RESEARCH ETHICS

NIH Guidelines for Stem Cell Research and Gamete Donors

Rather than informed consent, dispositional authorization may be the preferred strategy in obtaining gamete donations for embryonic stem cell research.

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Recent National Institutes of Health (NIH) guidelines regarding human embryonic stem cell (hESC) lines created from embryos remaining after infertility treatment (*1*) are expected to increase substantially the number of hESC lines eligible for U.S. federal funding. Although the guidelines require informed consent from embryo donors for derivation of hESC lines, such consent is not required from third-party donors (not an intended parent) whose gametes were used to create the embryos. This is in contrast to many state, national, and international recommendations (*2*–*8*). We argue that dispositional authorization after disclosure regarding hESC research should be obtained from third-party gamete donors, but that the requirements may be more flexible and less complex than for informed consent.

Need for Gamete Donor Authorization

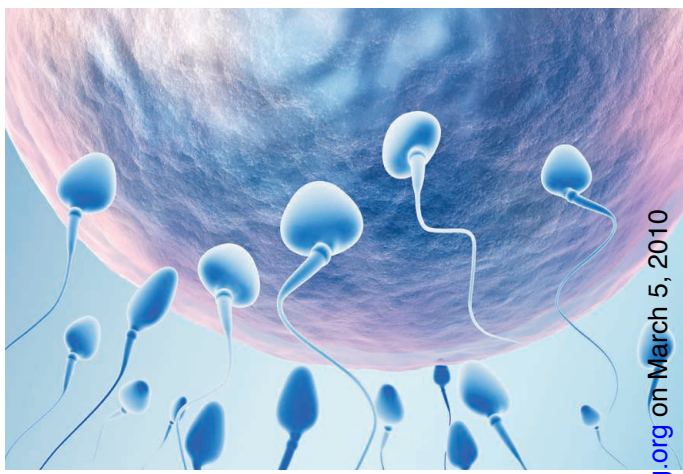
Gamete donors for in vitro fertilization (IVF) programs sign a form giving the IVF patient legal authority to determine the disposition of embryos created with their gametes after infertility treatment has been completed. The unrestricted legal power of such blanket dispositional authorization includes options that were not specifically mentioned to the donor. However, such legal authority may be ethically problematic if the gamete donor was not told—and therefore may not appreciate—what options the IVF patient might choose, including hESC research. Some donors may object to research using embryos made from their gametes (*9*). One reason underlying such objections may be that some donors may regard gametes as having special status compared with somatic cells because of their reproductive potential, with reproduction being a highly personal and private matter. However, gametes are not typically granted the same special status as embryos, which may be perceived to have the moral status of persons (*10*). Using embryos for research without permission of third-party oocyte donors could fail to respect donors as persons (*11*), breaching a fundamental principle of bioethics (*12*).

We analyze below two other models for gamete donors to allow IVF patients to make decisions about embryos remaining after completion of infertility treatment.

Informed Consent

Informed consent is an "opt-in" process; individuals are not required to participate as patients or research participants and agree to only those procedures specified in the consent form. For instance, oocyte donors give informed consent to the clinical procedures of ovarian stimulation and oocyte retrieval (*13*). However, detailed consent forms are not required for many important, very private decisions currently made by third-party gamete donors during dispositional authorization (e.g., forgoing parental rights to children conceived with their gametes and allowing the IVF patient to donate embryos to another infertility patient). It would be unfair to require gamete donors to follow stricter standards to authorize the donation of embryos to hESC research than to authorize these other major decisions.

There are also pragmatic barriers to requiring informed consent from gamete donors for hESC research. Stem cell researchers typically get involved with embryo donation only after an IVF patient inquires about it; they do not interact with gamete donors or write forms for granting dispositional authority. Considerable efforts by IVF clinicians to obtain consent from oocyte donors for potential future research may raise concerns about conflicts of interest (*14*) and could compromise the informed consent process for the complex medical procedures of ovarian stimulation and oocyte retrieval (*15*). Recontacting gamete donors after the IVF patient has completed infertility treatment to seek consent for embryo research may be viewed as an invasion of privacy and also may not be feasible.



