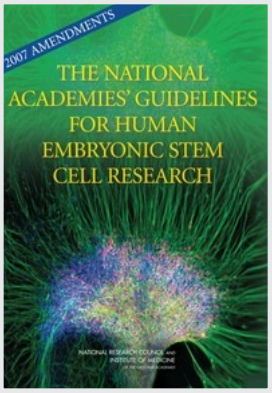

2007 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research

DETAILS

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Human Embryonic Stem Cell Research Advisory Committee, National Research Council

2007 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
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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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The Committee would like to acknowledge the input received from members of the stem cell research and oversight communities as well as the speakers and participants in its meetings.

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:

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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 **Floyd E. Bloom**, The Scripps Research Institute, and **Janet D. Rowley**, University of Chicago. 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.

Contents

2007 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research

INTRODUCTION

The National Academies' report *Guidelines for Human Embryonic Stem Cell Research* 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 that are of concern to some people, the Guidelines are intended to make explicit how research with hES cells can be pursued most responsibly. While the Guidelines are primarily intended to address researchers in the United States, they may have applicability internationally as well.

The 2005 publication of the Guidelines offered a common set of ethical standards for a field that, due to the absence of comprehensive federal funding, was lacking national standards for research. Many have found the guidelines useful, but several constituencies identified sections of the Guidelines that they believe should be clarified. In addition, numerous scientific organizations and individuals encouraged the National Academies to establish an advisory committee to keep the Guidelines up to date, given the rapid pace of scientific developments in the field of stem cell research. Further,

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

The Advisory Committee will meet two to three 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.

they urged the National Academies to consider correcting or clarifying aspects of the Guidelines in the light of experience.

Responding to these requests for revision and ongoing monitoring, the Human Embryonic Stem Cell Research Advisory Committee was established in 2006 with support from The Ellison Medical Foundation, The Greenwall Foundation, and the Howard Hughes Medical Institute.

The Human Embryonic Stem Cell Research Advisory Committee has engaged in a number of efforts to gather information about the need, if any, for revision of the Guidelines. The Committee met for the first time in July 2006 and heard from a number of invited guests representing organizations and academic institutions that are actively involved in stem cell research. In addition, in early November 2006, the Committee organized a symposium at which invited speakers reviewed the latest scientific developments, described how these developments might affect the analysis of associated ethical issues, and identified possible effects on the workability or justifiability of the current Guidelines. The Committee also hosted a panel discussion at the symposium for representatives of seven Embryonic Stem Cell Research Oversight (ESCRO) committees.[1] This panel shared their experiences in working with the content and procedures of the Guidelines.

[1]The 2005 Guidelines called for institutions involved in hES cell research to establish ESCRO committees to provide institutional oversight on all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research.

As an ongoing effort, the Committee is also monitoring discussions of the Guidelines held by others, such as the April 2006 Association of American Medical Colleges (AAMC) meeting for medical school administrators to discuss the conduct and management of stem cell research at their institutions, a discussion which encompassed a review and critique of the Guidelines, and which was summarized for the Committee at its July meeting.[2] The Committee has also established a listserv for ESCRO committee members and staff to communicate and share questions and answers, and will be hosting a series of regional meetings in the spring of 2007 to bring together ESCRO committee members and staff, receive input from ESCRO committees, and clarify the Guidelines. In addition, members of the Committee have been actively soliciting input from their colleagues and receiving comments via a Web site[3] established for this purpose.

The Committee identified issues that appeared to merit consideration of revisions of the Guidelines. This report addresses issues that are both in need of amendment and amenable to prompt solution. The Committee is issuing this first set of amendments primarily to clarify or re-emphasize earlier recommendations and conclusions. Because the changes being made are minor and affect only Sections 1 and 2 of the Guidelines, this brief letter report is the best method of communicating these changes. Future deliberations of the Committee will deal with items for which additional information gathering and more extensive debate and discussion will probably be necessary. For example, the Committee has received numerous comments both praising and disputing the current policy on no compensation for oocyte donors. Similarly, some commenters have expressed dissatisfaction with the current restrictions on research using chimeras or have asked for further guidance on how to evaluate such research. More time will be required for the Committee to give adequate consideration to these and other issues and it will report on its findings in the future.

