification of the relevant research institution.
- Are permissible after additional review by an Embryonic Stem Cell Research Oversight (ESCRO) committee, as described in Section 2.0 of the guidelines.
- Should not be conducted at this time.

Because of the sensitive nature of some aspects of hES cell research, these guidelines in many instances set a higher standard than is required by laws or regulations with which institutions and individuals already must comply.

1.3(a) hES cell research permissible after currently mandated reviews

Purely *in vitro* hES cell research that uses previously derived hES cell lines is permissible provided that the ESCRO committee or equivalent body designated by the investigator's institution (see Section 2.0) receives documentation of the provenance of the cell lines including (i) documentation of the use of an acceptable informed consent process that was approved by an Institutional Review Board (IRB) or foreign equivalent for their derivation (consistent with Section 3.6) and (ii) documentation of compliance with any additional required review by an Institutional Animal Care and Use Committee (IACUC), Institutional Biosafety Committee (IBC), or other institutionally mandated review. To determine whether the proposed research meets the requirements of this section, the ESCRO committee may choose to conduct an *expedited review* of such research proposals. In this context, "expedited review" means that the ESCRO committee chair or others des-

ignated by the committee chair act on behalf of the committee to determine that the hES cells have been acceptably derived (see Section 1.6) and report to the entire committee.

1.3(b) hES cell research permissible only after additional review and approval

(i) Generation of new lines of hES cells by whatever means.

(ii) Research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development. Particular attention should be paid to at least three factors: the extent to which the implanted cells colonize and integrate into the animal tissue; the degree of differentiation of the implanted cells; and the possible effects of the implanted cells on the function of the animal tissue.

(iii) Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

1.3(c) hES cell research that should not be permitted at this time

The following types of research should not be conducted at this time:

(i) Research involving *in vitro* culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first.

(ii) Research in which hES cells are introduced into nonhuman primate blastocysts or in which any embryonic stem cells are introduced into human blastocysts.

In addition:

(iii) No animal into which hES cells have been introduced such that they could contribute to the germ line should be allowed to breed.

1.4 Obligations of Investigators and Institutions

All scientific investigators and their institutions, regardless of their field, bear the ultimate responsibility for ensuring that they conduct themselves in accordance with professional standards and with integrity. In particular, people whose research involves hES cells should work closely with oversight bodies, demonstrate respect for the autonomy and privacy of those who donate gametes, blastocysts, or somatic cells and be sensitive to public concerns about research that involves human embryos.

1.5 Use of NIH-Approved hES Cell Lines

1.5(a) It is acceptable to use hES cell lines that were approved in August 2001 for use in U.S. federally funded research.

1.5(b) ESCRO committees should include on their registry a list of NIH-approved cell lines that have been used at their institution in accord with the requirement in Section 2.0 of the Guidelines.

1.5(c) Presence on the list of NIH-approved cell lines constitutes adequate documentation of provenance, as per Section 6.1 of the Guidelines.

1.6 Acceptability of Research Using hES Cell Lines Imported from Other Institutions or Jurisdictions

1.6(a) Before approving use of hES and hPS cell lines imported from other institutions or jurisdictions, ESCRO committees should consider whether such cell lines have been "acceptably derived."

1.6(b) "Acceptably derived" means that the cell lines were derived from gametes or embryos for which

(i) the donation protocol was reviewed and approved by an IRB or, in the case of donations taking place outside the United States, a substantially equivalent oversight body;
(ii) consent to donate was voluntary and informed;
(iii) donation was made with reimbursement policies consistent with these Guidelines; and
(iv) donation and derivation complied with the extant legal requirements of the relevant jurisdiction.

1.6(c) ESCRO committees should include on their registry a list of cell lines that have been imported from other institutions or jurisdictions and information on the specific guidelines, regulations, or statutes under which the derivation of the imported cell lines was conducted. This is in accord with the requirement in Section 2.0 of the Guidelines that calls for ESCRO committees to maintain registries listing the cell lines in use at their institutions.

2.0 ESTABLISHMENT OF AN INSTITUTIONAL EMBRYONIC STEM CELL RESEARCH OVERSIGHT COMMITTEE

To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution should have activities involving hES cells overseen by an Embryonic Stem Cell Research Oversight (ESCRO) committee. This committee could be internal to a single institution or established jointly with one or more other institutions. Alternatively, an institution may have its proposals reviewed by an ESCRO committee of another institution, or by an independent ESCRO committee. An ESCRO committee should include independent representatives of the lay public as well as persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research. It must have suitable scientific, medical, and ethical expertise to conduct its own review and should have the resources needed to coordinate the management of the various other reviews required for a particular protocol. A pre-existing committee could serve the functions of the ESCRO committee provided that it has the ~~recommended~~ expertise recommended here and representation to perform the various roles described in this report. For example, an institution might elect to constitute an ESCRO committee from among some members of an IRB. But the ESCRO committee should not be a subcommittee of the IRB, as its responsibilities extend beyond human subject protections. Furthermore, much hES cell research does not require IRB review. The ESCRO committee should:

(a) Provide oversight over all issues related to derivation and use of hES cell lines.
(b) Review and approve the scientific merit of research protocols.
(c) Review compliance of all in-house hES cell research with all relevant regulations and these guidelines.
(d) Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators.

An institution conducting stem cell research should make information from the registries (including, but not necessarily limited to, project abstracts and source of funding) available to the public and the media through the institution's Web site.

(e) Facilitate education of investigators involved in hES cell research.

An institution that maintains its own ESCRO committee should also conduct periodic audits of the committee to verify that it is carrying out its responsibilities appropriately. Auditable records include documentation of decisions regarding the acceptability of research proposals and verification that cell lines in use at the institution were acceptably derived (see Section 1.6). Institutions should make the results of these audits available to the public.

