Cell Stem Cell
Perspective

Importing Human Pluripotent Stem Cell Lines Derived at Another Institution: Tailoring Review to Ethical Concerns

Bernard Lo,[1,2,*] Lindsay Parham,[1,2] Christopher Broom,[1,2] Marcelle Cedars,[3] Elena Gates,[3] Linda Giudice,[3,4] Dina Gould Halme,[5] William Hershon,[10] Arnold Kriegstein,[4,6] Pui-yan Kwok,[7] Michelle Oberman,[11] Clifford Roberts,[8] and Richard Wagner[9]
[1]Program in Medical Ethics
[2]Department of Medicine
[3]Department of Obstetrics, Gynecology, and Reproductive Sciences
[4]Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research
[5]Office of the Dean of the School of Medicine
[6]Department of Neurology
[7]Department of Dermatology
[8]Office of the Vice-Chancellor for Research
[9]The Human Research Protection Program
University of California, San Francisco, San Francisco, CA 94143, USA
[10]Disability Rights California, San Francisco, CA 94501, USA
[11]Santa Clara University School of Law, Santa Clara, CA 95053, USA
*Correspondence: bernard.lo@ucsf.edu
DOI 10.1016/j.stem.2009.01.013

Stem cell researchers commonly use human pluripotent stem cell lines derived by other investigators. Researchers may use lines derived elsewhere, provided that their derivation met consensus core standards. Some types of derivation raise heightened levels of ethical concern and require greater scrutiny. To maintain public trust, research institutions need to justify why they allow researchers to use lines whose derivation would not have been permitted locally.

Exchanging human pluripotent stem cell lines between institutions across state and international borders will promote discovery, confirmation, and future therapeutic applications in the emerging field of stem cell research. Therefore, researchers may wish to work with human stem cell lines that were derived at institutions in other jurisdictions. Such sharing of materials also minimizes the number of oocytes, embryos, and somatic cells used. However, dilemmas arise because jurisdictions and institutions may have conflicting standards on ethical issues; in some cases, those lines might have been derived under conditions that would not be permitted at the importing institution. Although it may not be illegal for researchers to import and work on such lines, there may be serious ethical concerns about undermining the home jurisdiction's ethical standards (Daley et al., 2007; Mathews et al., 2006; Skene, 2007). For example, in 2007, the United Kingdom decided to allow women providing oocytes for research to receive some payments for lost wages or discounts on their IVF care (Human Fertilization and Embryology Authority, 2007). Using such arrangements, UK researchers now are trying to derive a line using somatic cell nuclear transfer (SCNT). If their efforts are successful, other scientists will want to carry out additional research with this line. However, under the National Academies of Science (NAS) guidelines for human stem cell research or under laws in states such as California, donors of materials for stem cell research may not receive payments or other consideration in excess of out-of-pocket expenses (National Research Council and Institute of Medicine, 2005). Therefore, institutions in the United States will have to decide if their researchers can use lines derived under such circumstances.

It may be difficult to obtain accurate information about lines derived in the past at other institutions. In several highly publicized cases, key ethical facts were misrepresented or overlooked. For example, clinical IVF programs in Romania lied about payments to oocyte donors and were accused of exploiting donors (Heng, 2006; Higgins, 2004). In the SCNT scandal in Korea, in addition to fabricating data and committing financial fraud, the principal investigator lied about payments to oocyte donors, the recruitment of donors, and medical complication rates (Chong, 2006; Chong and Normile, 2006; Normile et al., 2006). Recently it has been alleged that problems with the consent forms for several National Institutes of Health (NIH)-approved embryonic stem cell lines went undetected for years (Streiffer, 2008). This was partly a result of the lack of publicly available documentation about the provenance of those lines, which was not remedied until a Freedom of Information Act request was filed with the NIH.

Institutions using human pluripotent stem cell lines derived at another institution need to ensure that they were derived in an ethically appropriate manner. The level of review should be tailored to the level of ethical concern that the derivation procedure raises. Human embryonic stem cell (hESC) lines derived using fresh oocytes and embryos raise heightened concerns about the medical risks of oocyte donation, undue influence, compensation to oocyte donors, and compromise of the reproductive goals of a woman in infertility treatment. However, hESC lines derived from frozen embryos and induced pluripotent stem (iPS) cell lines derived from somatic cells raise fewer ethical concerns. Thus, review procedures for hESC lines derived using

fresh oocytes need to be more intensive than review procedures for stem cell lines derived from frozen embryos or somatic cells.

Three questions need to be addressed regarding the use of stem cell lines derived elsewhere. First, what ethical standards for human pluripotent stem cell derivation should be required everywhere in the world? Second, what review procedures are needed to determine whether the derivation of a particular line at another institution met these standards? Under what conditions may an institution defer to review carried out in a second institution? Third, under what circumstances may researchers use human pluripotent stem cell lines whose derivation would not have been permitted in their own jurisdiction? For instance, may a jurisdiction that does not allow oocyte donors to receive payment greater than expenses allow researchers to import stem cell lines derived from fresh oocytes whose donors received such payments?

What Research Ethics Standards Should Apply in All Countries?

Donation of biological materials for the derivation of human pluripotent stem cell lines should meet core ethical standards in consensus international research guidelines. First, the risks to research participants, such as oocyte donors, must be minimized and reasonable in light of the prospective benefits. Second, informed and voluntary consent must be obtained as a matter of respect for donors. Payment should not present an undue inducement to donors. As a procedural safeguard, the derivation should have been approved by an institutional review board (IRB) or similar oversight panel that is independent of the investigators. These ethical standards are identified as fundamental in international standards such as the Helsinki Declaration, the Council for International Organizations of Medical Sciences (CIOMS), and International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice (GCP) standards; in United States regulations for the protection of human subjects (Council for International Organizations of Medical Sciences, 2002; Department of Health and Human Services, 2005; International Conference on Harmonization, 2007; U.S. Food and Drug Administration, 2007; World Medical Association); and in stem cell-specific standards from the International Society for Stem Cell Research (ISSCR), the U.S. National Academy of Sciences, the California Institute for Regenerative Medicine, and others (California Institute for Regenerative Medicine, 2006; International Society for Stem Cell Research, 2006; National Academy of Sciences, 2005; National Institutes of Health, 1994; Streiffer, 2008).