Four changes to the Guidelines are discussed herein:

1. clarifying the phrase "provenance of the cell lines" (changes to Section 1.2);
2. use of the hES cells approved for use in federally-funded research (addition of Section 1.4);

[2]A summary of the AAMC meeting was subsequently published as "Human Embryonic Stem Cell Research: Regulatory and Administrative Challenges." This AAMC monograph is available at <http://www.aamc.org/publications>.

[3]<http://www.nationalacademies.org/stemcells>.

3. importation of hES cell lines into an institution or jurisdiction (addition of Section 1.5); and
4. allowing ESCRO committees to serve multiple institutions (changes to Section 2.0 and addition of Section 2.1).

These amended Guidelines supersede those issued in 2005 by the Committee on Guidelines for Human Embryonic Stem Cell Research. It is important that these clarifications be interpreted in context with the complete set of amended Guidelines, which is included at the end of this report. It is also worth noting that these Guidelines continue to use the word "blastocyst" to refer to the stage of embryonic development from which hES cells are obtained. Both the public and the scientific community are engaged in conversation about the best terminology by which to describe this field of research, and the Committee will be attentive to those discussions as they develop.

This report also discusses two additional issues that do not result in formal changes to the Guidelines: (a) the lack of informed consent from sperm donors for some frozen in vitro fertilization (IVF) blastocysts and (b) advice for ESCRO committees in establishing criteria for considering the science in hES cell research proposals.

CLARIFYING THE PHRASE "PROVENANCE OF THE CELL LINES"

The National Academies' Human Embryonic Stem Cell Research Advisory Committee has received many comments from the scientific community questioning the meaning of the phrase "provenance of the cell lines," which occurs in Sections 1.2(a) and 6.1, to describe documentation of the derivation of stem cell lines. The wording of Section 1.2(a) is confusing due to unintended redundancy. It asks for documentation of the provenance of cell lines, documentation of appropriate informed consent in their derivation, and evidence of compliance with required review by an Institutional Review Board (IRB) and other committees, all of which address approximately the same issue. This makes it appear that "documenting the provenance of the cell lines" is something other than documenting informed consent and IRB approval. In order to resolve this confusion, the text of Section 1.2(a) is rewritten (see underlined wording) to read:

1.2(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.

USE OF NIH-APPROVED hES CELL LINES

The National Academies' Guidelines were issued a few years after a limited number of cell lines were deemed as useable in federally funded research in the United States.[4] As of the publication of this report in early 2007, these "NIH-approved cell lines" are the only hES cell lines that may be used in federally funded research.

NIH-approved cell lines were derived before August 2001 under protocols that predated the issuance of the National Academies' Guidelines in 2005. Nonetheless, NIH's agreement to fund research using these lines was premised on confirmation that all the cell lines in question were derived from blastocysts that were donated without payment, with voluntary, informed consent, and pursuant to an IRB-approved protocol. The precise details of the consent process for the NIH-approved cell lines may not have included each element called for in the National Academies' Guidelines. In particular, the Guidelines require informed consent from all embryo, gamete, and somatic cell donors, even anonymous gamete donors. For the

[4]"President Discusses Stem Cell Research," August 9, 2001. <http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html>.

NIH-approved cell lines, the presence or absence of anonymously donated gametes cannot be confirmed, thus rendering impossible a determination of whether consent was obtained from all gamete donors. The NIH-approved cell lines were, however, derived from embryos that were donated under protocols that were substantially similar to those contemplated by the Guidelines.

