Informed Consent and Human Embryonic Stem Cell Research

Regenerative Medicine in the 21st Century: Managing Uncertainty at the Global Level

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Overview

- Review of Some of the Problems
  - Omissions
  - Restrictions

- Ethical and Policy Considerations
  - Retrospective vs. Prospective Requirements
  - The Persistent Problem
Two Kinds of Problems

- Restrictions: The consent process included language that set limitations on the research in which the cell lines can be used.

- Omissions: The consent process failed to disclose important information about the research in which the cell lines would be used.
Problematic Omissions

1. The nature of the research, esp. with regard to activities that donors could find morally objectionable
2. That the cells will be cultured indefinitely and shared with other researchers
3. The voluntary nature of donation, esp. that medical care will not be affected either way
4. That the embryos will be destroyed in the research
5. Risks of regret and breach of confidentiality
Omissions: BresaGen

“if fertilization occurs with too many sperm or if embryos form but are not developing or living, scientific study of these may be undertaken.”

Omits:
1. The nature of the research, esp. with regard to activities that donors could reasonably find morally objectionable
2. The duration of the research and whether the materials will be shared with other researchers
3. The voluntary nature of donation, esp. that medical care will not be affected either way
4. That the embryos will be destroyed in the research
5. Risks of regret and breach of confidentiality
Omissions: Embryo Destruction

- UCSF only: “The embryos will not survive the stem cell derivation process”

The other forms did not clearly state that the embryo would be destroyed, although some described the derivation process in some detail.
Omissions: Risks

- UCSF and UW only: Loss of privacy if confidentiality of subjects’ records is breached

- All the forms omit to mention the possibility of regret if a donor changes his or her mind after the embryo is destroyed
Omissions: Chimeras

- All of the forms omit to tell donors that cells derived from their embryos might be used to make human/nonhuman chimeras.

- No direct, systematic data on donor attitudes, but...
## Omissions: Chimeras

<table>
<thead>
<tr>
<th>Source</th>
<th>Plants</th>
<th>Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTA (1987)</td>
<td>6.6 (out of 10) average acceptability with genetically modifying plant cells</td>
<td>5.3 with animal cells</td>
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<tr>
<td>Hoban et al. (1992)</td>
<td>23% opposed plant GE</td>
<td>53% opposed animal GE</td>
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<td>Rutgers Food Policy Institute (2002)</td>
<td>37% disapproved strongly or somewhat of GE plants; 22% said it was wrong</td>
<td>68% disapproved strongly or somewhat of GE animals; 55% said it was wrong</td>
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<td>Pew (2003)</td>
<td>6.08 mean comfort level</td>
<td>2.81 mean comfort level</td>
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<td>Pew (2003)</td>
<td>81% said that producing more affordable pharmaceuticals was a good reason to genetically modify plants; 14% said it was a bad reason</td>
<td>49% said that it was a good reason; 42% said it was a bad reason</td>
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<tr>
<td>Source</td>
<td>Finding</td>
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<td>UK Dept of Health Review of the HFEA (2006)</td>
<td>“[T]here is considerable public unease with the possible creation of embryos combining human and animal material....”</td>
<td></td>
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<td>Baylis (2009) on HFEA Consultation Process</td>
<td>“[T]he data from three of the four [HFEA] consultation mechanisms showed 67 percent, 48 percent, and 47 percent &quot;against&quot; humanesque cytoplasmic hybrid embryo research, compared with 17.5 percent, 35 percent, and 39 percent &quot;for&quot; such research. (There are no percentages reported for the deliberative work [with 44 participants]). “</td>
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Omissions: Chimeras

So:

- General tenor
- Systematic data on public attitudes towards species-mixing in other contexts (transgenic plants and animals)
- UK data on public attitudes towards chimeras, cybrid, and hybrids
Omissions: Chimeras

Of those not opposed to embryo research in general
Omissions: Chimeras

- Would be better to have direct, systematic data on *donor* attitudes towards chimeras

- Would be even better to know what the individual donors think. Hence, the importance of asking them during the consent process
Limitations: Cellartis

- "In this current project we only wish to develop a technique for longer-term cultivation of those cells which otherwise had been rejected. .... After the studies are completed all cells will be destroyed."

- August 9, 2001: Placed on the NIH Registry
- October 2003: Received permission to send cells to Canada without reconsenting
- April 2004: Received permission to reconsent donors regarding sharing of cells (1 couple withdrew)
- 2nd FOIA: NIH never received, much less reviewed, the form used to reconsent the donors.
Restrictions: Technion-Israel

- Consent form: “I am free to stop my participation in the experiment at all times.”

- MTA: “Upon termination of the Research Program, the Recipient and the Recipient Scientist shall return all Material to the Provider, or upon the Provider’s request, destroy the material and advise the Provider in writing of such destruction.”
“Because of these embryonic properties, certain experiments which would be controversial for whole human embryos would be controversial for these cell lines. In particular, two experiments that will not be performed with embryonic cell lines derived from this study are: (i) Intermixing of human embryonic cells with an intact embryo, either human or nonhuman....”
“Embryo”

- Scott Gilbert, Developmental Biology: “the study of animal development has traditionally been called embryology, referring to the fact that between fertilization and birth the developing organism is known as an embryo.”