An institution that uses an external ESCRO committee should nevertheless ensure that the registry and educational functions of an internal ESCRO committee are carried out by the external ESCRO committee on its behalf or internally by other administrative units. Those institutions that use external ESCRO committees are also responsible for ensuring that these committees are likewise carrying out their responsibilities appropriately.

2.1 For projects that involve more than one institution, review of the scientific merit, justification, and compliance status of the research may be carried out by a single ESCRO committee if all participating institutions agree to accept the results of the review.

3.0 PROCUREMENT OF GAMETES, BLASTOCYSTS, OR CELLS FOR hES GENERATION

3.1 An IRB, as described in federal regulations at 45 CFR 46.107, should review all new procurements of all gametes, blastocysts, or somatic cells for the purpose of generating new hES or hPS cell lines. This includes the procurement of blastocysts in excess of clinical need from infertility clinics; blastocysts made through IVF specifically for research purposes; ~~and~~ oocytes, sperm, and somatic cells donated for development of hES cell lines derived through NT or by parthenogenesis or androgenesis; and hPS cells derived by any means that require human subjects review.

3.2 Consent for donation should be obtained from each donor at the time of donation. Even people who have given prior indication of their intent to donate to research any blastocysts that remain after clinical care should

nonetheless give informed consent at the time of donation. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

3.3 When donor gametes have been used in the IVF process, resulting blastocysts may not be used for research without consent of all gamete donors.

3.4 Payment and Reimbursement

3.4(a) No payments, cash or in-kind, may be provided for donating blastocysts in excess of clinical need for research purposes. People who elect to donate stored blastocysts for research should not be reimbursed for the costs of storage prior to the decision to donate.

3.4(b) Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for NT) should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB. Direct expenses may include costs associated with travel, housing, child care, medical care, health insurance, and actual lost wages. No payments beyond reimbursements, cash or in-kind, should be provided for donating oocytes for research purposes. Similarly, no payments beyond reimbursements should be made for donations of sperm for research purposes or of somatic cells for use in NT.

3.5 To facilitate autonomous choice, decisions related to the creation of embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research. Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells should not be the same person.

3.6 In the context of donation of gametes, blastocysts, or somatic cells for hES cell research or for hPS cell research that requires human subjects review, the informed-consent process, should, at a minimum, provide the following information.

(a) A statement that the blastocysts, gametes, or somatic cells will be used to derive hES or hPS cells for research that may include research on human transplantation.
(b) A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation.

(c) A statement as to whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hES or hPS cell lines.
(d) If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines.
(e) An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells. (Traceable information, however, must be secured to ensure confidentiality.)
(f) A statement that derived hES or hPS cells and/or cell lines might be kept for many years.
(g) A statement that the hES or hPS cells and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models.
(h) Disclosure of the possibility that the results of study of the hES or hPS cells may have commercial potential and a statement that the donor will not receive financial or any other benefits from any future commercial development.
(i) A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.
(j) A statement that embryos will be destroyed in the process of deriving hES cells.
(k) A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.
(l) A statement of the risks involved to the donor.

In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others. For example, donors might agree to have their materials used for deriving new hES cell lines but might not want their materials used, for example, for NT. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored. Investigators and stem cell banks are, of course, free to choose which cell lines to accept, and are not obligated to accept cell lines for which maintaining information about specific research use prohibitions would be unduly burdensome.

New derivations of stem cell lines from banked tissues obtained prior to the adoption of these guidelines are permissible provided that the original dona-

tions were made in accordance with the legal requirements in force at the place and time of donation. This includes gametes, blastocysts, adult stem cells, somatic cells, or other tissue. In the event that these banked tissues retain identifiers linked to living individuals, human subjects protections may apply.

3.7 Clinical personnel who have a conscientious objection to hES cell research should not be required to participate in providing donor information or securing donor consent for research use of gametes or blastocysts. That privilege should not extend to the care of a donor or recipient.

3.8 Researchers may not ask members of the infertility treatment team to generate more oocytes than necessary for the optimal chance of reproductive success. An infertility clinic or other third party responsible for obtaining consent or collecting materials should not be able to pay for or be paid for the material obtained (except for specifically defined cost-based reimbursements and payments for professional services).

4.0 DERIVATION OF hES CELL LINES

4.1 Requests to the ESCRO committee for permission to attempt derivation of new hES cell lines from donated embryos or blastocysts must include evidence of IRB approval of the procurement process (see Section 3.0 above).

4.2 The scientific rationale for the need to generate new hES cell lines, by whatever means, must be clearly presented, and the basis for the numbers of embryos and blastocysts needed should be justified.

4.3 Research teams should demonstrate appropriate expertise or training in derivation or culture of either human or nonhuman ES cells before permission to derive new lines is given.

4.4 When NT experiments involving either human or nonhuman oocytes are proposed as a route to generation of ES cells, the protocol must have a strong scientific rationale. Proposals that include studies to find alternatives to donated oocytes in this research should be encouraged.

4.5 Neither blastocysts made using NT (whether produced with human or nonhuman oocytes) nor parthenogenetic or androgenetic human embryos

may be transferred to a human or nonhuman uterus or cultured as intact embryos *in vitro* for longer than 14 days or until formation of the primitive streak, whichever occurs first.

4.6 Investigators must document how they will characterize, validate, store, and distribute any new hES cell lines and how they will maintain the confidentiality of any coded or identifiable information associated with the lines (see Section 5.0 below). Investigators are encouraged to apply the same procedures and standards for characterization, validation, storage, and distribution to hPS cell lines.

5.0 BANKING AND DISTRIBUTION OF hES CELL LINES

There are several models for the banking of human biological materials, including hES cells. The most relevant is the U.K. Stem Cell Bank. The guidelines developed by this and other groups generally adhere to key ethical principles that focus on the need for consent of donors and a system for monitoring adherence to ethical, legal, and scientific requirements. As hES cell research advances, it will be increasingly important for institutions that are obtaining, storing, and using cell lines to have confidence in the value of stored cells—that is, that they were obtained ethically and with the informed consent of donors, that they are well characterized and screened for safety, and that the conditions under which they are maintained and stored meet the highest scientific standards. Institutions engaged in hES research should seek mechanisms for establishing central repositories for hES cell lines—through partnerships or augmentation of existing quality research cell line repositories and should adhere to high ethical, legal, and scientific standards. At a minimum, an institutional registry of stem cell lines should be maintained. Institutions are encouraged to consider the use of the same procedures for banking and distribution of hPS cell lines.

