

Donating embryos for human embryonic stem cell (hESC) research: a committee opinion

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hESC research is an ethically acceptable use of human embryos that are in excess of those needed to meet the fertility goals of patients. The ethical basis for this view and issues to be considered during the informed consent process for the donation of embryos are developed in this document. This report replaces the Committee's 2009 report, "Donating spare embryos for stem cell research" (*Fertil Steril* 2009;91:667-70). (*Fertil Steril*® 2013;100:935-9. ©2013 by American Society for Reproductive Medicine.)

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KEY POINTS

- hESC research is an ethically acceptable disposition for human embryos in excess of those needed to meet the fertility needs of patients.
- The final decisions on the donation of embryos to hESC or other research should occur after the patients' infertility needs are met or the patients discontinue therapy.
- The consent process should inform donors of the nature of hESC derivation. When possible, and if known, it also is recommended that the specific research project, the source of funding, the potential commercial value of the research, and anticipated clinical applications be disclosed. Policies on confidentiality and maintenance of the donors' privacy should be in place and presented as part of the consent process. Donors' personal information should be deidentified as best as possible.
- Consent materials should stipulate that donated embryos could be stored for a long period of time in a tissue bank and would be manipulated and destroyed during the research process, and lines containing the donors' DNA could be kept and grown for years and used for future studies yet unknown. Whenever possible, someone other than the treating physician should pursue requests for embryos for hESC research purposes in order to minimize concerns over conflicts of interest and undue influence. Patients should be informed that refusal to participate will not affect their medical care and that embryos used for research will not be transferred to a woman's uterus for possible pregnancy. Patients should be informed of financial incentives, if any, that the investigator/physician or the institution/organization has in the research. Patients should acknowledge that they will neither receive nor share financial incentives gained from the use of their donated embryos.
- Embryos designated for research should not be bought or sold with a monetary exchange or other valuable consideration.
- Embryos created through the use of a third-party gamete donor should be used for hESC research only if specific consent for such use was provided by the gamete donor in advance of the creation of the embryos.

The ability to isolate and culture hESCs, which was first reported in 1998, has opened a promising area of medical research (1). Derived from the inner cell mass of blastocyst-stage embryos, isolated hESCs remain undifferentiated and pluripotent, and different from adult stem cells, in that hESCs may give rise to all cell types found in the human body. Furthermore, hESCs are thought to be able to proliferate indefinitely in an undifferentiated state (2). Researchers predict that, if coaxed to differentiate in culture, hESCs can be used to create specialized cells to treat a wide range of diseases and conditions, including Parkinson disease, Alzheimer disease, cancer, spinal cord injury, and juvenile-onset diabetes. Other envisioned uses of hESCs include

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research to understand cell specialization, transplantation and regenerative medicine, as well as the development and testing of new drugs on specific cell types (3).

hESC research has provoked considerable debate about law, ethics, and policy. Currently, US federal law does not prohibit research in which embryos are donated for hESC purposes. However, ample discussion exists about federal policy and government funding due to stated objections and public concerns. Among other commissions, the National Bioethics Advisory Commission considered the question of federal funding of hESC research in 1999 and recommended that the government fund both the derivation and use of hESCs from spare donated embryos. The Clinton administration proposed funding only the use of hESC, and the National Institutes of Health subsequently issued guidelines to oversee the process. Before any grants were made, however, a change of administration occurred. After further review of the issue, President George W. Bush announced on August 9, 2001 that his administration would consider for funding only those proposals using hESCs from cell lines that had been derived and cultured by that date (4). Although this decision opened the door to fundable research, many scientists questioned whether the pre-existing cell lines would be adequate and appropriate for the research or therapies to which they might lead. In addition, hESCs derived before August 9, 2001 were cultured in their undifferentiated state on a feeder layer of embryonic mouse cells, which rendered these cell lines unacceptable for clinical trials.

On March 9, 2009, President Barack H. Obama issued Executive Order 13505: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells (5). This executive order stated that the Secretary of Health and Human Services may support and conduct responsible, worthy human stem cell research, including hESC research, to the extent permitted by law. These guidelines permit embryos remaining after infertility treatment to be used in the creation of hESC lines and are expected to substantially increase the number of hESC lines eligible for federal funding.

New cell lines were needed for clinical trials to commence. Privately funded investigators sought additional donated embryos to obtain new hESC lines for research in their own laboratories. New sources of embryos enable investigators to study the derivation process itself, secure more cells from the initial embryo source if necessary, and culture cell lines from varied genetic sources (6).

A primary source of embryos for future hESC research is likely to be embryos donated by couples undergoing in vitro fertilization (IVF) who no longer want or need their embryos for fertility treatment. The Ethics Committee considers here the conditions under which such embryos ethically may be made available to researchers seeking hESCs and propose ethical guidelines for conducting research. This consideration is preceded by a summary of differing perspectives about the ethics of embryo research.