If These Consensus Guidelines Were Violated, May Other Researchers Still Use the Derived Stem Cell Lines?

On the one hand, using such previously derived human stem cell lines allows some good to come from the risks and inconvenience that the donors of research materials experienced. There are no further physical risks to donors. However, such use would fail to respect as persons those donors whose consent was not sought, who were not informed of the proposed type of research activity, or who would have objected to it. There might also be violations of privacy and confidentiality if the lines are identifiable. Furthermore, such use may erode ethical behavior by other researchers. If some stem cell researchers were permitted to take advantage of lax standards or weak oversight in certain jurisdictions, other investigators throughout the world would be at a considerable disadvantage in a highly competitive field. They therefore would have strong incentives to reject these consensus standards. Eventually the most permissive practices might prevail. In a global research environment, stem cell research may move to countries that lack "restrictive policies" (Brown, 2007). These slippery-slope concerns are cogent because it would be difficult to set a policy that allows use of one human stem cell line that was derived in an unethical manner while preventing the sharing of additional such lines in the future. In addition, use of such lines may be problematic per se. Philosophers have debated whether it is wrong for one person to "take up and incorporate fruits or byproducts of someone else's illicit action" in order to carry out an essential part of one's own project (Kaveny, 2000).

What Obligations Do Researchers and Institutions Using Stem Cell Lines Derived Elsewhere Have to Verify that Consensus Standards Have Been Met?

A scientist may not avoid moral responsibility by claiming that she had no control over collaborators' actions or that she did not know what they did. In cases of egregious scientific misconduct, scientists have been criticized even though they claimed that they were not aware that collaborators had falsified or fabricated data (Culliton, 1983; Holden, 2006; Rennie, 2008). While researchers cannot be expected to know all the details of a collaborator's work, they need to be satisfied that consensus core ethical standards were met. Although trusting collaborators is an honored scientific tradition, it would be naive to simply rely on a colleague's word that the stem cell line was derived ethically. Researchers importing human stem cell lines and their institutions need to make reasonable efforts to verify that a line was derived in an ethical manner. Requiring documentation is one such necessary step in assessing whether consensus ethical standards were met, although it would not protect against intentional deception. What kinds of evidence, however, should an institution require to determine that the derivation met consensus ethical standards? At the University of California, San Francisco (UCSF), the Stem Cell Research Oversight Committee (SCRO) has decided that the level of review must be proportionate to the level of ethical concerns about the method of derivation.

The next sections suggest how SCROs and researchers should take into account a number of considerations when deciding whether it is permissible to use a line derived in another jurisdiction.

Review of Human Pluripotent Stem Cell Lines that Raise Relatively Low Levels of Ethical Concern

Stem Cell Lines Derived from Frozen Embryos Remaining after Completion of IVF Treatment

Figure 1 presents recommendations for such lines derived from embryos created for reproductive purposes before April 2005, when the National Academy of Sciences (NAS) recommended ethical standards for hESC research. Lines derived after this date will be considered in the next section.

Legal Compliance. At a minimum, the derivation should have complied with all applicable legal and clinical standards for in vitro fertilization (IVF) in that jurisdiction at that time.

