NIH Guidelines on Human Embryonic Stem Cell Research in Context: Clarity or Confusion?

By Karen H. Rothenberg, J.D., M.P.A. & Michael R. Ulrich

Restrictions on federal funding for human embryonic stem cell (hESC) research under President Bush[1] stimulated a number of states and the private sector to fund stem cell research, resulting in a patchwork of varying guidelines throughout the country.[2] The National Institutes of Health's (NIH) guidelines were expected to change all of this.[3] With President Obama following through on his assurance to remove restrictions,[4] stem cell researchers assumed they would find clarity when the new NIH Guidelines on Human Embryonic Stem Cell Research were promulgated to outline an ethical framework to determine which research was eligible for federal funding.[5] As part of this process, the NIH examined the guidelines developed by the National Academies of Science (NAS)[6] and the International Society for Stem Cell Research (ISSCR),[7] which had been guiding many states and private institutions funding stem cell research.[8]

The NIH took a unique approach that is both more and less restrictive than the NAS and ISSCR guidelines and has resulted in some confusion.[9] If we want to strive to encourage scientific collaboration along state lines and internationally, we must be able to put the NIH guidelines in context to move forward with ethical stem cell research. Toward this goal, we highlight below the similarities and differences on key ethical issues in hESC research.[10]

Procurement of Materials

Prior to the issuance of the NIH guidelines, the NAS and ISSCR published guidelines with scopes of what was ethically permissible for research. The NAS and ISSCR allow a full range of stem cell creation from research embryos, gametes, somatic cells, parthenogenesis, and androgenesis.[11] Additionally, certain types of chimeric research are allowable, with both institutions recommending additional oversight.[12] In terms of payment, the NAS permits clinical need payments for donating blastocysts and/or morulae and reimbursements of direct expenses as a result of hormonal inducements for oocyte donors.[13] Meanwhile, the ISSCR prohibits merely *undue* inducements, implying that an oversight committee could authorize those inducements that do not risk coercion.[14]

A close look at the NIH guidelines reveals that the primary distinction between research eligible for federal funding now and the research allowed under the Bush administration is basically the date of derivation. The NIH guidelines still restrict embryos to those created for fertility treatment and that are no longer needed, do not allow payments of any kind, and require informed consent.[15] This restrictive approach may have been the most disappointing to hopeful researchers who were eager to utilize the creation of stem cells with specific genetic mutations allowing the study of the genetics of those diseases.[16] Despite NAS and ISSCR approval for a full range of stem cell creation, the NIH adopted a more conservative and incremental approach,[17] at least for the near future.

Review Process

Due to the scientific and controversial nature of hESC research, both the NAS and ISSCR implemented an added layer of review to the standard Institutional Review Board (IRB).[18] Both state that the procurement of materials from humans demands that institutional review be conducted and approval granted.[19] The added layer of protection provides further expertise to address the complex ethical and scientific issues raised by stem cell research.[20]

In contrast, the NIH guidelines state that local IRB review may be required, but only if the stem cells can be linked to living individuals.[21] Although it would appear the NIH is less restrictive with respect to the local review process, they do create another federal review body, the Working Group (WG).[22] The WG is formed to review cell lines derived from embryos donated before the effective date of the NIH guidelines, rather than grandfathering them in, as well as those created prospectively.[23] While the eligibility requirements for donations after the effective date are set,[24] the WG is to consider these factors when making recommendations regarding eligibility for NIH funding for cell lines created before the effective date.[25]

Informed Consent

Securing informed and voluntary consent is a pillar of ethical research that is meant to protect the rights of the subject. In this context, informed consent raises interesting challenges because the infertility clinic is not typically the setting for research, but rather for

achieving the clinical goal of assisted reproduction. Generally, the NIH guidelines closely parallel both the NAS and ISSCR guidelines with respect to the content of informed consent.[26] However, guidance must also be clear on when consent should be obtained, who should obtain the consent, and who should provide consent for the potential of future stem cell research—not an issue generally relevant to the assisted reproduction mindset.[27]

Surprisingly, the NAS guidelines make no mention regarding when consent must be given by the embryo donor or whether the infertility doctor and researcher must be different individuals.[28] However, since the NAS guidelines apply to all gamete donations, they include a specification that written agreement must be obtained at gamete donation with one of the potential uses listed being embryo research.[29] The ISSCR takes a different approach, requiring consent be given at the time of donation, yet they do allow for review to determine that using materials for research may be acceptable if prior consent exists and re-consent is prohibitively difficult.[30] While the ISSCR states that in gamete donation and embryo creation, the treating physician should not be the researcher, as well, they qualify it and allow an exception if separation is not feasible.[31]

The NIH guidelines, which parallel the ISSCR guidelines, require consent at the time of donation of materials and necessitate separation between the creation of embryos for reproduction and the decision to donate.[32] Still, the NIH also asserts that the attending physician and the researcher should not be the same person unless separation is impractical.[33] However, ISSCR guidelines for consent apply to all gamete donors,[34] whereas the NIH merely requires consent from those in control of the embryo.[35] Although the NIH followed the ISSCR standards closely with regards to when consent should be obtained and by whom, its decision to deviate from both professional bodies in terms of not requiring gamete consent is puzzling and requires further examination.