5.1 Institutions that are banking or plan to bank hES cell lines should establish uniform guidelines to ensure that donors of material give informed consent through a process approved by an IRB and that meticulous records are maintained about all aspects of cell culture. Uniform tracking systems and common guidelines for distribution of cells should be established.

5.2 Any facility engaged in obtaining and storing hES cell lines should consider the following standards:

(a) Creation of a committee for policy and oversight purposes and creation of clear and standardized protocols for banking and withdrawals.

(b) Documentation requirements for investigators and sites that deposit cell lines, including
  (i) A copy of the donor consent form.
  (ii) Proof of Institutional Review Board approval of the procurement process.
  (iii) Available medical information on the donors, including results of infectious-disease screening.
  (iv) Available clinical, observational, or diagnostic information about the donor(s).
  (v) Critical information about culture conditions (such as media, cell passage, and safety information).
  (vi) Available cell line characterization (such as karyotype and genetic markers).

A repository has the right of refusal if prior culture conditions or other items do not meet its standards.

(c) A secure system for protecting the privacy of donors when materials retain codes or identifiable information, including but not limited to
  (i) A schema for maintaining confidentiality (such as a coding system).
  (ii) A system for a secure audit trail from primary cell lines to those submitted to the repository.
  (iii) A policy governing whether and how to deliver clinically significant information back to donors.

(d) The following standard practices:
  (i) Assignment of a unique identifier to each sample.
  (ii) A process for characterizing cell lines.
  (iii) A process for expanding, maintaining, and storing cell lines.
  (iv) A system for quality assurance and control.
  (v) A Web site that contains scientific descriptions and data related to the cell lines available.
  (vi) A procedure for reviewing applications for cell lines.
  (vii) A process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).
  (viii) A system for auditing compliance.

(ix) A schedule of charges.
(x) A statement of intellectual property policies.
(xi) When appropriate, creation of a clear Material Transfer Agreement or user agreement.
(xii) A liability statement.
(xiii) A system for disposal of material.

(e) Clear criteria for distribution of cell lines, including but not limited to evidence of approval of the research by an embryonic stem cell research oversight committee or equivalent body at the recipient institution.

6.0 RESEARCH USE OF hES CELL LINES

Once hES cell lines have been derived, investigators and institutions, through ESCRO committees and other relevant committees (such as an IACUC, an IBC, or a radiation safety committee) should monitor their use in research.

6.1 Institutions should require documentation of the provenance of all hES cell lines, whether the cells were imported into the institution or generated locally. ~~Notice to~~ The institution should obtain ~~include~~ evidence of IRB approval of the procurement process and of adherence to basic ethical and legal principles of procurement as described in Sections 1.3(a) and 1.6. In the case of lines imported from another institution, documentation that these criteria were met at the time of derivation will suffice.

6.2 *In vitro* experiments involving the use of already derived and coded hES cell lines will not need review beyond the ~~notification required~~ review described in Sections 1.3(a) and ~~in Section~~ 6.1.

6.3 Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding the use of hES cells.

6.4 All protocols involving the combination of hES cells with nonhuman embryos, fetuses, or adult animals must be submitted to the local IACUC for review of animal welfare issues and to the ESCRO committee for consideration of the consequences of the human contributions to the resulting chimeras. (See also Section 1.3(c)(iii) concerning breeding of chimeras.)

6.5 Transplantation of differentiated derivatives of hES cells or even hES cells themselves into adult animals will not require extensive ESCRO committee review. If there is a possibility that the human cells could contribute in a major organized way to the brain of the recipient animal, however, the scientific justification for the experiments must be strong, and proof of principle using nonhuman (preferably primate) cells, is desirable.

6.6 Experiments in which hES cells, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses and allowed to develop into adult chimeras need more careful consideration because the extent of human contribution to the resulting animal may be higher. Consideration of any major functional contributions to the brain should be a main focus of review. (See also Section 1.3(c)(iii) concerning breeding of chimeras.)

6.7 Introduction of hES cells into nonhuman mammalian blastocysts should be considered only under circumstances in which no other experiment can provide the information needed. (See also Sections 1.3(c)(ii) and 1.3(c)(iii) concerning restrictions on breeding of chimeras and production of chimeras with nonhuman primate blastocysts.)

6.8 Research use of existing hES cells does not require IRB review unless the research involves introduction of the hES cells or their derivatives into patients or the possibility that the identity of the donors of the blastocysts, gametes, or somatic cells is readily ascertainable or might become known to the investigator.

7.0 RECOMMENDATIONS FOR RESEARCH ON NON-EMBRYO-DERIVED HUMAN PLURIPOTENT STEM CELLS (hPS CELLS)

7.1 Derivation

Because non-embryo-derived hPS cells are derived from human material, their derivation is covered by existing IRB regulations concerning review and informed consent. No ESCRO committee review is necessary, although the IRB may always seek the advice of an ESCRO committee if it seems desirable. The IRB review should consider proper consent for use of the derived hPS cells. Some of the recommendations for informed consent that apply to hES cells also apply to hPS cells (see Section 3.6), including informed consent to genetic manipulation of resulting pluripotent stem cells and their

use for transplantation into animals and humans and, potentially, in future commercial development.

7.2 Use in *in Vitro* Experiments

Use of hPS cells in purely *in vitro* experiments need not be subject to any review beyond that necessary for any human cell line except that any experiments designed or expected to yield gametes (oocytes or sperm) should be subject to ESCRO committee review.