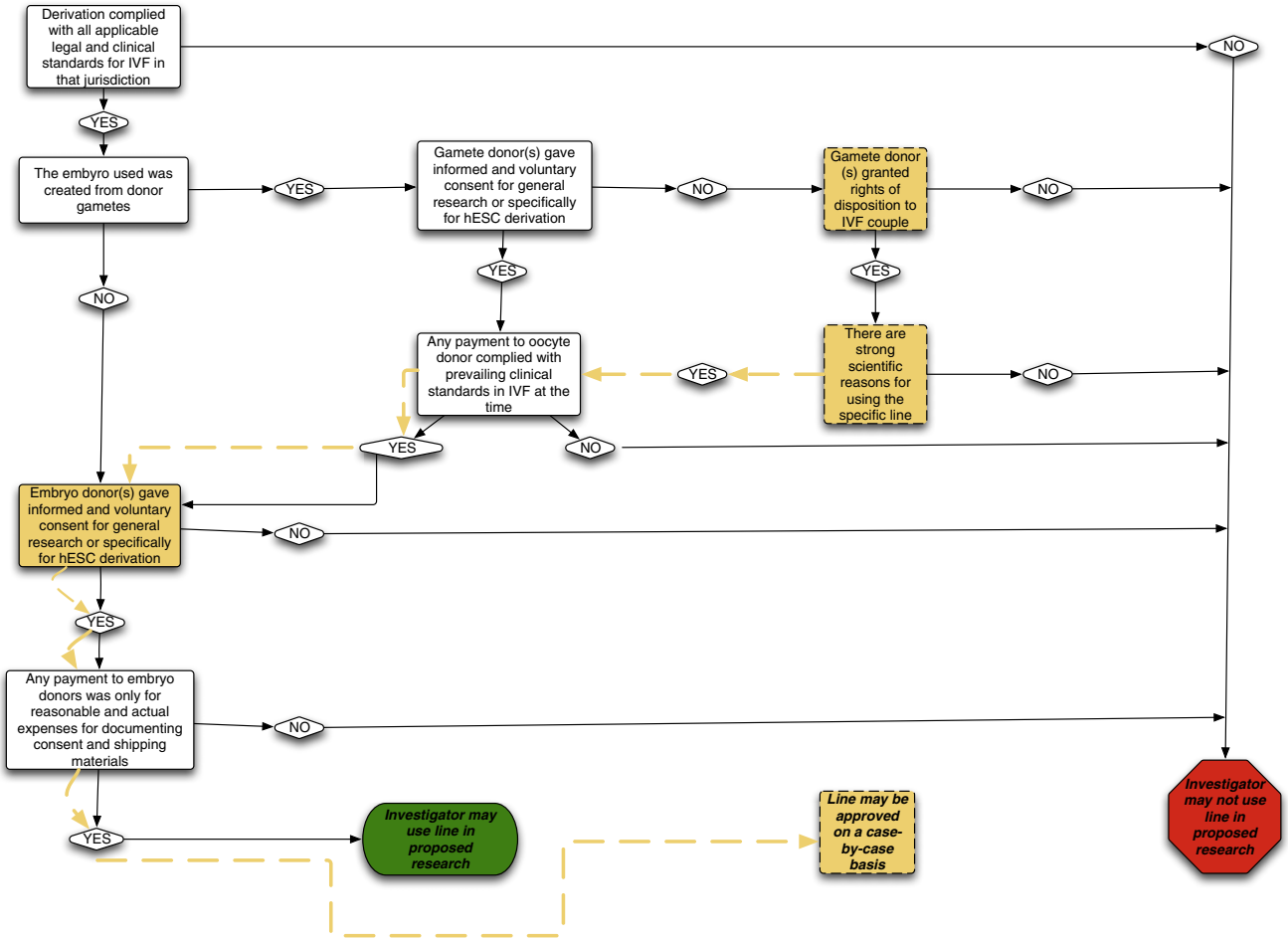

Figure 1. When May an Investigator Use an hESC Line Derived at Another Institution from a Frozen Embryo Created before April 2005 for Reproductive Purposes?
Yellow boxes and arrows allow consideration of exceptions on a case-by-case basis. See text for details.

Consent. With stem cell lines that are derived from frozen embryos remaining after a woman or couple has completed infertility treatment, the main ethical concerns are informed consent for stem cell research and payment to the embryo or gamete donors. There is no additional physical risk to oocyte donors, who have already experienced the risks of hormonal manipulation and oocyte retrieval in order to achieve reproductive goals. The ethical concern is that a person who donated gametes or embryos for research purposes may not want those materials used for hESC research or was not asked for consent (Lo et al., 2003). Explicit and voluntary consent for use of reproductive materials in hESC or SCNT research should ideally have been obtained from any gamete donors as well as embryo donors (National Academy of Sciences, 2005).

Payment. Any payment to a gamete donor(s) that was provided previously in the context of infertility treatment should comply with prevailing clinical standards in IVF practices. The use of frozen embryos for research provides no additional inducement to gamete donors because at the time of donation all gametes were intended for use in infertility treatment.

To avoid undue inducement with embryo donors, there should be no payment for frozen embryos beyond reimbursement for reasonable and actual expenses for documenting consent and shipping materials. There is no rationale for paying embryo donors for materials that have already been obtained as part of clinical care but are no longer needed for that purpose, just as patients are not paid for research use of pathological specimens obtained during clinical care.

Exceptional Cases. An exception may be made to "grandparent" in older lines that were derived from embryos created before explicit consent for hESC derivation became the standard of care (Sugarman and Siegel, 2008a, 2008b). A 1994 NIH panel on human embryo research recommended that consent from embryo and gamete donors be required; however, that report was never officially adopted. Subsequent guidelines and articles also called for various aspects of informed consent for hESC derivation (Lo et al., 2003; National Bioethics Advisory Commission, 1999; Streiffer, 2008). Although these recommendations are ethical best practices, it is controversial whether they should be considered a requirement for researchers. However, the April 2005 National Academies' *Guidelines for Human Embryonic Stem Cell Research* may be regarded as definitive because it is a consensus, peer-reviewed report and has been widely adopted as institutional policy and state regulation (Lomax