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A Modified Approach

We conclude that informed consent from third-party gamete donors should not be required for hESC research. Instead, we recommend a model of dispositional authorization after options for embryo disposition have been disclosed, including hESC research, discarding embryos, and donation to another IVF patient. Informing gamete donors of options respects the donors by making the decision to grant disposition rights to the IVF patient more informed. Most gamete donors grant blanket dispositional authority to the IVF patient. Some gamete donors may not be willing to accept some dispositional options, such as hESC research. An IVF patient should consider such preferences at the beginning of infertility treatment when selecting a gamete donor. However, IVF patients are free to

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choose another donor who will grant unrestricted dispositional authority; thus, the gamete donor cannot control the dispositional decisions of the IVF patient.

At present, disclosure of dispositional options to gamete donors may be carried out as a clinical best practice and is recommended by many legal advisors to IVF practices, although it is not required. For frozen embryos created years ago, disclosure is even more variable.

The standards for disclosing information about hESC research should be comparable to disclosure of information about other dispositional options. It would be desirable to inform gamete donors about features of disposition options that may be pertinent to decisions about disposition but may not be common knowledge (*16*) [e.g., the possibility of patents on hESC discoveries and what provisions, if any, will be in place for sharing royalties (*17*)]. Donors should have the opportunity to ask questions or obtain additional information about disposition options.

But information given to gamete donors about hESC research need not include all the basic elements required in consent forms for human subjects research (*13*). For example, it would be misleading to say that refusal to participate in research will involve no loss of benefits; a prospective gamete donor who is unwilling to grant blanket dispositional authorization may not be selected as a donor and would then not receive compensation.

In this context, the ethical rationale—respect for gamete donors and their preferences—may be satisfied by more flexible procedures and documentation than those for informed consent for research. Disclosing the option of hESC research, along with other available options for embryo disposition, might be done in several ways. Documentation would be unambiguous if the form granting legal dispositional authority listed hESC research as an option. Alternatively, dispositional options, including hESC research, could be described in a separate document, and the form granting dispositional authority need not explicitly mention hESC research, provided that the IVF practice, oocyte donor agency, or sperm bank documents or attests that they provided information about disposition options and that research was given as an option.

Recommended Policy Changes

NIH guidelines should be revised. For hESC lines derived from embryos created after the date of the revised guidelines, dispositional authorization after disclosure from third-party gamete donors should be required. This may be documented by evidence that the donor (i) was told hESC research was an option for the disposition of frozen embryos remaining after the IVF patient had completed treatment, and (ii) then granted the IVF patient dispositional authority over embryos created with the donor's gametes. Gamete donors still must provide informed consent for medical procedures.

Exceptions to dispositional authorization after disclosure may be justified on a case-by-case basis (for example, as determined by NIH). hESC lines already in existence at the time revised guidelines are issued may be used (*18*) if the following three criteria are met: (i) the gamete donor granted dispositional authority to the IVF patient, even without documentation that the gamete donor was told research was an option, (ii) there are strong scientific reasons to use them, and (iii) other legal requirements are met (*19*). For example, the particular hESC line may be the only line that has been derived under good manufacturing process standards or that matches a specific phenotype (*20*).

A more thorough consent process for embryo donors is warranted than for third-party gamete donors, given the special moral status ascribed to embryos (*10*). IVF patients donating embryos for hESC derivation should still give informed consent, consistent with new NIH guidelines (*1*) and other policies (*21*).

For stem cell science to continue to progress, it would be highly desirable to have consistency among standards and regulations (*1*–*8*). If such harmonization is achieved, many IRBs and oversight bodies will likely allow NIH-eligible hESC lines to be used for any otherwise acceptable hESC research.