A. The Puzzling Approach to Gamete Donor Consent

Informed consent is critical to the assurance of ethical research, making certain that no person contributes to research that is inconsistent with his or her own values, interests, or preferences.[36] In fact, some would argue that informed consent may be even more vital in hESC research given its controversial nature.[37] For gamete donors, especially women who provide oocytes, assisting infertile couples is not contextually the same as potentially providing material that may contribute to stem cell research.[38] We cannot assume they would consent to their materials being used as a part of research. For research to be ethical, it is imperative that individuals not be treated merely as a means to an end,[39] and the unauthorized use of gametes, particularly oocytes, which require serious and invasive medical procedures, walks dangerously close to this line and may even cross it. The fact that a person's genetic information may be available to researchers for an undetermined amount of time without the donor's knowledge should only increase apprehension.

When the NIH issued its initial draft guidelines, there was no inclusion of a gamete consent requirement.[40] Despite concerns expressed in the public comments, the final guidelines did not contain a gamete consent requirement.[41] Rather, the guidelines provided that "the NIH requests consent from 'the individual(s) who sought reproductive treatment' because this/these individual(s) is/are responsible for the creation of the embryo(s) and, therefore, its/their disposition."[42] The NIH felt this was sufficient but added that "with regard to gamete donation, the risks are associated with privacy and, as such, are governed by requirements of the Common Rule, where applicable."[43]

It is difficult to determine which part of the NIH's response is more disconcerting, the answer or the reasoning behind it. Failing to require gamete consent goes against broad consensus in the field.[44] Not only is this decision at odds with the NAS and ISSCR guidelines discussed earlier,[45] but it is also contrary to state and international guidelines that relied on the professional consensus on the issue.[46] The NIH dismissed this wide accord with a simple explanation that appears to deal with privacy, only one of the ethical concerns at issue in this context.

Certainly, gamete consent implicates privacy, but the NIH guidelines do not even appear overly concerned with that. While privacy alludes to the potential of being re-contacted, something a gamete donor may not desire, it also relates to the fact that stem cells may be kept for many years and genetic information may be available to researchers for a lengthy period of time, as well.[47] An individual's genetic information being readily available without their knowledge seems ethically problematic and has the potential to erode trust in the future of research.[48]

Recently, Bernard Lo et al. proposed a modified consent process that they argued would respect third party gamete donors while not placing too onerous a requirement on the institutional personnel obtaining authorization.[49] While informed consent would not be necessary, the dispositional authorization would be allowed once the options, including hESC research, were disclosed.[50] Lo et al. reasoned that implementing detailed gamete consent would be unfairly strict compared to other major decisions made during dispositional authorization, including foregoing parental rights and allowing the IVF patient to donate to another infertility patient.[51] Furthermore, they argued that obtaining consent at the time of donation would raise concerns about conflicts of interest and could interfere with the informed consent of the medical procedures, while contacting gamete donors once infertility treatment is complete could be an invasion of privacy and may be impractical.[52] They also suggest that the dispositional options could be described in a separate document or that the authorization document did not need to explicitly mention hESC research if the infertility treatment program confirms that they provided the options, including research.[53]

While the NIH's decision not to require gamete consent was problematic, the solution proposed by Lo et al. is incomplete. There should be considerably valid reasoning behind any decision to reject the ethical norm of informed consent, and the rationale that consent is not strict in terms of other dispositional decisions falls short. Moreover, this reasoning seems to ignore distinct differences in the dispositions being considered. Consenting to forego parental rights and allowing future embryos to be donated to another couple fit within the assisted reproduction framework. Consent to research does not fall within the same context and, therefore, may not be in the mindset of someone choosing to donate his or her gamete for infertility treatment. Consequently, moral respect for autonomy

would presume that gamete donors have the right to choose what their materials are used for and that consent should be explicit and specific.[54]

The risks and potential harm that may result from ovarian stimulation and oocyte retrieval further support a meaningful informed consent process.[55] The donor should be fully informed of why they are undergoing these risks of a bodily invasion, including the potential that their eggs may be used in hESC research. Perhaps sperm donors do not need the same level of protection, but for the egg donor, there should be no shortcuts to protecting their bodily integrity and trust.