7.3 Use in Experiments Involving Transplantation of hPS Cells into Animals at Any Stage of Development or Maturity

7.3(a) Research involving transplantation of pluripotent human cells derived from non-embryonic sources into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by ESCRO committees and IACUCs, as are similar experiments that use hES cells.

7.3(b) ESCRO committees should review the provenance of hPS cells as they review the provenance of hES cells (see Section 1.6) to ensure that the cell lines were derived according to ethical procedures of informed consent as monitored by an IRB or equivalent oversight body.

7.3(c) Proposals for use of hPS cells in animals should be considered in one of the following categories:

(i) Permissible after currently mandated reviews and proper documentation [see Section 1.3(a)]: experiments that are exempt from full ESCRO committee review but not IACUC review (experiments that involve only transplantation into postnatal animals with no likelihood of contributing to the central nervous system or germ line).

(ii) Permissible after additional review by an ESCRO committee, as described in Section 2.0 of the Guidelines [see Section 1.3(b)]: experiments in which there is a significant possibility that the implanted hPS cells could give rise to neural or gametic cells and tissues. Such experiments need full ESCRO committee and IACUC review and would include generation of all preimplantation chimeras and neural transplantation into embryos or perinatal animals. Particular attention should be paid to at least three factors: the extent to which the

implanted cells colonize and integrate into the animal tissue; the degree of differentiation of the implanted cells; and the possible effects of the implanted cells on the function of the animal tissue.

(iii) Should not be conducted at this time [see Section 1.3(c)]:

(1) Experiments that involve transplantation of hPS cells into human blastocysts.
(2) Research in which hPS cells are introduced into nonhuman primate embryos, pending further research that will clarify the potential of such introduced cells to contribute to neural tissue or to the germ line.

7.4 Multipotent Neural Stem Cells

It is also relevant to note that neural stem cells, although not pluripotent, are multipotent and may have the potential to contribute to neural tissue in chimeric animals. ESCRO committees should decide whether they wish to review and monitor such experiments with neural stem cells in a similar fashion.

7.5 Prohibition on Breeding

No animal into which hPS cells have been introduced such that they could contribute to the germ line should be allowed to breed.

7.6 Guidance for Banking and Distribution

Institutions should consider the value of banking and distributing hPS cells using the guidance and rules that are already in place for hES cells and the value of including hPS cell lines in their registries.

8.0 INTERNATIONAL COLLABORATION

If a U.S.-based investigator collaborates with an investigator in another country, the ESCRO committee may determine that the procedures prescribed by the foreign institution afford protections consistent with these guidelines, and the ESCRO committee may approve the substitution of some of or all of the foreign procedures for its own.

9.0 CONCLUSION

The substantial public support for hES cell research and the growing trend by many nonfederal funding agencies and state legislatures to support this field requires a set of guidelines to provide a framework for hES cell research. In the absence of the oversight that would come with unrestricted federal funding of this research, these guidelines will offer reassurance to the public and to Congress that the scientific community is attentive to ethical concerns and is capable of self-regulation while moving forward with this important research.

To help ensure that these guidelines are taken seriously, stakeholders in hES cell research—sponsors, funding sources, research institutions, relevant oversight committees, professional societies, and scientific journals, as well as investigators—should develop policies and practices that are consistent with the principles inherent in these guidelines. Funding agencies, professional societies, journals, and institutional review panels can provide valuable community pressure and impose appropriate sanctions to ensure compliance. For example, ESCROs and IRBs should require evidence of compliance when protocols are reviewed for renewal, funding agencies should assess compliance when reviewing applications for support, and journals should require that evidence of compliance accompanies publication of results.

As individual states and private entities move into hES cell research, it will be important to initiate a national effort to provide a formal context in which the complex moral and oversight questions associated with this work can be addressed on a continuing basis. Both the state of hES cell research and clinical practice and public policy surrounding these topics are in a state of flux and are likely to be so for several years. Therefore, the committee believes that a national body should be established to assess periodically the adequacy of the policies and guidelines proposed in this document and to provide a forum for a continuing discussion of issues involved in hES cell research. New policies and standards may be appropriate for issues that cannot now be foreseen. The organization that sponsors this body should be politically independent and without conflicts of interest, should be respected in the lay and scientific communities, and able to call on suitable expertise to support this effort.

Appendix B

Glossary[1]

Adult stem cell—An undifferentiated cell found in a differentiated tissue that can renew itself and (with limitations) differentiate to yield the specialized cell types of the tissue from which it originated.

Androgenesis—Development in which the embryo contains only paternal chromosomes.

Autologous transplant—Transplanted tissue derived from the intended recipient of the transplant. Such a transplant helps to avoid complications of immune rejection.

Blastocoel—The cavity in the center of a blastocyst.

Blastocyst—A preimplantation embryo of 50–250 cells depending on age. The blastocyst consists of a sphere made up of an outer layer of cells (the trophectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).

Blastomere—A single cell from a morula or early blastocyst, before the differentiation into trophectoderm and inner cell mass.

Bone marrow—The soft, living tissue that fills most bone cavities and contains hematopoietic stem cells, from which all red and white blood cells evolve. The bone marrow also contains mesenchymal stem cells from which a number of cell types arise, including chondrocytes, which produce cartilage, and fibroblasts, which produce connective tissue.

[1]New or modified wording is indicated by underlining, deleted text by ~~strikeout~~.

Chimera—An organism composed of cells derived from at least two genetically different cell types. The cells could be from the same or separate species.

Differentiation—The process whereby an unspecialized early embryonic cell acquires the features of a specialized cell, such as a heart, liver, or muscle cell.

DNA—Deoxyribonucleic acid, a chemical found primarily in the nucleus of cells. DNA carries the instructions for making all the structures and materials the body needs to function.

Ectoderm—The outermost of the three primitive germ layers of the embryo; it gives rise to skin, nerves, and brain.

Egg cylinder—An asymmetric embryonic structure that helps to determine the body plan of the mouse.