References and Notes

1. NIH, National Institutes of Health Guidelines on Human Stem Cell Research (NIH, Bethesda, MD, 2009); http://stemcells.nih.gov/policy/2009guidelines.htm.
2. National Research Council and Institute of Medicine, *2007 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research* (Nattaional Academies Press, Washington, DC, 2007); www.nap.edu/catalog.php?record_id=11871.
3. California Institute for Regenerative Medicine, CIRM MES Regulations Title 17, California Code of Regulations Section 100010–100110 (CIRM, San Francisco, CA, 2009); www.cirm.ca.gov/ reg/pdf/Reg100100_SM_Acct_Standards.pdf.
4. International Society for Stem Cell Research (ISSCR), *Guidelines for the Conduct of Human Embryonic Stem Cell Research* (ISSCR, Deerfield, IL, 2006); www.isscr.org/guidelines/index.htm.
5. Human Fertilisation and Embryo Authority (HFEA), Guidance: Consent to use and storage of gametes and embryos; Note 5A, Interpretation of mandatory requirements (HFEA, London, 1991); www.hfea.gov.uk/336.html#guidanceSection3718.
6. Australian Government National Health and Medical Research Council, Prohibition of Human Cloning for Reproduction Act of 2002 (Attorney General's Department, Australian Government, Canberra, 2002); www.nhmrc.gov.au/publications/synopses/prohibitsyn.htm.
7. Parliament of Canada, Assisted Human Reproduction Act, SC 2004, chap. 2; http://laws.justice.gc.ca/PDF/Statute/A/A-13.4.pdf.
8. European Group on Ethics in Science and New Technologies to the European Commission, *The Ethics Review of hESC FP7 Research Projects* (European Communities, 2007); http://ec.europa.eu/european_group_ethics/avis/index_en.htm.
9. About 25% of women who provided oocytes to patients in infertility clinics said they would not want their oocytes to be used for research (*22*). In an IVF program, 13% of oocyte donors would not be willing to donate embryos created from their eggs for research, and 5% were unsure (*23*). Among prospective (not actual) oocyte donors, 10% would not be comfortable if embryos made using their oocytes were donated for research (*24*).
10. National Bioethics Advisory Commission (NEBAC), *Ethical Issues in Human Stem Cell Research* (NEBAC, Rockville, MD, 1999).
11. B. Lo *et al.*, *Science* **301**, 921 (2003).
12. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research* (Office of Human Subjects Research, NIH, Bethesda, MD, 1979).
13. For research, informed consent forms must be approved by an Institutional Review Board and should contain specific required elements, including the risks and benefits of research participation and its alternatives (*25*). U.S. regulations on human subjects research do not apply to research with existing biological materials that investigators cannot link to the donors. The ethical justification for this exception is that few patients would object if a leftover tube of blood or surgical specimen were de-identified and used for research. Nonetheless, because hESC research is sensitive, NIH requires consent from embryo donors even if the materials are de-identified, a policy consistent with other standards (*21*).
14. G. P. Lomax, Z. W. Hall, B. Lo, *PLoS Med.* **4**, e114 (2007).
15. The primary concerns of IVF physicians and oocyte donor agencies are (i) that donors appreciate that the medical procedures present risks (requiring donor consent), and (ii) that they will have no parental rights regarding children produced from their oocytes, and that the IVF patient may choose to donate frozen embryos to another IVF patient or destroy them (requiring donor dispositional authority). These issues may be more thoroughly discussed and documented than potential downstream hESC research, which some IVF physicians and donor agencies may regard as a secondary issue.
16. J. W. Berg, C. W. Lidz, P. S. Appelbaum, *Informed Consent: Legal Theory and Clinical Practice* (Oxford Univ. Press, New York, ed. 2, 2001).
17. R. Korobkin, S. R. Munzer, *Stem Cell Century: Law and Policy for a Breakthrough Technology* (Yale Univ. Press, New Haven, CT, 2007).
18. J. Sugarman, A. W. Siegel, *Science* **322**, 379 (2008).
19. B. Lo *et al.*, *Cell Stem Cell* **4**, 115 (2009).
20. Exceptions may also be permitted for frozen embryos already in existence when the guidelines are revised if it is uncertain whether third-party gamete donors were told that hESC research was a dispositional option. Because it is not known before hESC lines are derived whether they will have significant scientific advantages over other lines, stricter standards should be applied for such exceptions than in the case of hESC lines already in existence.
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23. R. Klitzman, M. V. Sauer, *Reprod. Biomed. Online* **18**, 603 (2009).
24. N. Adsuar *et al.*, *Fertil. Steril.* **84**, 1513 (2005).
25. Department of Health and Human Services, Protection of Human Subjects, **45** Code of Federal Regulations, part 46 (2005); www.dhhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

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