Conclusion

The NIH guidelines provide some clarity that procurement of materials will be restricted to discarded embryos from infertility treatment and that the review process at the local level may require minimal local IRB review. The informed consent for embryo donors has been clearly outlined in a strict ethical framework to conform with established professional guidelines. Recent action by the Working Group makes it clear that this is an area the WG takes seriously and cell lines will be rejected if ethical guidelines for consent are not followed.[56] One exception is the lack of a full informed consent process for the gamete donor—an ethical issue that needs further attention.[57]

It must be recognized that part of the ethical and practical challenges highlighted in this article result from trying to create ethical standards for future research in the clinical infertility context. Although the NIH failed to provide sufficient rationale for their departure from accepted professional guidelines, stem cell researchers and the ethics community should work together with their colleagues in their institutions and professional organizations to promote continuing discussion on how best to integrate and improve the NIH guidelines in the future. We can only hope that the NIH will take notice and amend the guidelines to respond to evolving ethical and scientific standards.

NIH Comparison Chart

	NIH Guidelines for Research using Human Stem Cells (2009)	MD Stem Cell Research Act (2006)	NAS Guidelines for Human Embryonic Stem Cell Research (2008)	ISSCR Guidelines for the Conduct of Human Embryonic Stem Cell Research (2006)
Funding Source	NIH	State of Maryland	National Academies (NAS)	International Society for Stem Cell Research (ISSCR)
Scope	hESCs and certain uses of induced pluripotent stem cells.	hESCs and adult stem cells.	Pluripotent and multipotent stem cells; all derivation of hESC lines, including those derived from blastocysts made for reproduction and research, as well as somatic cell nuclear transfer, parthenogenesis or androgenesis.	The procurement, derivation, banking, distribution, and use of cells and tissues taken from pre-implantation stages of human development.
hESCs Defined	Cells that are (1) derived from the inner cell mass of blastocyst stage human embryos, (2) are capable of dividing without differentiating for a prolonged period in culture, and (3) are known to develop into cells and tissues of the three primary germ layers	Unused material		Cells covered include those from gametes, embryos, or somatic cells, as well as those from oocytes and embryos generated for research purposes, parthenogenesis, androgenesis, nuclear transfer, or other means of somatic cell reprogramming.

NIH Comparison Chart
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	NIH Guidelines for Research using Human Stem Cells (2009)	MD Stem Cell Research Act (2006)	NAS Guidelines for Human Embryonic Stem Cell Research (2008)	ISSCR Guidelines for the Conduct of Human Embryonic Stem Cell Research (2006)
Eligibility Requirements	Varies: (1) **For hESCs donated in the US on or after the Guidelines' effective date:** *The hESCs should have been derived from human embryos that:* (a) were created using IVF for reproductive purposes and no longer needed; (b) were donated by individuals who sought reproductive treatment and gave voluntary consent for embryos to be used for research; (c) and for which consent and documentation can be assured (see requirements below under "Informed Consent and Documentation Requirements") **[Note: Steps a-c are referred to in the Guidelines as IIA)** (2) **For hESCs donated before the effective date:** (a) The hESCs should have been derived from human embryos that comply with the above requirements for hESCs donated in the US on or after the effective date (IIA); or (b) Approved by a Working Group of the Advisory Committee to the Director (ACD) (see description of Working Group process below under "Relevant Non-IRB Review Process") (3) **For hESCs donated outside of the US before the effective date:** (a) The hESCs should have been derived from human embryos that comply with the above requirements for hESCs donated in the US before the effective date (4) **For hESCs donated outside the US on or after the effective date:** (a) The hESCs should have been derived from human embryos that comply with the above requirements for hESCs donated in the US on or after the effective date (IIA); or (b) Assurance along with supporting information that prove the alternative procedural standards of the foreign country where the embryo was donated provide protections at least equivalent to those provided by IIA.	(1) Practitioner treating for infertility shall provide info allowing for informed and voluntary decision about disposition of hESCs; (2) Unused material may not be an oocyte; (3) Person donating material for research shall provide health care practitioner with written consent for the donation.	Varies: (1) Purely in vitro hESCs research using previously derived hESC lines is permissible provided the ESCRO committee or equivalent body receives documentation of the provenance of the cell lines, including: (a) Documentation of the use of an acceptable informed consent process that was approved by an IRB or foreign equivalent for their derivation; and (b) Documentation of compliance with any additional required review by an IACUC, IBC, or other institutionally mandated review. (2) For all new procurements of all gametes, blastocysts, or somatic cells for the purpose of generating new hESC or hPSC lines an IRB review should take place. (3) For hESC and non-hESC research involving nonhuman animals there should be review by ESCRO committees and IACUCs. (4) Women who undergo hormonal induction to generate oocytes for research should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB (this includes costs associated with travel, housing, child care, medical care, health insurance, and actual lost wages). (a) No payments beyond reimbursements should be made for donations of sperm for research or of somatic cells for NT.	(1) All experiments using hESC research, human embryos or embryonic cells, or that entail incorporating human totipotent or pluripotent cells into animal chimeras, shall be subject to review, approval, and ongoing monitoring by an oversight mechanism or body, Stem Cell Research Oversight (SCRO). (2) Review must include: (a) Appropriate scientific justification for performing the research using the specified material is required. (b) Appropriate expertise and/or training of the investigators to perform the stated experiments must be ascertained. (c) Project proposal should include a discussion of alternative methods, and provide a rationale for employing the requested human materials, the proposed methodology, and for performing the experiments in a human rather than animal model system. (3) For donating embryos or gametes generated in the course of clinical treatment, no reimbursement of direct expenses or financial considerations of any kind may be provided. (4) There must be review to ensure there are no undue inducements.