Electroporation—Method of introducing DNA into a cell.

Embryo—An animal in the early stages of growth and differentiation that are characterized by cleavage, laying down of fundamental tissues, and the formation of primitive organs and organ systems; especially the developing human individual from the time of implantation to the end of the eighth week after conception, after which stage it becomes known as a fetus.[2]

Embryoid bodies (EBs)—Clumps of cellular structures that arise when embryonic stem cells are cultured. Embryoid bodies contain tissue from all three germ layers: endoderm, mesoderm, and ectoderm. Embryoid bodies are not part of normal development and occur only in vitro.

Embryonic disk—A group of cells derived from the inner cell mass of the blastocyst, which later develops into an embryo. The disk consists of three germ layers known as the endoderm, mesoderm, and ectoderm.

Embryonic germ (EG) cells—Cells found in a specific part of the embryo or fetus called the gonadal ridge that normally develop into mature gametes. The germ cells differentiate into the gametes (oocytes or sperm).

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[2]http://www.nlm.nih.gov/medlineplus/mplusdictionary.html. In common parlance, "embryo" is used more loosely and variably to refer to all stages of development from fertilization until some ill-defined stage when it is called a fetus. There are strictly defined scientific terms such as "zygote," "morula," and "blastocyst" that refer to specific stages of preimplantation development (see Chapter 2 of NRC and IOM, 2005). In this report, we have used the more precise scientific terms where relevant but have used the term "embryo" where more precision seemed likely to confuse rather than clarify.

Embryonic stem (ES) cells—Primitive (undifferentiated) cells derived from the early embryo that have the potential to become a wide variety of specialized cell types.

Endoderm—Innermost of the three primitive germ layers of the embryo; it later gives rise to the lungs, liver, and digestive organs.

Enucleated cell—A cell whose nucleus has been removed.

Epidermis—The outer cell layers of the skin.

Epigenetic—Refers to modifications in gene expression that are controlled by heritable but potentially reversible changes in DNA methylation or chromatin structure without involving alteration of the DNA sequence.

Epithelium—Layers of cells in various organs, such as the epidermis of the skin or the lining of the gut. These cells serve the general functions of protection, absorption, and secretion, and play a specialized role in moving substances through tissue layers. Their ability to regenerate is excellent; the cells of an epithelium may replace themselves as frequently as every 24 hours from the pools of specialized stem cells.

Feeder cell layer—Cells that are used in culture to maintain pluripotent stem cells. Feeder cells usually consist of mouse embryonic fibroblasts.

Fertilization—The process whereby male and female gametes unite to form a zygote (fertilized egg).

Fibroblasts—Cells from many organs that give rise to connective tissue.

Gamete—A mature male or female germ cell, that is, sperm or oocyte, respectively.

Gastrulation—The procedure by which an animal embryo at an early stage of development produces the three primary germ layers: ectoderm, mesoderm, and endoderm.

Gene—A functional unit of heredity that is a segment of DNA located in a specific site on a chromosome. A gene usually directs the formation of an enzyme or other protein.

Gene targeting—A procedure used to produce a mutation in a specific gene.

Genital ridge—Anatomic site in the early fetus where primordial germ cells are formed.

Genome—The complete genetic material of an organism.

Genotype—Genetic constitution of an individual.

Germ cell—A sperm or egg or a cell that can become a sperm or egg. All other body cells are called somatic cells.

Germ layer—In early development, the embryo differentiates into three distinct germ layers (ectoderm, endoderm, and mesoderm), each of which gives rise to different parts of the developing organism.

Germ line—The cell lineage from which the oocyte and sperm are derived.

Gonadal ridge—Anatomic site in the early fetus where primordial germ cells (PGCs) are formed.

Gonads—The sex glands—testis and ovary.

Hematopoietic—Blood-forming.

Hematopoietic stem cell (HSC)—A stem cell from which all red and white blood cells evolve and that may be isolated from bone marrow or umbilical cord blood for use in transplants.

Hepatocyte—Liver cell.

Heterologous—From genetically different individuals.

hES cell—Human embryonic stem cell; a type of pluripotent stem cell.

Histocompatibility antigens—Glycoproteins on the surface membranes of cells that enable the body's immune system to recognize a cell as native or foreign and that are determined by the major histocompatibility complex.

Homologous recombination—Recombining of two like DNA molecules, a process by which gene targeting produces a mutation in a specific gene.

hPS cells—Human pluripotent stem cells derived from non-embryonic sources.

Hybrid—An organism that results from a cross between gametes of two different genotypes.

Immune system cells—White blood cells, or leukocytes, that originate in the bone marrow. They include antigen-presenting cells, such as dendritic cells, T and B lymphocytes, macrophages, and neutrophils, among many others.

Immunodeficient mice—Genetically altered mice used in transplantation experiments because they usually do not reject transplanted tissue.

Immunogenic—Related to or producing an immune response.

Immunosuppressive—Suppressing a natural immune response.

Implantation—The process in which a blastocyst implants into the uterine wall, where a placenta forms to nurture the growing fetus.

Inner cell mass—The cluster of cells inside the blastocyst that give rise to the embryonic disk of the later embryo and, ultimately, the fetus.

Interspecific—Between species.

In utero—In the uterus.

In vitro—Literally, "in glass," in a laboratory dish or test tube; in an artificial environment.

***In vitro* fertilization (IVF)**—An assisted reproductive technique in which fertilization is accomplished outside the body.

In vivo—In the living subject; in a natural environment.

Karyotype—The full set of chromosomes of a cell arranged with respect to size, shape, and number.

Leukemia inhibitory factor (LIF)—A growth factor necessary for maintaining mouse embryonic stem cells in a proliferative, undifferentiated state.

Mesenchymal stem cells—Stem cells found in bone marrow and elsewhere from which a number of cell types can arise, including chondrocytes, which produce cartilage, and fibroblasts, which produce connective tissue.