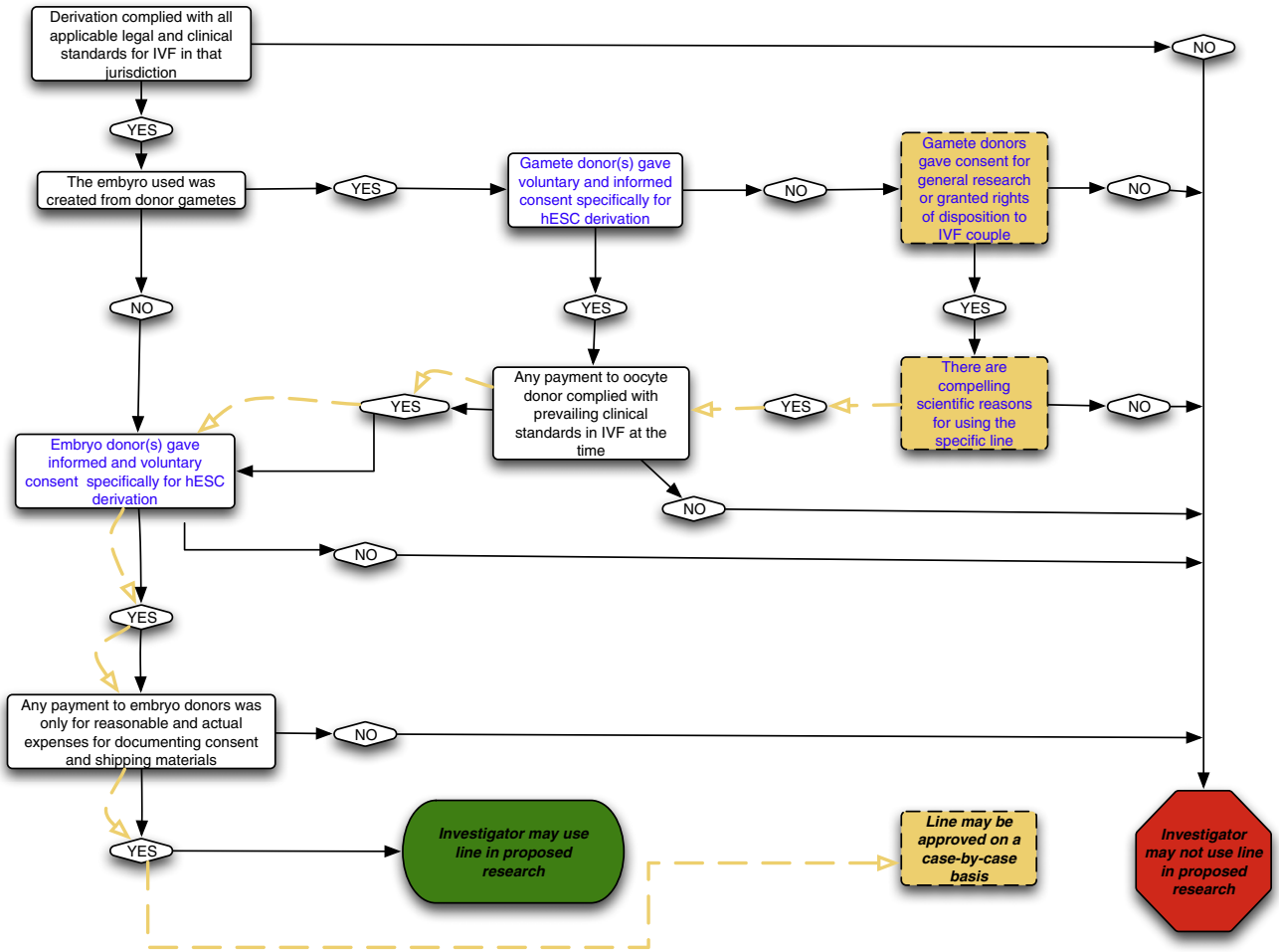

Figure 2. When May an Investigator Use an hESC Line Derived at Another Institution from a Frozen Embryo Created after April 2005 for Reproductive Purposes?
Blue text indicates different standards from those presented in Figure 1. Yellow boxes and arrows allow consideration of exceptions on a case-by-case basis. Please see text for explanation.

et al., 2007). Thus we suggest that it is acceptable in two situations for researchers to use hESC lines derived before April 2005 from donors who did not provide explicit consent. The first situation is that in which consent was obtained for research, but not specifically for stem cell research, and the proposed project is consistent with that consent. The second situation is that in which a gamete donor granted rights of disposition to the woman or couple in IVF treatment and there is a strong scientific reason to use the particular line. A "strong" scientific reason for using the derived hESC line would be that it has unique immunological properties that would be advantageous in transplantation or that it is the only line that has been differentiated into a specialized type of cell. Looking at Figure 1, the SCRO would follow the dotted yellow arrows to make a determination on a case-by-case basis as to whether a particular line may be used.

For lines derived from embryos created after the April 2005 NAS recommendations, there should be higher standards for consent from embryo and gamete donors, as the text highlighted in blue in Figure 2 describes. The yellow boxes and dashes show the path for consideration of exceptions. A "compelling" scientific reason should be required to use a line that does not meet the NAS consent standards, not just a "strong" reason. In our view, a line that is the only suitable one derived under Good Manufacturing Practice for clinical use would qualify, because the effort and expense of repeating the derivation might well be prohibitive. The scientific benefits, which are substantial, are therefore unlikely to be duplicated in other lines. When making a determination that there is a compelling scientific reason, the SCRO committee should state its justification explicitly.

Process of Review. We recommend that for hESC lines derived from frozen embryos, a researcher or research institution may rely on the review process carried out in another country or institution, provided the following four criteria are met. First, the policy in which the hESC line was derived incorporates the consensus core standards discussed above. Second, the donation of embryos for research met the ethical, legal, and institutional standards in place at the time. Third, a panel with appropriate expertise and experience approved the consent and derivation processes and carried out review appropriately.

Fourth, the derivation of the stem cell line did not contradict or exceed explicit provisions in the consent for donation of embryos to researchers (Streiffer, 2008).

In our experience at UCSF, it is difficult and time consuming to obtain such information. Many institutions do not have information about the review committee and process readily available and are not used to responding to such requests. Even obtaining the qualifications and experience of the review panel may be challenging. It may be particularly difficult to obtain information about hESC lines derived by for-profit companies that were bought out by another company.

In light of the relatively low level of risk in deriving hESC lines from frozen embryos, the UCSF SCRO decided that extensive time and effort for detailed verification is not warranted.

Thus, for such lines, UCSF has decided to rely on a letter signed by a responsible official from the institution where the line was derived stating that the derivation from frozen embryos was approved by the appropriate institutional committee, that the institution has adopted consensus core ethical guidelines (for example, the 2005 NAS guidelines or the 2007 ISSCR guidelines), and that the protocol met legal requirements in force at the time of derivation. In addition, in light of recent concerns about donor consent (Streiffer, 2008), the UCSF SCRO also reviews the consent form for the donation of embryos used for the derivation of stem cell lines.

To facilitate sharing of stem cell lines, institutions at which widely used lines were derived should post on the Internet documentation that SCROs at other institutions need to determine if they approve the use of the lines. Such information should include documentation of institutional approval, unsigned copies of consent forms, and a description of the process by which consent and materials were obtained.

Derived Lines. If a researcher proposes to use a secondary stem cell line derived from a hESC line for which the embryo or gamete donors did not explicitly consent for hESC research—for example, a committed cell line derived from a pluripotent cell line—the same standards and review process should apply. If the original cell line is determined to be acceptable according to the standards and procedures discussed above, then the derivative line should also be acceptable.

Induced Pluripotent Stem Cell Lines

Derivation of iPS Cell Lines. When deriving iPS cell lines, the main ethical concern is informed consent from the somatic cell donor. Preferably, consent should be obtained specifically to create human pluripotent stem cell lines. Consent, however, for unspecified future research suffices to derive the line, show that it is pluripotent, and carry out other basic research that is commonly carried out with other cells under such general consent. A researcher also may use deidentified cells donated for another purpose, provided that the use of the cells to derive an iPS cell line does not contradict the provisions of consent for the original donation.