NIH Comparison Chart
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Informed Consent and Documentation Requirements	All of the following must be assured and documentation provided: (1) All options available at facility explained; (2) No payments offered; (3) Ensure consenting to or refusing donation does not affect care; (4) Separation between donor's decision to create hESC for reproduction and donation for research: (a) Physician for care should not be same as researcher; (b) Consent for donation must be given at time of donation; (c) Must inform donor that consent can be withdrawn until hESCs are taken from embryo or linking info is gone (5) Donor must be informed of: (a) Embryos would be used to derive hESCs for research; (b) What happens to embryos in derivation of hESCs; (c) hESCs may be kept for many years; (d) Donation is made without restriction or direction regarding use; (e) Research not intended to provide direct medical benefit to donor; (f) Research may have commercial potential, but donor would not receive any benefit; (g) Whether info identifying the donor would be available to researchers.	Donor must be provided with the following options: (1) Storing or discarding unused material; (2) Donating for clinical purposes in treatment of infertility; (3) Donating for research purposes; (4) Donate material for adoption purposes.	(1) Informed consent should, at a minimum, provide the following information: (a) Cells will be used to derive hESCs or pluripotent cells for research that may include research on human transplantation. (b) Donation is made without any restriction or direction. (c) A statement as to whether the identities of the donors will be readily ascertainable. (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) Assurance that participants in research projects will follow applicable and appropriate best practices. (f) Cell lines might be kept for many years. (g) Cell lines might be used in research involving genetic manipulation of the cells or mixing of human and nonhuman cells in animal models. (h) Cells may have commercial potential and a statement that donor will not receive financial or any other benefits from commercial development. (i) Research isn't intended to provide direct medical benefit to the donor, except in cases of autologous donation. (j) Embryos will be destroyed in the process of deriving hESCs. (k) Neither consenting nor refusing donation will affect quality of care. (l) Statement of risks involved to donors. (2) Donors could also be given the option of agreeing to some forms of hESC research but not others. (3) Investigators must document how they will characterize, validate, store, and distribute any new hESC lines and how they will maintain the confidentiality of any coded or identifiable info associated with the lines.	(1) Informed consent must contain, at a minimum, the following statements: (a) Materials will be used in the derivation of totipotent or pluripotent cells for research. (b) Materials will be destroyed during the process of deriving the cells. (c) Derived cells might be kept for many years and used for future studies, many of which may not be predictable at this time. (d) Cells might be used in research involving genetic manipulation of the cells or generation of human-animal chimeras. (e) Donation is made without any restriction or direction. (f) Whether the donation is limited to specific research purposes and not others. (1) Consent shall notify donor, if applicable under governing law, of the possibility that permission for broader uses may later be granted and consent waived under appropriate circumstances by an IRB. (2) Consent process should explore whether donors have objections to the specific forms of research outlined in the research protocol. (g) Disclosure of what potential identifiers will be retained. (h) Disclosure of the possibility that any resulting cells may have commercial potential, and whether the donor will or will not receive financial benefits. (i) Disclosure of any present or potential future financial benefits to the investigator and the institution related to or arising from proposed research. (j) That the research is not intended to provide direct medical benefit to anyone, including the donor. (k) That neither consenting nor refusing to donate will affect the quality of care. (l) That there are alternatives to donating, and an explanation of what these are. (m) (for donation of embryos) that the embryos will not be used to produce a pregnancy.