Mesoderm—The middle layer of the embryonic disk, which consists of a group of cells derived from the inner cell mass of the blastocyst; it is formed at gastrulation and is the precursor to bone, muscle, and connective tissue.

Morula—A solid mass of 16–32 cells that resembles a mulberry and results from the cleavage (cell division without growth) of a zygote (fertilized egg).

Mouse embryonic fibroblast (MEF)—Cells used as feeder cells in culturing pluripotent stem cells.

Multipotent—Capable of differentiation into a limited spectrum of differentiated cell types.

Neural stem cell (NSC)—A stem cell found in adult neural tissue that can give rise to neurons, astrocytes, and oligodendrocytes.

Nuclear transfer (NT)—Replacing the nucleus of one cell with the nucleus of another cell.

Oocyte—Developing egg; usually a large and immobile cell.

Ovariectomy—Surgical removal of an ovary.

Parthenogenesis—Development in which the embryo contains only maternal chromosomes.

Passage—A round of cell growth and proliferation in culture.

Phenotype—Visible properties of an organism produced by interaction of genotype and environment.

Placenta—The oval or discoid spongy structure in the uterus from which the fetus derives its nourishment and oxygen.

Pluripotent cell—A cell that has the capability of developing into cells of all germ layers (endoderm, ectoderm, and mesoderm).

Precursor cells—In fetal or adult tissues, partly differentiated cells that divide and give rise to differentiated cells. Also known as progenitor cells.

Preimplantation genetic diagnosis (PGD)—A procedure applied to IVF embryos to determine which ones carry deleterious mutations predisposing to hereditary diseases.

Primary germ layers—The three initial embryonic germ layers—endoderm, mesoderm, and ectoderm—from which all other somatic tissue types develop.

Primordial germ cell—A cell appearing during early development that is a precursor to a germ cell.

Primitive streak—The initial band of cells from which the embryo begins to develop. The primitive streak establishes and reveals the embryo's head-tail and left-right orientations.

Pseudopregnant—Refers to a female primed with hormones to accept a blastocyst for implantation.

Somatic cell—Any cell of a plant or animal other than a germ cell or germ cell precursor.

Somatic cell nuclear transfer (SCNT)—The transfer of a cell nucleus from a somatic cell into an egg (oocyte) whose nucleus has been removed.

Stem cell—A cell that has the ability to divide for indefinite periods *in vivo* or in culture and to give rise to specialized cells.

Teratoma—A tumor composed of tissues from the three embryonic germ layers. Usually found in ovary or testis. Produced experimentally in animals by injecting pluripotent stem cells to determine the stem cells' abilities to differentiate into various types of tissues.

Tissue culture—Growth of tissue *in vitro* on an artificial medium for experimental research.

Transfection—A method by which experimental DNA may be put into a cultured cell.

Transgene—A gene that has been incorporated into a cell or organism and passed on to successive generations.

Transplantation—Removal of tissue from one part of the body or from one individual and its implantation or insertion into another, especially by surgery.

Trophectoderm—The outer layer of the developing blastocyst that will ultimately form the embryonic side of the placenta.

Trophoblast—The extraembryonic tissue responsible for negotiating implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.

Undifferentiated—Not having changed to become a specialized cell type.

Xenograft or xenotransplant—A graft or transplant of cells, tissues, or organs taken from a donor of one species and grafted into a recipient of another species.

Zygote—A cell formed by the union of male and female germ cells (sperm and egg, respectively).

Appendix C

Committee Biographical Sketches

COCHAIRS

R. Alta Charo, JD, is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin–Madison, on the faculties of both the Law School and the Medical School. In 2006, she was Visiting Professor of Law the University of California, Berkeley Boalt Hall School of Law. Professor Charo is the author of nearly 100 articles, book chapters, and government reports on such topics as voting rights, environmental law, family planning and abortion law, medical genetics law, reproductive technology policy, science policy, and medical ethics. Professor Charo is a member of the boards of the Alan Guttmacher Institute and the Foundation for Genetic Medicine, a member of the National Medical Advisory Committee of the Planned Parenthood Federation of America, and a member of the ethics advisory boards of the International Society for Stem Cell Research, the Juvenile Diabetes Research Foundation, and WiCell. In 2005, she was appointed to the ethics standards working group of the California Institute for Regenerative Medicine and was elected a fellow of the Wisconsin Academy of Sciences, Arts and Letters. In 1994, Professor Charo served on the National Institutes of Health Human Embryo Research Panel; and from 1996 to 2001, she was a member of the presidential National Bioethics Advisory Commission and participated in drafting its reports *Cloning Human Beings* (1997), *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity* (1998), *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999), *Ethical Issues in Human Stem Cell Research* (1999), *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (2001), and *Ethical and Policy Issues in Research Involving Human Participants* (2001). She was a member of the National Academies' Board on Life Sciences from 2001 until 2007 and since 2006 has been a member of the Institute of Medicine (IOM) Board on

Population Health and Public Health Practices. Professor Charo was elected to IOM in 2006.

Richard O. Hynes, PhD, is the Daniel K. Ludwig Professor for Cancer Research at the David H. Koch Institute for Integrative Cancer Research and Department of Biology at MIT and a Howard Hughes Medical Institute Investigator. He was formerly head of the Biology Department and then director of the Center for Cancer Research at the Massachusetts Institute of Technology. His research focuses on fibronectins and integrins and the molecular basis of cellular adhesion, both in normal development and in pathological situations, such as cancer, thrombosis, and inflammation. Dr. Hynes's current interests are cancer invasion and metastasis, angiogenesis, and animal models of human disease states. He is a member of the National Academy of Sciences and the Institute of Medicine and is a fellow of the Royal Society of London and the American Academy of Arts and Sciences. In 1997, he received the Gairdner International Foundation Award. In 2000, he served as president of the American Society for Cell Biology and testified before Congress about the need for federal support and oversight of embryonic stem cell research. He cochaired the 2005 National Academies *Guidelines for Human Embryonic Stem Cell Research* and is a governor of the Wellcome Trust, UK.