Norms and procedures evolve, but it would be unnecessarily rigid to discourage institutions that follow the National Academies' Guidelines from working on the cell lines that are eligible for federal funding. The protocols under which the NIH-approved cell lines were derived were consistent with ethical norms then in place, were substantially similar to those now adopted in these Guidelines, and were adequately documented. The Committee considers the NIH-approved cell lines to be a special category because they are governed by a unique set of federal pronouncements (presidential statement and NIH rules). The intention of "grandfathering" the NIH-approved cell lines is to avoid precluding hES cell research that would otherwise be rendered difficult or impossible for investigators using NIH funding who wish to follow the National Academies' Guidelines. The clarification is not intended to "encourage" the use of these cell lines, either inside or outside the United States. For these reasons, retroactive application of the Guidelines is not warranted in this circumstance.

Therefore, the Guidelines are amended by adding a new Section 1.4:

1.4 Use of NIH-Approved hES Cell Lines

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

(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.

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

IMPORTATION OF hES CELL LINES INTO AN INSTITUTION OR JURISDICTION

Institutions following the National Academies' Guidelines may find themselves considering proposals for the importation of cell lines derived according to different rules, such as those from the United Kingdom, Canada, and the California Institute for Regenerative Medicine. These cell lines, while meeting all legal requirements of the respective jurisdictions for cell line derivation, may not have been derived in a manner that accords in every detail with the National Academies' Guidelines. For example, hES cell line derivations in the United Kingdom are managed through a licensing procedure that differs from the IRB and ESCRO committee review processes recommended in the Guidelines. Within the United States, state laws may vary from the Guidelines. California's laws, regulations, and guidelines, for example, though consistent with the Guidelines, apply some additional requirements concerning the details of the consent form, conflict-of-interest disclosures, and management of adverse medical events that may result from the donation of oocytes. As other states regulate such research, some state laws may differ from the Guidelines in some details but be sufficiently similar to be substantially equivalent.

Section 7.0 of the National Academies' Guidelines anticipates this problem in the international context. Section 7.0 specifically contemplates acceptance of cell lines derived under the extant legal and ethical regimes of another country provided that those regimes are substantially equivalent to the regime laid out in the Guidelines. This deference facilitates collaboration among institutions and shows proper respect for the diversity of authority in this area. This is analogous to the technique by which the U.S. federal government determines whether to accept the ethical and procedural norms of foreign research ethics review bodies as acceptable proxies for domestic IRB review.

Section 7.0 of the current National Academies' Guidelines reads: "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."

Therefore, without in any way suggesting that the addition of a new section should be construed by ESCRO committees to revoke any of the requirements of these Guidelines with respect to new donations or cell line derivations undertaken at their own institutions, the Guidelines are amended

by adding a new Section 1.5. This section applies to cell lines derived both before and after release of the Guidelines. ESCRO committees can review pre-2005 derivations and determine whether or not they are acceptable, following the guidance in new Section 1.5.

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

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

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

(1) 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;
(2) consent to donate was voluntary and informed;
(3) donation was made with reimbursement policies consistent with these Guidelines; and
(4) donation and derivation complied with the extant legal requirements of the relevant jurisdiction.

(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.

ESCRO COMMITTEES SERVING MULTIPLE INSTITUTIONS

The report *Guidelines for Human Embryonic Stem Cell Research* laid out a series of recommendations pertaining to the composition and role of ESCRO committees. Based on feedback from the community, it appears that

some of these recommendations need clarification. Although the text of Chapter 3 contains the statement that "In some cases, smaller institutions may wish to avail themselves of the services of larger facilities that have ESCRO committees," the idea that it is acceptable for institutions to use a nonlocal (external) ESCRO committee was unintentionally omitted from the wording of Section 2.0 of the Guidelines. Furthermore, since the Guidelines were issued in April 2005, it has become clear that there are other models for establishing ESCRO committees consistent with the principles of the Guidelines. New alternatives for the organization of IRB reviews are currently emerging that can serve as models for ESCRO review.