ETHICS OF HUMAN EMBRYO RESEARCH

Human embryo research has elicited diverse and conflicting perspectives since the early days of in vitro fertilization. The

ASRM Ethics Committee acknowledges the diversity of opinions regarding these topics among ASRM membership, no different from that seen in the general community. Discussions about the human embryo frequently are framed in terms of the embryo's moral status. An important distinction arises between those who regard the embryo as a person with all the protections accorded to fellow human beings and those who regard the embryo as deserving respect as a potential human but not the same respect accorded to persons. Those who believe the embryo has the moral status of persons expect that the embryo should be accorded all the rights of these individuals. The embryo is vulnerable, under this perspective, and needs protection. Some believe that this status begins at fertilization, when the DNA from the female and male gamete unite to create a unique entity with a novel genetic composition. Others believe that the status begins later, when the primitive streak begins to develop at approximately 14 days after fertilization and when the embryo will, if it survives, be more likely to develop into a single individual (7).

Most who believe that the embryo has a status distinctly different from adults and children regard the embryo as a potential human being worthy of special respect but not entitled to the same rights as persons. This perspective is applied particularly to the embryo used in research, which ranges in development from a single cell to hundreds of cells, has no nervous system, and has a limited chance of developing to birth. The possibility of twinning or regression to a nonviable entity up to the 14th day after fertilization is consistent with the notion that the embryo lacks individuality. Moreover, according to this point of view, the early embryo lacks the criteria traditionally equated with human status.

The ASRM Ethics Committee has consistently held to the second perspective, which regards the embryo as a *potential* human being worthy of special respect (8–11). The ASRM Ethics Committee regards embryo research as ethically acceptable if it is likely to provide significant new knowledge that may benefit human health and if it is conducted in ways that accord the embryo respect. The ASRM Ethics Committee, along with commissions and advisory bodies from around the world, has developed core expectations about how research involving embryos may be conducted ethically (11–13). Among other things, it is expected that patients must give informed consent to donate their embryos for research, embryos should not be kept cleaving more than 14 days after fertilization, and there should be no bartering, buying, or selling of embryos. It also is expected that the investigator bears the burden of justifying the worthiness of the research, uses the smallest possible number of embryos, submits proposals to review by an Institutional Review Board, has no satisfactory alternative to using embryos, and expects important clinical data to accrue from the research.

The ability of scientists to isolate and culture hESCs has evoked renewed discussions about the ethics of embryo research. Advocates of hESC research argue that preimplantation embryos would be discarded and that it is appropriate to gain some benefit from them. In light of the potentially significant impact on regenerative medicine, they argue that it may even be morally obligatory to pursue this research. They also

note that donation for embryo research is an extension of the patients' authority over the disposition of embryos.

Critics, on the other hand, argue that research causing the destruction of embryos is wrong. In addition, they argue that stem cells derived from sources other than embryos also hold potential for diagnosis and therapy. They also express concern that the research will lead to the treatment of embryos as commodities and a consequent diminished respect for embryos. The matter of whether embryos may ethically be created for hESC research through in vitro fertilization or somatic cell nuclear transfer remains a topic of continued debate and elusive consensus (14–20).

INFORMED CONSENT AND THE DONATION OF EMBRYOS FOR hESC RESEARCH

A distinct feature of hESC investigations is the intent to derive cell lines that may continue to divide indefinitely and be used by researchers for many years to come. Such cell lines eventually may have considerable commercial value. In addition, they potentially may be traced to donors (14). For these and other reasons, it is appropriate to revisit recommendations about what should be conveyed to patients in the donation process, when, and by whom. There exists evidence that some patients who have embryos prefer donation for research to other options, such as discarding embryos (21). These recommendations aim to protect the autonomous interests of patients faced with deciding the disposition of embryos they no longer want or need.

What Information to Convey to Potential Donors?

Informed consent is a basic requirement for the ethical conduct of all research involving human subjects, including studies using human embryos. Patients who donate embryos may take a range of considerations into account in making their decisions (22–24). During the consent process for embryo donation for research, patients should be told of the risks and benefits of donation. For example, a risk might arise if the patients were later to wish they still had the embryos available for their fertility efforts. A benefit might be the satisfaction of knowing that they have contributed to research designed to advance medical therapies. Patients also should be told of the purpose and nature of hESC research, that the research may have commercial value, and that they will not share in any financial gain resulting from their donation. They should be told that they may change their minds about donation at any time until the experiment begins, that their status in the infertility program will not be affected if they do not donate spare embryos, and that no embryos used in the study will be transferred for pregnancy (11).

In the case of embryo donation for hESC research, other considerations also may be relevant. Given the potential wide range of uses for hESCs, patients should be informed of the specific research project, if known, or at least of the category of anticipated research, such as reproductive research, development of therapies for disease, or product development. Patients also should know that hESC research

typically involves deriving cells from the inner cell mass of an embryo at the blastocyst stage, which leads to the embryo's destruction.