MEMBERS

Eli Y. Adashi, MD, MS, FACOG, is professor of medical science and the former dean of medicine and biological sciences and the Frank L. Day Professor of Biology at the Warren Alpert Medical School of Brown University. Previously, Dr. Adashi served as the professor and chair of the Department of Obstetrics and Gynecology at the University of Utah Health Sciences Center. Dr. Adashi is a member of the Institute of Medicine, a member of the Association of American Physicians, and a fellow of the American Association for the Advancement of Science. Dr. Adashi is a former member of the Advisory Council of the National Institute of Child Health and Human Development and a former president of the Society for Reproductive Endocrinologists, the Society for Gynecologic Investigation, and the American Gynecological and Obstetrical Society. Dr. Adashi is also a former examiner and director of the Division of Reproductive Endocrinology of the American Board of Obstetrics and Gynecology. He is a founding member and treasurer and more recently chair of the advisory committee of the Geneva-based Bertarelli Foundation,

dedicated to promoting the welfare of the infertile couple and to addressing the current "epidemic" of high-order multiple gestations.

Brigid L.M. Hogan, PhD, is the George Barth Geller Professor and chair of the Department of Cell Biology, Duke University Medical Center. Before joining Duke, Dr. Hogan was an investigator of the Howard Hughes Medical Institute and Hortense B. Ingram Professor in the Department of Cell Biology at Vanderbilt University Medical Center. Dr. Hogan earned her PhD in biochemistry at the University of Cambridge. She was then a postdoctoral fellow in the Department of Biology at the Massachusetts Institute of Technology. Before moving to the United States in 1988, Dr. Hogan was head of the Molecular Embryology Laboratory at the National Institute for Medical Research in London. Her research focuses on the genetic control of embryonic development and morphogenesis, using the mouse as a model system. Her laboratory developed methods for deriving mouse pluripotential embryonic germ cell lines. She was cochair for science of the 1994 National Institutes of Health Human Embryo Research Panel and a member of the 2001-2002 National Academies Panel on Scientific and Medical Aspects of Human Cloning. Within the last few years, Dr. Hogan has been elected to the Royal Society of London, the American Academy of Arts and Sciences, the Institute of Medicine, and the National Academy of Sciences.

Marcia Imbrescia is the owner of Peartree Design, a landscape design firm, and was previously the media director for Drumbeater, a high-technology advertising agency. She holds BA degrees in marketing and journalism and a graduate certificate in landscape design. Ms. Imbrescia has a passion for health advocacy and helping people with illness and disability. She is a member of the Board of Trustees of the Arthritis Foundation (AF), for which she has participated as a volunteer at the chapter and national levels. She served as a member (1996-1998 and 2001) and chairperson (2002-2003) of AF's American Juvenile Arthritis Organization. In 1992, she received the Volunteer of the Year Award from the Massachusetts Chapter of AF. Her volunteer efforts include program development, conference planning, public speaking, fundraising, and advocacy. She served on the National Academies Committee on Guidelines for Human Embryonic Stem Cell Research in 2004-2005.

Terry Magnuson, PhD, is Sarah Graham Kenan Professor and chair of the Department of Genetics at the University of North Carolina. He also directs the Carolina Center for Genome Sciences and is the program director of cancer genetics at the Lineberger Comprehensive Cancer Center. Dr. Magnuson's

research interests include mammalian genetics, genomics, and development. His laboratory has developed a high-throughput system to study the effects of mutations on mouse development with mouse embryonic stem cells. He is particularly interested in the role of chromatin remodeling complexes in such processes as autosomal imprinting, X-inactivation, and anterior-posterior patterning of axial structures in mammals. He is an elected member of the American Academy of Arts and Sciences and was a member of the Board of Directors of the Genetics Society of America and of the Society for Developmental Biology.

Linda B. Miller, OTR, MS in hospital administration, is president of the Washington, DC–based Volunteer Trustees Foundation, a consortium of not-for-profit hospital governing boards. She has extensive experience in trustee education, advocacy, and the legal, ethical, and policy issues facing voluntary health care institutions. Recently, she has worked closely with the states' attorneys general in developing guidelines for protecting the community interest in the sale and conversion of nonprofit hospitals and in designing models for practice and legal oversight. She was elected to membership in the Institute of Medicine (IOM) in 1997.

Ms. Miller has been a frequent speaker on health-policy issues and has been published extensively in both the medical and popular press, including the *New England Journal of Medicine*, *Health Affairs*, *USA Today*, the *Washington Post,* and the *New York Times*. She served as a special assistant to the secretary of health, education, and welfare (now the Department of Health and Human Services) and on numerous health-related policy councils and advisory committees, including the National Institutes of Health's Consensus Panel on Liver Transplantation and, most recently, IOM's Committee on Spinal Cord Injury. Ms. Miller serves on the Advisory Board of the University of Louisville–based Institute for Cellular Therapeutics, headed by Suzanne Ildstad, which does research in adult bone marrow transplantation, and has been a member of several academic and health-care institutions' boards of governors, including those of Blythedale Children's Hospital in New York, Capital Hospice in the national capital region, and Cornell University's Alumni Council.

Jonathan D. Moreno, PhD, is the David and Lyn Silfen University Professor and professor of medical ethics and of the history and sociology of science at the University of Pennsylvania. He is also a senior fellow at the Center for American Progress. Until 2007, he was the Emily Davie and Joseph S. Kornfeld Professor of Biomedical Ethics at the University of Virginia, where

he also directed the Center for Biomedical Ethics. Dr. Moreno is a member of the Institute of Medicine. He is also a bioethics adviser for the Howard Hughes Medical Institute, a faculty affiliate of the Kennedy Institute of Ethics at Georgetown University, and a fellow of the Hastings Center. During 1995-1996, he was senior policy and research analyst for the President's Advisory Committee on Human Radiation Experiments; and during 1998-2000, he was a senior consultant for the National Bioethics Advisory Commission. He cochaired the 2005 National Academies Committee on Guidelines for Human Embryonic Stem Cell Research and is a consultant to the Ethical, Social and Cultural Program of the Bill & Melinda Gates Foundation Grand Challenges in Global Health initiative for ethical and regulatory issues related to stem cell research in China.