For example, the National Cancer Institute (NCI) has established a "Central IRB Initiative"[5] that is "designed to help reduce the administrative burden on local IRBs and investigators while continuing a high level of protection for human research participants." The NCI states that a local IRB's use of the Central IRB would facilitate the review of clinical trial protocols. The initiative is sponsored by NCI in consultation with the Department of Health and Human Services' Office for Human Research Protections (OHRP). OHRP's current guidance in the form of "Frequently Asked Questions" on its Web site[6] addresses institutions that do not have internal IRBs and provides options that include negotiating agreements with other institutions to have research reviewed as well as the use of commercial or independent IRBs. Finally, a November 2005 workshop summary report on "Alternative Models of IRB Review"[7] sponsored by the National Institutes of Health, OHRP, AAMC, and the American Society for Clinical Oncology explored the use of up to 10 alternative models, such as sharing materials among local IRBs, institutions relying on review by the IRB of another institution, and sites forming consortia to use a single IRB in a collaborative process. Although acceptance of the use of such alternative models for IRBs has not yet been indicated in updated guidance from OHRP or the Food and Drug Administration, the trend toward collaborative efforts is a topic that is actively under discussion and offers the possibility of more efficient and timely IRB (and, by analogy, ESCRO committee) review. The Tri-Institutional ESCRO Committee established by Rockefeller University, Memorial-Sloan Kettering Cancer Center, and Weill Medical College of Cornell University is an example of a single committee serving three research

[5]See <http://www.ncicirb.org/> for more information about the initiative.
[6]<http://www.hhs.gov/ohrp/faq.html>.
[7]<http://www.hhs.gov/ohrp/sachrp/documents/AltModIRB.pdf>.

institutions. Although the Committee on Guidelines for Human Embryonic Stem Cell Research quite clearly intended to allow for the use of shared or central ESCRO committees, it failed to state that explicitly. Therefore, Section 2.0 of the Guidelines is amended. (New wording is underlined.)

For projects involving more than one institution, there have also been concerns about the difficulty of multiple ESCRO committee reviews. Section 2.1 is added to explicitly allow—but not require—that multi-institution collaborations can be reviewed by a single ESCRO committee.

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 preexisting committee could serve the functions of the ESCRO committee provided that it has the recommended expertise 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

(1) provide oversight over all issues related to derivation and use of hES cell lines,
(2) review and approve the scientific merit of research protocols,
(3) review compliance of all in-house hES cell research with all relevant regulations and these guidelines,
(4) maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators, and
(5) facilitate education of investigators involved in hES cell research.

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.

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.

FROZEN IVF BLASTOCYSTS DERIVED FROM ANONYMOUS SPERM DONORS: ABSENCE OF INFORMED CONSENT

Members of the scientific community raised concerns that the National Academies' Guidelines require that donors of all embryos, gametes, and somatic cells give informed consent for the use of their tissues for the derivation of human embryonic stem cell lines. Specifically, Section 3.3 of the Guidelines states that "When donor gametes have been used in the IVF process, resulting blastocysts may not be used for research without consent of all gamete donors." This requirement might preclude the use of frozen blastocysts from IVF clinics, which do not customarily request informed consent from sperm donors. The Committee, therefore, was asked to consider the effects this requirement might have on the available supply of

blastocysts for hES cell research and whether the population of frozen blastocysts now residing at IVF clinics needs to be "grandfathered" or exempt from the requirement for sperm donor consent.

To evaluate these effects, the Committee contacted the Society for Assisted Reproductive Technology (SART), which is actively involved in the collection of data on outcomes from its member IVF clinics. SART works closely with the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Wyden Act) to reflect accurately outcomes of the procedures commonly used in IVF practices.[8] The information returned in response to the Committee's request indicated that the number of blastocysts created with anonymous donor sperm in SART member practices is only about 3.5 percent.[9]

Given this small number, it is the Committee's view that maintaining the requirement for sperm donor consent in cases where human embryonic stem cell lines are to be derived from excess IVF clinic blastocysts should not significantly affect the availability of blastocysts for donation to research. The Committee, therefore, has concluded that it is not necessary to modify the Guidelines by "grandfathering" the frozen embryo population in IVF clinics and exempting them from the informed consent requirement for sperm donors. In light of the inability to determine whether any of these donors would have foregone sperm donation had they known of possible nonreproductive uses of the resulting blastocysts, the existing Guidelines reasonably balance respect for the gamete donors' expectations with the needs of the research community.