In the case of iPS, payment to somatic cell donors is not as great a concern as with gamete or embryo donors. Donating somatic cells is not as ethically sensitive as donating reproductive cells, and donors commonly receive a small payment when undergoing biopsies in other types of research without raising concerns about undue influence. The review process for iPS cell lines should be the same as for hESC lines derived from frozen embryos remaining after IVF treatment.

Human Stem Cell Lines that Raise Higher Levels of Ethical Concern

Some methods of deriving human pluripotent stem cell lines raise higher levels of ethical concern. Our analysis goes beyond previous discussions of sharing stem cell lines derived in another jurisdictions by suggesting more specific guidelines and procedures to assist oversight committees who must approve such sharing (Beauchamp and Childress, 2001; Daley et al., 2007; Mathews et al., 2006; Skene, 2007).

hESC Lines Derived Using Fresh Oocytes or Fresh Embryos

Such lines raise additional concerns about medical risk and, if materials are shared between researchers and a woman in infertility treatment, concerns about compromising reproductive goals (see Figure 3) (Cohen et al., 2008; Lomax et al., 2007).

Legal Compliance. At a minimum, the derivation should comply with all applicable legal and clinical standards for IVF in that jurisdiction.

Consent. When stem cell lines are derived by using fresh oocytes or fresh embryos, there are ethical concerns about consent and medical risks to donors. Consent for donation of such materials for research should be specific, informed, and voluntary. If any gamete or embryo donors had low education, lived in poverty, or had dependent relationships with investigators, it should be explained how it was determined that their consent was both informed and voluntary.

Exception for Compelling Scientific Reasons. A hESC line that does not meet these consent requirements may be granted an exception to be used. For example, a hESC line that was derived from fresh oocytes or embryos obtained before April 2005 may not meet the NAS standards for specific consent for hESC derivation. The SCRO may determine on a case-by-case basis that compelling scientific reasons to use the line outweigh ethical concerns about consent. For example, in a case in which a gamete donor(s) granted dispositional control to an IVF couple, a compelling scientific reason to grandfather the line might be that it was derived under Good Manufacturing Practice for clinical use.

Medical Risks. In research, risks to participants must be minimized. The concern here is that attempts may be made to retrieve a larger-than-usual number of oocytes. The risk of ovarian hyperstimulation syndrome (OHSS) is increased if a large number of oocytes is sought (Giudice et al., 2007). The most direct method to assess risk is to compare the incidence of severe OHSS in the women who donated oocytes for research to the incidence at experienced, skilled IVF centers with comparable donors. However, the number of cases will be small, and the confidence intervals around the rates will be wide. In addition, there should be documentation of procedures designed to minimize risks to donors, such as excluding donors at high risk for complications, using appropriate hormonal dosage, aiming for a modest number of oocytes, monitoring for excessive ovarian stimulation, and canceling an induction cycle when the risk of OHSS is unacceptable (Balen, 2005; Giudice et al., 2007).

Oocyte Sharing. There are additional ethical concerns if oocytes from a donor cycle were used for both reproductive purposes and for research. For example, fresh oocytes might

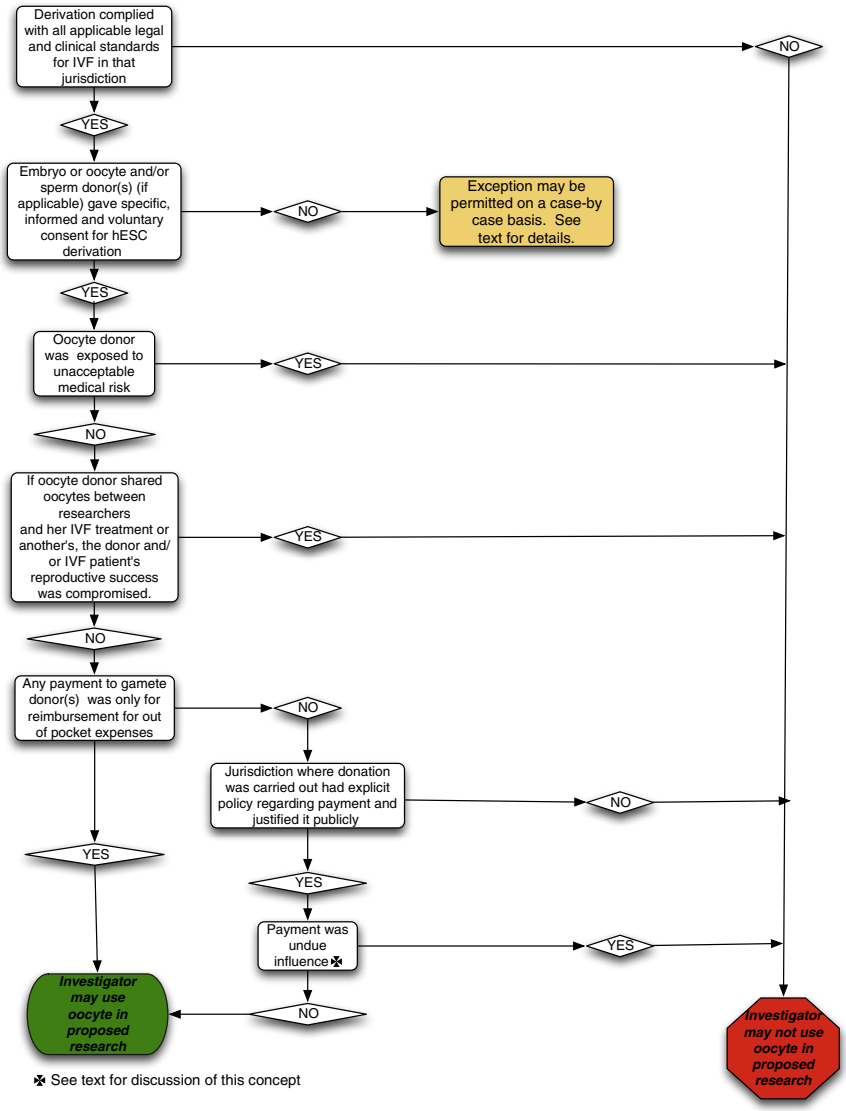

Figure 3. When May an Investigator Use hESC Lines Derived at Another Institution from Fresh Oocytes or Fresh Embryos?