- Merriam-Webster’s: “a vertebrate at any stage of development prior to birth or hatching”

- OED On-Line Dictionary: “The offspring of an animal before its birth (or its emergence from the egg)”
Restrictions: WARF

- **“Embryo”**
  - Merriam Webster’s: “an animal in the early stages of growth and differentiation that are characterized by cleavage, the laying down of fundamental tissues, and the formation of primitive organs and organ systems”

- **UW SCRO**
  - No introductions of WARF’s original lines through Carnegie Stage 23 (mice E16; rats E17.5; chicks E10; pigs E32.5)
  - Preference for performing introductions through Carnegie Stage 23 only using lines derived under consent forms that informed donors of this possibility (such as WA15 and WA16), when doing so does not hinder the research objectives.
Some Ethical Theses

- The Prospective Thesis: It is ethically permissible to derive a new hESC line from an embryo only if the embryo donors provide informed consent.

- The Weaker Retrospective Thesis: Other things equal, performing research with an already existing hESC line derived with higher quality consent is ethically preferable to using an already existing hESC line derived with lower quality consent.

- The Stronger Retrospective Thesis: It is ethically permissible to perform research using an already existing hESC line (even if anonymized) only if the embryo donors provided informed consent.
Implementations

- Implements the Prospective Thesis
  - US Common Rule extended to non-federally funded research
  - UK Human Fertilization and Embryology Authority (HFEA)
  - Canadian Institutes of Health Research Guidelines (CIHR)
  - Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells
  - California Institute for Regenerative Medicine (CIRM)
- Implements the Stronger Retrospective Thesis
  - Clinton’s 2000 NIH Guidelines
  - Bush’s 2001 Policy
  - Castle-DeGette Bill (US)
  - Obama’s 2009 Guidelines
  - UK Stem Cell Bank
  - Canadian Institutes of Health Research Guidelines (CIHR)
  - Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells
Arguments against the Stronger Retrospective Thesis

1. Until the National Academies’ Guidelines were published in 2005, no one had thought about informed consent in the context of procuring embryos for research.

- Objection
  - HERP (1994)
  - ASRM (1997)
  - NBAC (1999a)
  - NBAC (1999b)

HERP (1994): “These concerns [about consent to embryo donation] parallel concerns addressed by well-established ethical guidelines for all human research.”
Arguments against the Stronger Retrospective Thesis

2. All legitimate research uses of already existing anonymized cell lines are exempt from the U.S. federal human subjects regulations altogether (2004 OHRP Guidance)

- Objections
  - Overly narrow view of people’s rights and interests in even their run-of-the-mill donated human biological materials
  - Especially narrow view of people’s rights and interests in the disposition of their embryos
  - Goes much farther than people are willing to publicly go; poses significant risk to public trust in the hESC research enterprise
  - Consent form language can generate rights, both in terms of explicit restrictions and in terms of inferences donors might make about the scope of research based on omissions
  - Still would not be in compliance with guidelines and policies that implement the Stronger Retroactive Ethical Thesis
Embryos Are Not Viewed as Analogous to Residual Blood Spots

- Wendler (2006): In 4 out of 5 studies reviewed, 93-99% of people expressed a willingness to donate leftover samples for research; in the other 83% did.

- Syrop et al. (1995): 9% chose to donate surplus embryos for research; 44% chose discard over donate to research.

- McMahon et al. (2003): 10% probable, 34% possible that they would donate their surplus embryos for research.

- Bangsbøll et al. (2004): 57% expressed willingness to donate surplus embryos for hESC research.

- Lyerly and Faden (2007): 50% of couples with cryopreserved embryos would be willing to donate surplus embryos for hESC research.

- UK Dept. of Health Consultation (2005): “public opinion remains cautious and divided over the ethics of human embryo research”

- Costs of a false positive are vastly different.
Arguments against the Stronger Retrospective Thesis

3. Retrospectively requiring informed consent conflates a right with its remedy, i.e., even supposing it a fact that donor’s rights were violated, it does not follow that the correct remedy is to stop using their donations.

- Objections:
  - The donor’s rights are not violated when the embryo is procured, but only when the terms of the consent form are breached.
  - Thus, we can avoid violating the donor’s rights by complying with the terms of the consent form.
The Persistent Problem

- Pluripotent cells obtained from embryos → preference or requirement for informed consent

- Already existing, anonymized cell lines → generic consent or no consent

- Significant conceptual tension in trying to obtain informed consent for unanticipated, unspecified future uses
  - Informed waiver of informed consent
The Persistent Problem: Helpful Language

- George Daley, Children’s Hospital Boston

- “Once the eggs and embryos leave [Children’s Hospital Boston], all identifying information will be gone. We won’t know any longer which eggs and embryos are yours. Research on your eggs and embryos, or any embryonic stem cells made from them, cannot be stopped.”

- “Once an embryo or egg has been used in the research described in this consent form, you will no longer have any control over your embryo or egg.”
The Persistent Problem: Helpful Language

- “If embryonic cell lines are made, these lines may be used by many scientists doing stem cell research. Researchers may study many different conditions and illnesses.... [W]e cannot guarantee that research at outside institutions will be done with the same legal and ethical standards that are used at Children’s Hospital.”

- “Embryonic stem cell lines made in these experiments, or cells made from these stem cell lines, might also be used in other kinds of research. This might involve changing or exchanging the genes of the cells, or perhaps mixing human cells and nonhuman cells.”
The Persistent Problem: Helpful Language

“You may feel nervous or uncertain about the use of your materials to create embryonic stem cell lines for use in research. If so, you should not take part in this study.”
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