CONSIDERING THE SCIENCE IN hES CELL RESEARCH PROPOSALS: ADVICE FOR ESCRO COMMITTEES

It has been brought to the Committee's attention that some ESCRO committees would appreciate additional guidance on how to evaluate research proposals that are submitted for ESCRO committee review. In several places, the Guidelines emphasize the need to consider the scientific rationale for an experiment as part of the ethical analysis of the experiment. Although this section of this report does not amend the Guidelines, the

[8]See <http://www.sart.org/WhatIsSART.html> for more information about this data collection effort.

[9]2004 SART CORS© database.

Committee has compiled a list of questions that ESCRO committees may wish to consider when evaluating the scientific aspects of proposals for research involving hES cells. Many of these questions are contained in the 2005 report *Guidelines for Human Embryonic Stem Cell Research* but are distributed throughout the report. Not all of these questions will be applicable to every situation. Neither will answers to these questions necessarily be definitive with respect to the acceptability of the proposed research. Their goal is to ensure that the relevant scientific and ethical issues are considered.

Sample Questions for Reviewing hES Cell Research

- What is the scientific question being asked by the proposed research involving hES cells? Does the underlying hypothesis address an important scientific question? Could the question reasonably be addressed in any other way?
- Does the research team have the appropriate expertise and training in deriving or culturing either human or nonhuman stem cells? If training is the primary purpose of the proposal, is the training being conducted under the supervision of appropriate experts?
- Has the investigator articulated a compelling rationale for using human stem cells instead of nonhuman stem cells?
- Has the investigator articulated a compelling rationale for using hES cells instead of other types of stem cells?
- Has the investigator justified the selection of the stem cell line(s) to be used?
- Has the investigator articulated a rationale for creating a new stem cell line or could the proposed research be conducted with existing cell lines? If more than one cell line is to be derived, has the investigator justified the number he/she proposes to make?

Additional questions arise in considering protocols involving introduction of hES cells or cellular derivatives thereof into an animal host to form a chimera. Some of those questions were addressed in the 2005 *Guidelines for Human Embryonic Stem Cell Research*, and the committee intends to revisit these issues in future discussions.

Appendix A
National Academies' Guidelines for Human Embryonic Stem Cell Research, Amended as of February 2007[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

[1]New or modified wording is indicated by underlining.

pertaining to biomedical research in general. The National Academies are issuing these guidelines for the use of the scientific community, including researchers in university, industry, or other private-sector research organizations.

1.1(a) What These Guidelines Cover

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

(1) blastocysts made for reproductive purposes and later obtained for research from in vitro fertilization (IVF) clinics,
(2) blastocysts made specifically for research using IVF,
(3) Somatic cell nuclear transfer (NT) into oocytes.

The guidelines do not cover research that uses nonhuman stem cells.

Many, but not all, of the guidelines and concerns addressed in this report are common to other areas of human stem cell research, such as

(1) research that uses human adult stem cells,
(2) 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.

Institutions and investigators conducting research using such materials should consider which individual provisions of these guidelines are relevant to their research.

1.1(b) 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.

1.2 Categories of hES Cell Research

These guidelines specify categories of research that

(a) Are permissible after currently mandated reviews and proper notification of the relevant research institution.
(b) Are permissible after additional review by an Embryonic Stem Cell Research Oversight (ESCRO) committee, as described in Section 2.0 of the guidelines.
(c) 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.

1.2(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.

1.2(b) hES Cell Research Permissible Only After Additional Review and Approval

(1) Generation of new lines of hES cells by whatever means.
(2) 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 the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.
(3) 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.

1.2(c) hES Cell Research That Should Not Be Permitted at This Time

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

(1) 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.
(2) 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:

(3) No animal into which hES cells have been introduced at any stage of development should be allowed to breed.

1.3 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.

1.4 Use of NIH-Approved hES Cell Lines

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

(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.

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

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

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

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

(1) 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;
(2) Consent to donate was voluntary and informed;
(3) Donation was made with reimbursement policies consistent with these Guidelines; and
(4) Donation and derivation complied with the extant legal requirements of the relevant jurisdiction.