be shared between a woman in IVF treatment and researchers, or researchers might receive oocytes that failed to fertilize or that were too immature for reproductive use. There is no additional medical risk to oocyte providers who are already undergoing oocyte retrieval for reproductive purposes, provided that hormonal dosing protocols are not intensified. However, oocyte sharing might compromise reproductive outcomes for the woman in infertility treatment, particularly when oocytes other than those that are immature or fail to fertilize are shared. In this setting, the reproductive success and interests of the woman in infertility treatment should not be compromised.

Direct evidence that the woman in infertility treatment did not have her reproductive interests compromised would be that reproductive outcomes in women who shared oocytes with researchers were similar to outcomes in women at the IVF clinic who had all oocytes available for use in reproduction (Revazova et al., 2007). Supporting evidence that reproductive outcomes were not compromised can be obtained from the safeguards in the donation protocol.

If researchers receive oocytes that failed to fertilize or fresh embryos that are not of reproductive quality, there are again concerns about compromising the reproductive goals of the woman in infertility treatment. The embryologist who decides that these materials are not suitable for reproductive purposes should be independent of the research team, be blinded as to whether such materials would be discarded or used for research, and have no financial interest in companies with a financial stake in human stem cell research (California Institute for Regenerative Medicine, 2006; Lomax et al., 2007).

Some women who could not otherwise afford IVF might be willing to accept a lower pregnancy rate in order to obtain subsidized or free IVF cycles by providing oocytes for research. This determination must be an informed decision made by the woman undergoing treatment (California Institute for Regenerative Medicine, 2006).

Payment or Consideration to Oocyte Donors in Excess of Expenses

Jurisdictions have conflicting policies about payment to oocyte donors. Reimbursement to oocyte donors for out-of-pocket expenses presents no ethical problems, because donors gain no financial advantage from participating in research. However, payment to oocyte donors in excess of reasonable out-of-pocket expenses is controversial, and jurisdictions have different policies (Spar, 2007). Good arguments can be made both for and against paying donors of research oocytes more than just their expenses (Hyun, 2006).

Jurisdictions and institutions that forbid such payments need to decide whether researchers may use human stem cell lines derived elsewhere using embryos whose oocyte donors were paid. Several considerations should be taken into account.

First, what kind of policy in the other jurisdiction allowed payment? Some policies have a strong claim to be respected elsewhere because they represent the values and culture of that jurisdiction and were carefully considered. For example, the UK enacted an explicit policy to allow such payment after public consultation and debate and careful deliberation and provided reasons to justify its decision (Human Fertilisation and Embryology Authority, 2006, 2007a, 2007b, 2007c). These reasons are understandable to persons from different religious or philosophical traditions (National Bioethics Advisory Commission, 1997).

Table 1. Information to Disclose to Donors Regarding Future Research

1. Genetic modifications of cells.
2. Injection of derived cells into nonhuman animals to demonstrate their function or safety, including the injection into the brains of nonhuman animals.
3. Large-scale genome sequencing.
4. Future research projects that cannot be anticipated currently.
5. Sharing cell lines with other researchers in other institutions and countries, with confidentiality protections.
6. Patenting scientific discoveries and developing commercial tests and therapies, with no sharing of royalties with donors.
7. Allogenic transplantation.
8. Reproductive research to create totipotent entities from gametes derived from pluripotent stem cells.

Even jurisdictions that ban payments should accept such carefully considered policies as embodying a reasonable difference of opinion on a complex issue. In contrast, some jurisdictions have no explicit policy regarding such payments. Thus payments are permitted simply because they are not forbidden, which may be a loophole rather than a deliberate policy. Such an approach has only weak claims to be accepted by other jurisdictions. Public policies are more deserving of respect if they are explicit, justified by reasons, and involve public deliberation (Gutman and Thompson, 1996).

Second, was the payment or consideration an undue influence? An undue inducement or undue influence is defined as "an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Very high payments to participants might be regarded as an undue influence, because they might lead persons to agree to inappropriately large risks they would otherwise not accept. The amount paid to participants should be specified, as well as how it compares with such benchmarks as typical hourly incomes for unskilled labor, the minimum wage, and the cost of living in that area. The review committee of the institution at which the line was derived should explain the reasons that led them to determine there was no undue influence. For instance, the researchers might have administered a questionnaire to ensure that donors appreciated the medical risks and any potential impact on reproductive outcomes. In addition, there might have been a waiting period to allow oocyte providers to reconsider their decision.

Other Sensitive Methods for Deriving Pluripotent Lines

Some approaches to deriving pluripotent stem cells, such as SCNT or use of nonhuman oocytes in SCNT, raise additional ethical controversies regarding natural ethical boundaries and human dignity (Human Fertilisation and Embryology Authority, 2007d; National Bioethics Advisory Commission, 1997; The President's Council on Bioethics, 2002). These techniques are not permitted in some jurisdictions. The issue is whether a different policy in the other jurisdiction has a strong claim to be respected because it was carefully deliberated on and justified, as discussed previously (Human Fertilisation and Embryology Authority, 2007d). In such instances, the donors of materials should have given consent for these specific techniques, rather than just general consent for "research" or "stem cell derivation." The researcher who wants to import the lines should explain why the project could not be carried out by other, less ethically sensitive methods, such as by using iPS cells.

Sensitive Downstream Stem Cell Research

Some types of downstream research with stem cells raise higher levels of ethical concern. Human allogenic transplantation and reproductive research to create a totipotent entity using gametes derived from pluripotent stem cells are likely to be particularly controversial; a significant percentage of donors of materials used to derive stem cells can be predicted to disapprove of them, and explicit consent is generally required for these activities in other settings (Aalto-Setala et al., 2009).