Pilar N. Ossorio, PhD, JD, is associate professor of law and bioethics at the University of Wisconsin–Madison and program faculty in the Graduate Program in Population Health at the university. Before taking her position there, she was director of the Genetics Section of the Institute for Ethics at the American Medical Association and taught as an adjunct faculty member at the University of Chicago Law School. For the 2006 calendar year, Professor Ossorio was a visiting professor of law at the University of California, Berkeley Boalt Hall School of Law.

Dr. Ossorio received her PhD in microbiology and immunology in 1990 from Stanford University. She went on to complete a postdoctoral fellowship in cell biology at Yale University School of Medicine. Throughout the early 1990s, Dr. Ossorio worked as a consultant for the federal program on the Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project; in 1994, she took a full-time position with the Department of Energy's ELSI program. In 1993, she served on the Ethics Working Group for President Clinton's Health Care Reform Task Force. Dr. Ossorio received her JD from the Boalt Hall School of Law in 1997. While there, she was elected to the legal honor society Order of the Coif and received several awards for outstanding legal scholarship.

Dr. Ossorio is a fellow of the American Association for the Advancement of Science (AAAS), on the Editorial Board of the *American Journal of Bioethics*, an adviser to the National Human Genome Research Institute on ethical issues in large-scale sequencing, and a member of the University of Wisconsin's institutional review board for health-sciences research. She is a past member of AAAS's Committee on Scientific Freedom and Responsibility, a past member of the National Cancer Policy Board in the Institute of Medicine, and a past member or chair of several working groups on genet-

ics and ethics. She has published scholarly articles in bioethics, law, and molecular biology.

E. Albert Reece, MD, PhD, MBA, is dean of the University of Maryland School of Medicine and vice president for medical affairs at the University of Maryland, Baltimore. Previously, he was vice chancellor and dean of the University of Arkansas College of Medicine. Dr. Reece received his undergraduate degree from Long Island University, his MD (Magna Cum Laude) from New York University, his PhD in biochemistry from the University of the West Indies, and his MBA from the Fox School of Business and Management of Temple University. He completed a residency in obstetrics and gynecology at Columbia University–Presbyterian Hospital and a fellowship in maternal-fetal medicine at Yale University School of Medicine. He served on the faculty at Yale for 10 years and was the chairman of the Department of Obstetrics, Gynecology and Reproductive Sciences at Temple University. Dr. Reece has published over 400 journal articles, book chapters, and abstracts and nine textbooks, including *Diabetes in Pregnancy*, *Medicine of the Fetus & Mother*, and *Fundamentals of Obstetric & Gynecologic Ultrasound*. He is an editor for the *Journal of Maternal-Fetal Medicine* and a reviewer for several other scientific journals. His research focuses on diabetes in pregnancy, birth defects, and prenatal diagnosis. Dr. Reece is a member of the Institute of Medicine.

Joshua R. Sanes, PhD, is professor of molecular and cellular biology and the Paul J. Finnegan Family Director of the Center for Brain Science at Harvard University. He was previously Alumni Endowed Professor of Neurobiology at the Washington University School of Medicine. Dr. Sanes earned a BA in biochemistry and psychology at Yale and a PhD in Neurobiology at Harvard. He studies the formation of the synapses that interconnect nerve cells, including pioneering work on the signals exchanged between nerve cells and their target muscles as new connections are made. He is also using the vertebrate visual system to examine how nerve cells develop and migrate to the right location in the body. He was elected a fellow of the American Association for the Advancement of Science in 1992 and a member of the National Academy of Sciences in 2002.

Harold T. Shapiro, PhD, is president emeritus of both Princeton University and the University of Michigan and is currently professor of economics and public affairs at Princeton University. His research interests include bioethics, the social role of higher education, hospital and medical-center administra-

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John E. Wagner, Jr., MD, is a professor of pediatrics at the University of Minnesota Medical School. He is the first recipient of the Children's Cancer Research Fund/Hageboeck Family Chair in Pediatric Oncology and also holds the Variety Club Endowed Chair in Molecular and Cellular Therapy. He is the director of the Division of Pediatric Hematology/Oncology and Bone Marrow Transplantation and scientific director of clinical research of the Stem Cell Institute. Dr. Wagner is a member of numerous societies, including the American Society of Hematology, the International Society of Experimental Hematology, and the American Society of Blood and Marrow Transplantation. He is a member of several honorary societies, including Alpha Omega Alpha (1980), the American Society of Clinical Investigation (2000), and the Association of American Physicians (2006). Dr. Wagner holds a patent on the isolation of the pluripotential quiescent stem cell population. Dr. Wagner holds a BA in biological sciences and a BA in psychology from the University of Delaware and an MD from Jefferson Medical College. Dr. Wagner's research has focused on the development of novel cellular therapies for tissue repair and suppression of the immune response using subpopulations of neonatal umbilical cord blood and adult bone marrow and peripheral blood. His projects are funded by the National Institutes of Health and industry. In addition, Dr. Wagner pioneered the use of embryo selection to "create" a perfectly tissue-matched stem cell donor for the treat-

ment of genetic disease. Dr. Wagner has written more than 180 articles and book chapters on hematopoietic stem cell transplantation. He cochairs the Graft Sources and Manipulation Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR), serves on the Scientific Board of Directors of the National Marrow Donor Program, and is a member of the Scientific and Medical Accountability Standards Working Group of the California Institute of Regenerative Medicine. Dr. Wagner has previously served as a member of the Institute of Medicine's Committee on Establishing a National Cord Blood Stem Cell Banking Program.