(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 preexisting committee could serve the functions of the ESCRO committee provided that it has the recommended expertise 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

(1) provide oversight over all issues related to derivation and use of hES cell lines,
(2) review and approve the scientific merit of research protocols,
(3) review compliance of all in-house hES cell research with all relevant regulations and these guidelines,
(4) maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators, and
(5) facilitate education of investigators involved in hES cell research.

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.

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 the procurement of all gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines, including 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.

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.

3.4a 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.

3.4b 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. No payments, cash or in-kind, should be provided for donating oocytes for research purposes. Similarly, no payments 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 or blastocysts for hES cell research, the informed consent process, should, at a minimum, provide the following information:

(a) A statement that the blastocysts or gametes will be used to derive hES 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 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 cells and/or cell lines might be kept for many years.
(g) A statement that the hES 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 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.

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).

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.

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 ESCRO 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 include evidence of IRB approval of the procurement process and of adherence to basic ethical and legal principles of procurement. 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 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 1.2(c)(3) 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 1.2(c)(3) 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 1.2(c)(2) and 1.2(c)(3) 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 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.

8.0 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 re-

search. 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, ESCRO committees 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

Committee Biographical Sketches

CO-CHAIRS

R. Alta Charo, J.D., 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 Medical School, and, in 2006, was Visiting Professor of Law at 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 topics including 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 as a fellow of the Wisconsin Academy of Sciences, Arts, and Letters. In 1994, Professor Charo served on the NIH Human Embryo Research Panel, and from 1996 to 2001 she was a member of the presidential National Bioethics Advisory Commission where she participated in drafting its reports on *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*, and *Ethical and Policy Issues in Research Involving Human Participants* (2001). Since 2001, she has been a member of the National Academies' Board on Life Sciences and since 2006, she has been a member of the Institute of Medicine's Board on Population Health and Public Health Practices. Professor Charo was elected to the Institute of Medicine in 2006.

Richard O. Hynes, Ph.D., is the Daniel K. Ludwig Professor for Cancer Research at the MIT Center for Cancer Research and Department of Biology, 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 MIT. 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' 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 co-chaired the 2005 National Academies' *Guidelines for Human Embryonic Stem Cell Research*.

MEMBERS

Eli Y. Adashi, M.D., M.S., FACOG, is currently the Dean of Medicine and Biological Sciences and the Frank L. Day Professor of Biology, 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 of the National Academies, 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 Endo-

crinologists, 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. Finally, Dr. Adashi 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, Ph.D., is the George Barth Geller Professor and Chair of the Department of Cell Biology, Duke University Medical Center. Prior to 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 Ph.D. in Biochemistry at the University of Cambridge. After completing her Ph.D. she was a postdoctoral fellow in the Department of Biology at MIT. 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 (EG) cell lines. She was Co-Chair for Science of the 1994 NIH Human Embryo Research Panel and a member of the 2001/2002 National Academies' Panel on Scientific and Medical Aspects of Human Cloning. Within the past 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 current owner of Peartree Design, a landscape design firm, and was previously the media director for Drumbeater, a high-technology advertising agency. She holds B.A. 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 member (1996–1998, 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, Ph.D., 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 processes such as autosomal imprinting, X-inactivation, and anterior-posterior patterning of axial structures in mammals. He is a member of the Board of Directors of the Genetics Society of America and of the Society for Developmental Biology.

Linda B. Miller, OTR, M.S. in Hospital Administration, is President of the Washington, D.C.-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, as well as in designing models for practice and legal oversight. She was elected to membership in the Institute of Medicine 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 *New York Times,* among others. She served as a Special Assistant to the Secretary of Health, Education and Welfare (now HHS) 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, the Institute of Medicine's Committee on Spinal Cord Injury. Ms. Miller currently serves on the Advisory Board of the University of Louisville-based Institute for Cellular Therapeutics, headed by Dr. Suzanne Ildstad, which does research in adult bone marrow transplant, and has been a member of several academic and health care institutions' board of governors, including Blythedale Childrens Hospital in New York, Capital Hospice in the national capital region, and Cornell University's Alumni Council, among others.