Researchers would fail to respect donors as persons if donors were not informed of the proposed type of research, or if donors would have objected to it (Aalto-Setala et al., 2009). Thus these types of sensitive downstream research should be permitted only if donors explicitly consented to them (Aalto-Setala et al., 2009).

Given the barriers to future research if the donor has not given consent, researchers deriving a new stem cell line can facilitate downstream research if they inform donors of the types of research that might be carried out in the future, as shown in Table 1. Donors should be given the option of consenting to only some of these research activities. However, we suggest that researchers use only materials from donors who agree to items 1–6 in Table 1, which are fundamental in basic and translational stem cell research whose goal is new therapies. If donors allowed only some of these activities, the scientific usefulness of the lines would be compromised; they could not be characterized fully, studied extensively, or differentiated into specialized cells.

Procedures for Review of Human Stem Cell Lines that Raise Higher Levels of Ethical Concern

Such human pluripotent stem cell lines might be approved through various review procedures, depending on the circumstances of the case.

Accept Original Review of Derivation. Review of the derivation by another institution may be accepted if certain criteria are met. First, the policy in the jurisdiction should incorporate core consensus ethical principles, should be explicit and accompanied by a rationale that is publicly available and understandable to persons from different religious and philosophical traditions, and should address concerns about undue influence.

Second, the original review of the derivation protocol should have been careful and rigorous. This might occur in several ways. Review by national bodies, such as those in the UK and Canada, and Australia (Canadian Institutes of Health Research, 2007; Human Fertilization and Embryology Authority, 2003; National Health and Medical Research Council, 2004), are likely to be equivalent to, if not superior to, oversight at importing institutions and therefore need not be duplicated. It is important, however, to note that uncritical reliance on original review by national bodies might be problematic; the NIH, for example, seems to have conducted little substantive review of the provenance for the hESC lines on its registry (Streiffer, 2008), relying instead on statements from the providers. Additionally, the

NAS deferred to the NIH in their decision to grandfather those lines into their 2007 guidelines.

Indirect assessments of another institution's review process might be problematic. SCROs are not accredited, so it is difficult to judge their expertise and procedures. A statement from the deriving institution's SCRO stating that it is in compliance with the latest NAS or ISSCR guidelines would strengthen an indirect assessment of that SCRO. If the SCRO is not fully in compliance with the NAS or ISSCR guidelines, a document showing how the SCRO's review process differs would also be helpful. Additionally, review bodies at other institutions might be deemed acceptable if the IRB for human subjects research has been accredited. Although human subjects review and stem cell research review are different, accreditation indicates an institutional commitment to rigorous review of research.

Review of Derivation by Institution Importing the Stem Cell Line. If the review process of the institution at which the stem cell line was derived does not satisfy these criteria, the institution where the line would be used will have to review the derivation protocol after the fact. The most direct way to do so is for the original review panel to share its reasoning with the SCRO of the institution at which the line would be used—for example, in detailed minutes or in a peer-reviewed publication. The latter committee can then judge whether it regards the review as thorough and the reasoning as persuasive. At UCSF, we have found such case-by-case reviews, which might need to assess informed consent processes in another country, to be highly labor intensive and often impractical. Because of these difficulties, we strongly prefer to obtain enough information to defer to the original review, as discussed previously.

Separation of Scientist Importing Stem Cell Line from Derivation. If a researcher uses an imported hSC line whose derivation would not have been permitted where she works, she should not instigate, direct, or coordinate the derivation of stem cell lines in the institution of origin. Otherwise, the collaboration could be considered a subterfuge to evade restrictions at the home institution.

In summary, stem cell lines may be shared across jurisdictions, provided that the derivation was carried out in accordance with consensus core ethical standards and that there is adequate evidence that these standards were met. Institutions need to be willing to explain to the public how they are overseeing human stem cell research and why they allow researchers to use a line whose derivation would not have been permitted there. In a new and sensitive field of research, such justification is essential to strengthen public trust.

ACKNOWLEDGMENTS

The authors would like to thank Elizabeth Blackburn, Arturo Alvarez-Buylla, and Greta Schnetzler for their thoughtful and insightful contributions to the UCSF Human Gamete and Embryonic Stem Cell Research Oversight Committee. We also thank three anonymous reviewers for their thoughtful and detailed criticisms, suggestions, and questions. B.L. is chair of the UCSF Stem Cell Research Oversight Committee and is cochair of the Standards Working Group of the California Institute for Regenerative Medicine, which recommends regulations for state-funded stem cell research. This work is supported by NIH Grant Number 1 UL1 RR024131-01 from the National Center for Research Resources (NCRR) and NIH Roadmap for Medical Research and by the Greenwall Foundation. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH or the Greenwall Foundation. B.L. is cochair of the Standards Working Group of the California Institute for Regenerative Medicine, which recommends regulations for state-funded stem cell research. All authors are members of or staff for the UCSF Stem Cell Research Oversight Committee.

WEB RESOURCES

Balen, A. (2005). Ovarian hyperstimulation syndrome—a short report for the HFEA. http://www.hfea.gov.uk/docs/OHSS_Report_from_Adam_Balen_2005(1).pdf.

California Institute for Regenerative Medicine (2006). CIRM MES regulations title 17 California code of regulations section 100010–100110. http://cirm.ca.gov/workgroups/pdf/Reformatted_MES_Regs.pdf.

Canadian Institutes of Health Research (2007). Updated guidelines for human pluripotent stem cell research. http://www.cihr-irsc.gc.ca/e/34460.html.

Council for International Organizations of Medical Sciences (2002). CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects. http://www.cioms.ch/frame_guidelines_nov_2002.htm.

Department of Health and Human Services (2005). Protection of Human Subjects. Title 45, Code of Federal Regulations, Part 46. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

Higgins, G. (2004). Egg donation 'surges' in Romania. BBC News. http://news.bbc.co.uk/2/hi/health/4118625.stm.