NIH Comparison Chart (continued)

	NIH Guidelines for Research using Human Stem Cells (2009)	MD Stem Cell Research Act (2006)	NAS Guidelines for Human Embryonic Stem Cell Research (2008)	ISSCR Guidelines for the Conduct of Human Embryonic Stem Cell Research (2006)
Informed Consent and Documentation Requirements *(continued)*			(4) Consent must be obtained from all gamete donors for use of embryos in research.	(n) (for experiments in embryonic stem cell derivation, somatic cell nuclear transfer, somatic cell reprogramming, parthenogenesis, or androgenesis) that the resulting cells derived would carry some or all of the DNA of the donor (2) Consent for donation should be obtained at the time of proposed transfer of materials to the research team. (3) Consent must be obtained from all gamete donors for use of embryos in research. (4) Donors should be informed that they retain the right to withdraw consent until the materials are actually used in research. (5) Decisions related to donation of gametes or creation of embryos for fertility treatment should be free of the influence of researchers, so wherever possible, the treating physician shouldn't also be the researcher. (6) A rigorous review by a SCRO mechanism or body can permit the use of materials for which prior consent exists but for which re-consent is prohibitively difficult.
IRB Review	May be required under 45 CFR 46 if: (1) The investigators are engaged in research involving human adult stem cells or induced pluripotent stem cells; or (2) The stem cells are individually identifiable (i.e., can be linked by investigators to specific living individuals either directly or indirectly)	Grant award is contingent upon recipient submitting IRB approval.	(1) An IRB should review all new procurements of all gametes, blastocysts, or somatic cells for the purpose of generating new hESC or pluripotent cell lines. (2) Non-embryo-derived pluripotent cells are covered by existing IRB regulations. (3) Informed consents must be approved by IRBs or foreign equivalent.	(1) Derivations of new lines by necessity involve procurement of materials from human subjects and, therefore, need IRB review. (a) The scientific rationale for the need to derive new cell lines must be provided, with justification of the numbers of pre-implantation embryos to be used. (b) Researchers must demonstrate appropriate expertise or training. (c) Investigators performing derivation should have a detailed, documented plan for characterization, storage, banking, and distribution of new lines. (d) Embryos made via nuclear transfer, parthenogenesis, androgenesis, or other in vitro means shall not be transferred to a human or non-human uterus or cultured in vitro intact as embryos for longer than 14 days or until formation of the primitive streak. (e) Investigators performing derivations should propose a plan to safeguard the privacy of the donor information.

NIH Comparison Chart
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	NIH Guidelines for Research using Human Stem Cells (2009)	MD Stem Cell Research Act (2006)	NAS Guidelines for Human Embryonic Stem Cell Research (2008)	ISSCR Guidelines for the Conduct of Human Embryonic Stem Cell Research (2006)
Relevant Non-IRB Review Board	NIH Working Group of the Advisory Group to the Director (ACD)	Maryland Stem Cell Research Commission	Embryonic Stem Cell Research Oversight (ESCRO) Committee	Stem Cell Research Oversight (SCRO) Committee
Relevant Non-IRB Review Process	The Working Group will make recommendations regarding eligibility to the ACD, who makes recommendations to the NIH director, who will make the final decision.	(1) During the peer review process, when applications are reviewed for scientific merit, a bioethicist with expertise in stem cells will review the bioethics plan. (a) The ethics plan must include, but not be limited to, ethical issues related to: cell type; cell line(s); animal welfare (i.e., IACUC); IRB review and related concerns regarding human subjects; and SCRO review. (2) Then approval must be granted by the Institutional Stem Cell Review Oversight (ISCRO) Committee, which reviews the proposed research on the stem cell lines by utilizing both NAS and ISSCR guidelines.	(1) 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. (2) ESCRO committees should: (a) Provide oversight over all issues related to derivation and use of hESC lines. (b) Review and approve the scientific merit of research protocols. (c) Review compliance of all in-house hESC research with all relevant regulations and these guidelines. (d) Maintain registries of hESC research conducted at the institution and hESC lines derived or imported by institutional investigators (info from the registries should be available to the public). (e) Facilitate education of investigators involved in hESC research.	(1) All experiments shall be subject to review, approval, and ongoing monitoring by a Stem Cell Research Oversight (SCRO) process. (a) SCRO process shall not replace other mandated reviews, such as IRB, unless the review is specifically designed to be comprehensive. (2) SCRO review shall be determined by the category of research: (a) Experiments that are permissible after review under existing mandates and by existing local committees, and are determined to be exempt from full SCRO review. (b) Forms of research that are permissible only after additional and comprehensive review by the SCRO process. (1) Derivation of new pluripotent cell lines. (2) Identity of the donor is readily ascertainable. (3) Stem cells are mixed with pre-implantation human embryos. (4) Cells of totipotent or pluripotent human origin are transplanted into living human subjects. (5) Research that generates chimeric animals using human cells. (3) Research that shouldn't be pursued at this time because of broad international consensus that such experiments lack a compelling scientific rationale or raise strong ethical concerns.