Patients and gamete donors also should be informed that the cell lines created through hESC research might exist indefinitely. They should be told that stem cells from embryos may have commercial value for a wide range of research and clinical purposes and they as donors will not share in the commercial value, if any. The clinic should develop a policy on privacy and confidentiality of donations and present this as part of the consent process. If identifiers are attached to the cell lines, the donors must be informed of this and of steps taken to assure their anonymity is protected as best possible. The donating parties must agree on the disposition of their embryos. If they cannot jointly agree to donate embryos for hESC research, the embryos should not be used.

Additionally, when third-party gamete donors are involved in the creation of embryos, hESC research should be permitted only on embryos in which the gamete donor has given written consent for such research, thereby giving the IVF patient(s) authority to determine the disposition of embryos created with the donor's gametes after infertility treatment has been completed (25). Some egg and sperm donors in the United States may have a moral objection to research and specifically to hESC research and therefore should be informed that embryos created with their donated material may in fact be used for these purposes (26). Therefore, gamete donors should indicate in their informed consent that they understand the recipient of their donation will have the right to determine the disposition of any remaining embryos, including donation to another couple or individual and the use of embryos in research including hESC research.

When Consent Should Be Obtained?

It is important that patients decide to donate embryos for research only after they have decided not to continue storing their embryos. Making separate decisions about whether or not to use embryos and donating them for research guards against pressure being placed on patients to donate their embryos. When embryos are created, patients often stipulate what should be done with their frozen embryos in the event of future contingencies such as death, divorce, or no contact with the clinic. These directives usually involve donating the embryos to other patients, donating them for research, or discarding them. If no death or divorce occurs, the patients make a separate decision about what should be done with the unused embryos when their fertility needs are met or they end their reproductive efforts with those embryos. At this point the investigator has the opportunity to discuss more thoroughly the option of donating embryos for research.

Using only frozen embryos for research ensures that time passes between the creation of embryos for conception and their donation for research. Still, it is reasonable to expect questions eventually to arise about the donation of fresh "spare" embryos (27). In general, fresh viable embryos should not be used for research purposes in order to protect the patient from undue influence by the treating physician or institution/organization and to avoid any conflict of interest

to provide embryos for hESC research. Donation of fresh embryos raises the possibility that a physician might induce a patient to allow insemination of extra eggs so that they may be donated for research. Moreover, this increases the chance that decisions will be made quickly and later regretted by patients. Without evidence that fresh embryos are significantly preferable to frozen embryos for hESC use, it is appropriate to use only unused embryos that have been frozen. In rare cases in which patients were opposed to embryo cryopreservation but not to embryo donation for hESC research, it would be ethically acceptable to donate fresh embryos for such research. However, because the number of embryos created and frozen should be determined by the patients' clinical needs, it is incumbent upon the physician to confirm in such cases that the patients are fully informed about the clinical implications of their decision to donate their fresh embryos. Finally, embryos that are found to be abnormal or undesired at the time of PGD (preimplantation genetic diagnosis) or PGS (preimplantation genetic screening) also may be donated for hESC use since they would be discarded by the patient as a natural result of testing.

In some situations, patients with stored embryos cannot be contacted despite efforts to reach them. The ASRM Ethics Committee has previously concluded that programs may consider embryos to be abandoned if clinics have taken diligent steps to contact the couple, no written instructions exist, and more than 5 years have elapsed without contact with the couple (28). Abandoned embryos may be discarded, but they should not be used for research or donated to other patients without prior consent. In some cases, patients may have given consent to use embryos for research but were not informed of the possibility of hESC research. The singular features of hESC research make it advisable not to use such embryos for hESC research unless patients have given *specific* advance consent for this use in case they cannot later be reached for a decision. Advance permission to use abandoned embryos for research may thus prevail for hESC studies if the patients have been informed of the possibility of hESC research and agree to the use of their embryos in this specific manner.

Who Should Obtain Consent?

Several advisory bodies have recommended that a person other than the fertility specialist should secure consent to donate embryos (2, 17, 18). The rationale is that this will ensure that the patients' reproductive needs are foremost and avoid conflicts of interest when the fertility specialist is also the investigator. In some circumstances, however, this guideline may be difficult to follow. It is possible, for example, that the fertility specialist who knows the patients, and is trusted by them, may be better able to conduct a frank discussion with the couple about donation for research and may secure more informed consent.

Moreover, using a separate person to secure consent may be difficult if the physician is part of the research team. The possibility of undue influence by the physician will be lessened if the request for a donation is made after the patients decide to dispose of their embryos. Still, the fact that the physician is also a researcher is relevant information and

should be conveyed to the patients along with a statement about incentives, if any, that the physician or the institution/organization has in the research. The rule that the number of embryos created and frozen must be determined by the clinical needs of the patients and not by research goals is especially pertinent when the physician is both the fertility specialist and the investigator. Human subject consents should be reviewed and approved by an Institutional Review Board and, where possible, a separate Stem Cell Research Committee that oversees the conduct of the research studies.

SUMMARY

The ASRM Ethics Committee affirms that it is ethically acceptable to derive and use hESCs in research to develop cell replacement therapies and to further other medical uses. This research should take place only within guidelines in place for embryo research in general and only under conditions that protect the free and informed consent of patients.

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