Jonathan D. Moreno, Ph.D., is the David and Lyn Silfen University Professor at the University of Pennsylvania. 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 of the National Academies. He is also a bioethics advisor 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 was a senior consultant for the National Bioethics Advisory Commission. He co-chaired 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 regarding stem cell research in China.

Stuart H. Orkin,[1] M.D., is the David G. Nathan Professor of Pediatrics at Harvard Medical School, Chair of the Department of Pediatric Onocology at the Dana-Farber Cancer Institute, and an Investigator with the Howard Hughes Medical Institute. His laboratory utilizes multidisciplinary approaches to understand how mammalian cells choose specific fates and how mutations in important transcriptional regulators lead to developmental defects or malignancy. Recent and ongoing work falls into several overlapping areas, including study of essential hematopoietic transcription factors, the genetic pathogenesis of two forms of leukemia, and whether some of the lessons of hematopoiesis may be applied to consideration of the pathogenesis of solid tumors. Finally, the fundamental properties of stem cells—pluripotency and self-renewal—are being addressed from a biochemical perspective in mouse embryonic stem (ES) cells. In the future, his laboratory will pursue the functions of the associated proteins in order to unravel the biochemistry of ES fate specification. This strategy may ultimately suggest how directed manipulation of somatic cells to an ES cell fate might be achieved.

Pilar N. Ossorio, Ph.D., J.D., is Associate Professor of Law and Bioethics at the University of Wisconsin–Madison, and Program Faculty in the Graduate

[1]Resigned from committee effective December 18, 2006.

Program in Population Health at UW. Prior to taking her position at UW, she was Director of the Genetics Section at 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 Ph.D. 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 also worked as a consultant for the federal program on the Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project, and 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 J.D. from the University of California at Berkeley School of Law (Boalt Hall) in 1997. While at Boalt 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 advisor to NHGRI on ethical issues in large-scale sequencing, and a member of UW'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 (Institute of Medicine), and has been a member or chair of several working groups on genetics and ethics. She has published scholarly articles in bioethics, law, and molecular biology.

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Harold T. Shapiro, Ph.D., 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/medical center administration, university administration, econometrics, statistics, and economics. Dr. Shapiro currently chairs the Board of Trustees of the Alfred P. Sloan Foundation, is presiding director for the Dow Chemical Company, and is a member of numerous boards including the Robert Wood Johnson Medical School, HCA, the Merck Vaccine Advisory Board, the Knight Foundation Commission on Intercollegiate Athletics, U.S. Olympic Committee, and the Stem Cell Institute of New Jersey. He is a former Chair of the Association of American Universities and the National Bioethics Advisory Committee and Vice Chair of the President's Council of Advisors on Science and Technology. He has also served on the Board of Directors of the National Bureau of Economic Research, Inc. and the Board of Trustees of the Universities Research Association, Inc. He has chaired and served on numerous National Academies committees including the Committee on the Organizational Structure of the National Institutes of Health and the Committee on Particle Physics. Dr. Shapiro was awarded the 2006 American Association for the

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John E. Wagner, Jr., M.D., 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 B.A. in Biological Sciences and a B.A. in Psychology from the University of Delaware and an M.D. 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. Projects are funded by both NIH (P01 CA65493, Biology and Transplantation of the Human Stem Cell; and N01-HB-37164, Somatic Cell Therapeutics) and industry (ViaCell, Inc., on the transplantation of expanded umbilical cord blood hematopoietic stem cells; and Athersys, Inc., on the large-scale development of multipotent adult progenitor cells). In addition, Dr. Wagner pioneered the use of embryo selection to "create" a perfectly tissue matched stem cell donor in the treatment of genetic disease. Dr. Wagner has authored more than 180 articles and book chapters on the subject of hematopoietic stem cell transplantation. He currently co-chairs the Graft Sources and Manipulation Working Committee of the Center of the International Blood and Marrow Transplant Research, 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.