NIH Comparison Chart (continued)

	NIH Guidelines for Research using Human Stem Cells (2009)	MD Stem Cell Research Act (2006)	NAS Guidelines for Human Embryonic Stem Cell Research (2008)	ISSCR Guidelines for the Conduct of Human Embryonic Stem Cell Research (2006)
Research Not Applicable	(1) NIH funding of the derivation of stem cells from human embryos is prohibited by the Dickey Amendment (2) Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes.	Not specified	Not specified	(1) Some examples of research that shouldn't be pursued at this time include: (a) In vitro culture of any post-fertilization human embryos or organized cellular structures that might manifest human organismal potential, regardless of derivation method, for longer than 14 days or until formation of the primitive steak begins. (b) Research in which any products of research involving human totipotent or pluripotent cells that are implanted into a human or non-human primate uterus. (c) Research in which animal chimeras incorporating human cells with the potential to form gametes are bred to each other.
Banking of Stem Cells	Not specified	Not specified	Not specified	(1) At a minimum, each repository must establish its own clear guidelines and make those available to the public. (2) For deposits, repository must receive documentation pertinent to the depositor's SCRO process. (3) Repositor should obtain all technical information from depositor (ex: methods used in derivation of lines, culture conditions, etc.).

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Professor Rothenberg is a leading national expert on legal issues in health care. Over the last decade she has focused her research primarily on the ethical, legal and social implications of genetic testing and research, including the legislative approaches to genetic information in the health insurance and employment context, the impact of genetic research on racial and ethnic populations and women's health care, and the use of genetic information in the courtroom. Her other research interests include health insurance, privacy, the role of gender in health care, AIDS, research ethics, the right to forego treatment, emergency care, and new reproductive technologies. Professor Rothenberg is a member and former Chair of the Maryland Stem Cell Research Commission and served as a co-Chair of the 2009 World Stem Cell Summit. Her recent research sabbatical included studying the use of theatre as an innovative tool to identify and encourage discussion of the unique ethical, legal and social issues posed by emerging technologies in health care. Professor Rothenberg is currently a Scholar-in-Residence at Columbia Law School and Senior Fellow at its Center for the Study of Law and Culture; a Visiting Professor at the Berman Institute of Bioethics at Johns Hopkins University; and is the Special Advisor to the President of UMB, consulting on stem cell issues and other interdisciplinary initiatives related to innovations in health care. She received both a B.A., magna cum laude and Phi Beta Kappa, from Princeton University and an M.P.A. from Princeton's Woodrow Wilson School of Public and International Affairs. She earned a J.D. from the University of Virginia School of Law where she was a member of the Order of the Coif.