Human Fertilisation and Embryology Authority (2006). The regulation of donor-assisted conception: a consultation on policy and regulatory measures affecting sperm, egg and embryo donation in the United Kingdom. http://www.hfea.gov.uk/docs/SeedConsult.pdf.

Human Fertilisation and Embryology Authority (2007a). HFEA code of practice: 7th edition. http://www.hfea.gov.uk/en/371.html.

Human Fertilisation and Embryology Authority (2007b). Donating eggs for research: safeguarding donors. http://www.hfea.gov.uk/en/1417.html.

Human Fertilisation and Embryology Authority (2007c). HFEA statement on donating eggs for research. http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-EF42B079/hfea/hs.xsl/1491.html.

Human Fertilisation and Embryology Authority (2007d). HFEA statement on its decision regarding hybrid embryos. http://www.hfea.gov.uk/en/1581.html.

Human Fertilization and Embryology Authority (2003). Code of practice: 6th edition. 2003. http://www.hfea.gov.uk/cps/rde/xbcr/SID-3F57D79B-4EECE5D8/hfea/Code_of_Practice_Sixth_Edition_-_final.pdf.

Human Fertilization and Embryology Authority (2007). FAQs about donating eggs for research. http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-EF42B079/hfea/hs.xsl/1496.html.

International Conference on Harmonization. (2007). http://www.ich.org.

International Society for Stem Cell Research (2006). Guidelines for the conduct of human embryonic stem cell research, version 1. http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf.

National Health and Medical Research Council (2004). Ethical guidelines on the use of assisted reproductive technology in clinical practice and research. http://www.nhmrc.gov.au/publications/synopses/e56syn.htm.

U.S. Food and Drug Administration (2007). Good clinical practice in FDA-regulated clinical trials. http://www.fda.gov/oc/gcp.

World Medical Association (2004). Declaration of Helsinki. http://www.wma.net/e/ethicsunit/helsinki.htm.

REFERENCES

Aalto-Setala, K., Conklin, B.R., and Lo, B. (2009). PLoS Biol., in press. 10.1371/journal.pbio.1000042.

Beauchamp, T.L., and Childress, J.F. (2001). Principles of Biomedical Ethics (New York: Oxford University Press), pp. 15–18.

Brown, S. (2007). Chron. High. Educ. *53*, A15.

Chong, S. (2006). Science *311*, 754–755.

Chong, S., and Normile, D. (2006). Science *311*, 22–25.

Cohen, C.B., Brandhorst, B., Nagy, A., Leader, A., Dickens, B., Isasi, R.M., Evans, D., and Knoppers, B.M. (2008). Cell Stem Cell *2*, 416–421.

Culliton, B. (1983). Science *220*, 31–35.

Daley, G.Q., Richter, L.A., Auerbach, J.M., Benvenisty, N., Charo, R.A., Chen, G., Deng, H.K., Goldstein, L.S., Hudson, K.L., Hyun, I., et al. (2007). Science *315*, 603–604.

Giudice, L., Santa, E., and Pool, R. (2007). Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research (Washington, D.C.: National Academies Press).

Gutman, A., and Thompson, D. (1996). Democracy and Disagreement (Cambridge: Harvard University Press).

Heng, B.C. (2006). Int. J. Gynaecol. Obstet. *95*, 302–304.

Holden, C. (2006). Science *311*, 928.

Hyun, I. (2006). Nature *442*, 629–630.

Kaveny, M.C. (2000). Theol. Stud. *61*, 280–313.

Lo, B., Chou, V., Cedars, M., Gates, E., Taylor, R., Wolf, L., Wagner, R., and Yamamoto, K. (2003). Science *301*, 921.

Lomax, G.P., Hall, Z.H., and Lo, B. (2007). PLoS Med. *4*, e114. 10.1371/journal.pmed.0040114.

Mathews, D.J., Donovan, P., Harris, J., Lovell-Badge, R., Savulescu, J., and Faden, R. (2006). Science *313*, 921–922.

National Academy of Sciences. (2005). Guidelines for Human Embryonic Stem Cell Research (Washington, D.C.: National Academies Press).

National Bioethics Advisory Commission. (1997). Cloning Human Beings (Rockville, MD: National Bioethics Advisory Commission).

National Bioethics Advisory Commission. (1999). Ethical Issues in Human Stem Cell Research (Rockville, MD: National Bioethics Advisory Commission).

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research (Washington, D.C.: U.S. Government Printing Office).

National Institutes of Health. (1994). Report of the Human Embryo Research Panel (Bethesda: National Institutes of Health).

National Research Council and Institute of Medicine. (2005). Guidelines for Human Embryonic Stem Cell Research (Washington, D.C.: National Academies Press).

Normile, D., Vogel, G., and Couzin, J. (2006). Science *311*, 156–157.

Rennie, D. (2008). In The Oxford Textbook of Clinical Research Ethics, E.J. Emanuel, C. Grady, R.A. Crouch, R.K. Lie, F.G. Miller, and D. Wendler, eds. (New York: Oxford University Press), pp. 795–804.

Revazova, E.S., Turovets, N.A., Kochetkova, O.D., Kindarova, L.B., Kuzmichev, L.N., Janus, J.D., and Pryzhkova, M.V. (2007). Cloning Stem Cells *9*, 432–449.

Skene, L. (2007). PLoS Med. *4*, e10. 10.1371/journal.pmed.0040010.

Spar, D. (2007). N. Engl. J. Med. *356*, 1289–1291.

Streiffer, R. (2008). Hastings Cent. Rep. *38*, 40–47.

Sugarman, J., and Siegel, A. (2008a). Cell Stem Cell *3*, 238–239.

Sugarman, J., and Siegel, A.W. (2008b). Science *322*, 379.

The President's Council on Bioethics. (2002). Human Cloning and Human Dignity: An Ethical Inquiry (Washington, D.C.: The President's Council on Bioethics).