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References

1. President's Council on Bioethics, *Monitoring Stem Cell Research* 1, 189 (Jan. 2004), available at: http://www.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.
2. See Timothy Caulfield et al., The Stem Cell Research Environment: A Patchwork of Patchworks, *5 Stem Cell Rev. & Rep.* 82, 84 (2009) ("the patchwork of regulations that has emerged within the U.S., where states differ dramatically on various regulatory issues.").
3. *National Institute of Health Guidelines on Human Stem Cell Research* (2009) [hereinafter *NIH Guidelines*], available at http://stemcells.nih.gov/policy/2009guidelines.htm.
4. Exec. Order No. 13,505, *74 Fed. Reg. 10,667* (Mar. 9, 2009).
5. See James W. Fossett, Beyond the Low-Hanging Fruit: Stem Cell Research Policy in an Obama Administration, 9 *Yale J. Health Pol'y L. & Ethics* 523, 523 (2009) (discussing the expectations of a major shift in federal policy that would create a break in the gridlock over stem cell research in Washington).
6. *The National Academies' Guidelines for Human Embryonic Stem Cell Research* (2010 Amendments) [hereinafter *NAS Guidelines*], available at http://books.nap.edu/openbook.php?record_id=12923&page=R1.
7. *The International Society for Stem Cell Research Guidelines for the Conduct of Human Embryonic Stem Cell Research* (2006) [hereinafter ISSCR GUIDELINES], available at http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf.
8. See Fossett, *supra* note 5, at 532 ("most states appear to have relied heavily for many of these issues on model guidelines promulgated by the National Academy of Sciences and the International Society for Stem Cell Research.").
9. See Michelle N. Meyer & James W. Fossett, The More Things Change: The New NIH Guidelines on Human Stem Cell Research, *19 Kennedy Inst. Of Ethics J.* 289, 303 (2009) (finding that the NIH guidelines informed consent standards are more rigorous than other standards in some regards and less rigorous in others); Fossett, *supra* note 5, at 523 (stating that significance in the change is difficult to assess).
10. For a more detailed comparison, including similarities and differences with Maryland policies, please see the attached chart following this article. The chart was created, in part, at the request of the Maryland Stem Cell Research Commission to compare and evaluate state stem cell policy in context with the NIH guidelines. See also Michael R. Ulrich, Comment, Follow the Leader?: Maryland's Response to the New Federal Stem Cell Guidelines, *13 J. Health Care L. & Pol'y* (forthcoming Supp. 2010) (discussing the regulatory and ethical implications of how Maryland might respond to the different approaches taken by the NIH, NAS, and ISSCR).
11. See *NAS Guidelines*, *supra* note 6, § 1.1(a) (covering all derivation of hESCs from spare embryos, research embryos, and SCNT into oocytes); *ISSCR Guidelines*, *supra* note 7, § 11.1 ("procurement of all gametes, embryos, or somatic cells.").
12. See *NAS Guidelines*, *supra* note 6, § 7.3(c) (discussing which types of research combining human stem cells and animals should be allowed and which should not); ISSCR GUIDELINES, *supra* note 7, § 10.2 (stating what chimeric research falls into the category of research that is permissible after additional review).
13. *NAS Guidelines*, *supra* note 6, § 3.4.
14. *ISSCR Guidelines*, *supra* note 7, § 11.1.
15. *NIH Guidelines*, *supra* note 3, § II(A).
16. See Meyer & Fossett, *supra* note 9, at 292 (finding that the NIH's departure from derivation norms was disappointing to hESC advocates); Andrew Siegel, Ethics of Stem Cell Research, *Stanford Encyclopedia of Philosophy* 1, 8 (Fall 2008), http://plato.stanford.edu/entries/stem-cells/ (discussing the benefits of creating embryos through cloning techniques).
17. See *NIH Guidelines*, Summary of Public Comments on Draft Guidelines [hereinafter Public Comments], http://stemcells.nih.gov/policy/2009guidelines.htm (giving the example of parthenogenesis and SCNT requiring women to donate oocytes, which involves medical procedures that have health and ethical implications). See also Siegel, *supra* note 16, at 1 (discussing ethical concerns of spare embryos, research embryos, and the use of cloning techniques); Stephen R. Latham, The Once and Future Debate on Human Embryonic Stem Cell Research, 9 *Yale J. Health Pol'y L. & Ethics* 483, 486 (2009) (finding controversy surrounding therapeutic and reproductive cloning).
18. See *NAS Guidelines*, supra note 6, § 1.3(a) (stating that ESCRO committees must review documentation of the informed consent process that was approved by the IRB or foreign equivalent along with any additional review that may be needed); *ISSCR Guidelines*, *supra* note 7, § 10.2 (defining a category of research that is permissible only after the additional SCRO review is completed).

References (continued)

19. *NAS Guidelines*, *supra* note 6, § 3.1; *ISSCR Guidelines*, *supra* note 7, § 12.1.
20. See *NAS Guidelines*, *supra* note 6, § 2.0 ("Review and approve the scientific merit of research protocols."); *ISSCR Guidelines*, *supra* note 7, § 8.1 ("monitoring by a special oversight mechanism or body equipped to evaluate the unique aspects of the science.").
21. *NIH Guidelines*, supra note 3, § I.
21. Id. § II(B).
22. Id.
23. Id. § II(A).
25. Id. § II(B).
26. See the attached chart following this article for more detailed information on the content of informed consent requirements under the respective guidelines.
27. Bernard Lo et al., Informed Consent in Human Oocyte, Embryo, and Embryonic Stem Cell Research, 82 *Fertility & Sterility* 559, 560 (2004).
28. See *NAS Guidelines*, *supra* note 6, § 3.0 (issuing no guidance on when to obtain consent for embryo donation or who should be obtaining the informed consent).
29. Id. § 3.3.
30. *ISSCR Guidelines*, *supra* note 7, § 11.2.
31. Id. § 11.4.
32. *NIH Guidelines*, *supra* note 3, § II(A)(3)(d).
33. Id. § II(A)(3)(d)(i).
34. *ISSCR Guidelines*, *supra* note 7, § 11.2.
35. *NIH Guidelines*, *supra* note 3, § II(A)(2).
36. Ezekiel J. Emanuel, David Wendler, & Christine Grady, What Makes Clinical Research Ethical?, 283 *J. Am. Med. Ass'n* 2701, 2706 (2000).
37. See generally Lo et al., *supra* note 27, at 559–60 (stating that informed consent is particularly important in oocyte and embryo research because of the strong emotions and diverse opinions it invokes); Siegel, *supra* note 16, at 1 (discussing those who find hESC research morally impermissible); Timothy Caulfield, Ubaka Ogbogu, & Rosario M. Isasi, Informed Consent in Embryonic Stem Cell Research: Are we Following Basic Principles, 176 *Canadian Med. Ass'n J.* 1724 (2007) (finding that stem cell research remains controversial, making it especially important to respect donors' wishes).
38. See Lo et al., *supra* note 27, at 560 (explaining that people may place special emotional and moral significance on their reproductive material and they may feel offended or wronged if this material is used for a particular type of research without their consent).
39. Emanuel, Wendler, & Grady, *supra* note 36, at 2706.
40. Mary A. Majumder & Cynthia B. Cohen, The NIH Draft Guidelines on Human Stem Cell Research, 324 *Science* 1648, 1648 (2009).
41. *NIH Guidelines*, *supra* note 3, § II(A)(2).
42. Public Comments, *supra* note 17.
43. Id.
44. Majumder & Cohen, *supra* note 40, at 1648.
45. See *NAS Guidelines*, *supra* note 6, § 3.3 (stating that donor gametes may not be used without consent); *ISSCR Guidelines*, *supra* note 7, § 11.2 ("Consent must be obtained from all gamete donors.").
46. See generally Fossett, *supra* note 5, at 532 (finding that most states relied on the NAS and ISSCR guidelines); *California Institute for Regenerative Medicine, The CIRM Medical and Ethical Standards Regulations* § 100100(b), available at http://www.cirm.ca.gov/workgroups/pdf/Reformatted_MES_Regs.pdf (applying informed consent requirements to donation of human gametes); *Empire State Stem Cell Board Contract Policy Statements and Conditions, Appendix A-2* § E (requiring informed consent for donation of all biological materials, including gametes); Assisted Human Reproduction Act § 40(3.1), 2004 S.C., ch. 2 (Can.) ("The Agency shall not issue a license under subsection (1) for embryonic stem cell research unless it has received the written consent of the original gamete providers."), available at http://laws.justice.gc.ca/eng/A-13.4/page-1.html; Human Fertilisation and Embryology Act, 1990, Consent to Treatment, Storage, Donation, Training and Disclosure of Information § 5A (Eng.) (stating that written informed consent must be obtained from gamete donors before the resulting embryos can be used for any research project and that gametes collected without proper consent may constitute assault).
47. *NIH Guidelines*, *supra* note 3, § II(A)(3)(e).
48. See Jeremy Sugarman, Human Stem Cell Ethics: Beyond the Embryo, 2 *Cell Stem Cell* 529, 530–31 (2008) (finding that there is a legitimate concern regarding privacy of information for those who provide cells when identifiers are often kept in hopes of using the cells or their derivatives in clinical settings); Caulfield, Ogbogu, & Isasi, supra note 37, at 1724 (finding that since stem cells are capable of revealing donor health information they may be viewed as an extension of the donor's health record, which is something the patient retains the right to control).
49. Bernard Lo et al., NIH Guidelines for Stem Cell Research and Gamete Donors, 327 *Science* 962, 962 (2010).
50. Id.
51. Id.
52. Id.
53. Id. at 963.
54. Lo et al., *supra* note 27, at 560. See also Caulfield, Ogbogu, & Isasi, *supra* note 37, at 1724 (stating that ensuring that donors' wishes are respected is especially important in stem cell research).
55. See Lo et al., *supra* note 27, at 560 ("consent process for oocyte donors needs to be more detailed than for sperm donors because they undergo greater physical risks and more complicated procedures.").
56. Forty-seven lines were rejected recently because the consent forms contained unusually broad language. Rob Stein, NIH Rejects Use of Dozens of Stem Cell Colonies by Federally Funded Researchers, *Wash. Post*, June 22, 2010, at A17. Despite the fact that these lines carried mutations for a variety of diseases and would be of great scientific value, NIH Director Francis Collins felt it was imperative that the NIH informed consent requirements, which are based on well-established norms, be applied stringently. Id.
57. See *supra* Part III.