Appendix C
Ethical Considerations Regarding Stem Cell Research

The aim of ethics is to identify principles of right action that can guide us in thinking about what we may do, what we must do, and what we must refrain from doing. Knowledge of these principles is not acquired through the natural sciences, although scientific knowledge can have an important bearing on ethical questions. Ethical reflection focuses on both our doing and our being. In part it attends to "the good"—to what is good for human beings, the goods we seek to realize in our action, and what we must do to flourish and be fulfilled. In part it attends to "the right"—clarifying our duties and obligations. And in part it attends to "character"—to the sort of persons we should be, the virtues we seek to cultivate, and the vices we seek to discourage.

There is a complicated relationship between what we learn through science and how we reflect on ethical, normative matters. Knowledge acquired from the natural sciences helps us think through what we should do and be, but it cannot provide answers to our moral questions, nor does it necessarily provide any special expertise for thinking about them. Our ethical judgments, however, must inform both the kinds of questions we choose to address through science and the methods we adopt in obtaining knowledge of the natural world. Both the ends and the means of science demand ethical scrutiny and ultimately public oversight.

The biomedical applications of stem cell research promise great benefits. But we cannot think about stem cell research simply in terms of the health benefits it might confer. We should also consider how those health benefits will contribute to our flourishing as human beings. We should think about what sorts of virtues and vices the pursuit of those benefits—the actions involved in stem cell research—will encourage. And we should consider how our ethical judgments relating to biomedical research will reflect on and shape our character as persons and as a society. These questions, in turn, require us to think about the human condition, the human good, and the meaning of human dignity.

In this appendix, we offer a brief summary of the moral claims underlying the stem cell debate before examining the ethical problems and questions connected to each of the techniques for obtaining stem cells.

Fundamental Moral Claims

Broadly speaking, there are three moral claims made concerning ES cells by participants in the debate over stem cell research. The first relates to the moral status of human embryos, the second relates to the potential medical therapies that could result from ES cell research, and the third relates to the contributions the research may make to our scientific knowledge.[1]

The question of the moral status of the embryo is the most contested and the most important of these three claims, since the different answers as to what moral status ought to be accorded to embryos each put different limits on what uses of embryos are morally permissible. Many proponents of embryonic stem cell research believe that the early embryo is merely a "clump of cells," lacking the characteristics and properties that define human being and human personhood.[2] The early embryo does not have the appearance of a fully developed human being. It has no face for us to see—indeed, to see the embryo at all, we need a microscope. It has no limbs or organs. It cannot survive on its own. It lacks the integrated development of nerves, muscles, and bones that enable us to move and act in the world. It lacks a central nervous system—and so cannot think, cannot feel pain, and is not self-aware. If the possession of any of those capacities is the defining threshold for a being to merit moral standing, then the embryo can be treated the same way we might treat any other bit of tissue.

Many opponents of embryo destruction argue that it is wrong, or even dangerous, to claim that human dignity and a right to life attach only to those human organisms who fulfill specific criteria. While a developing embryo does not have the manifest capacities of a fully developed human being, many persons who are young, sick, disabled, or developmentally challenged also lack some of these capacities. We may erode our respect for the human dignity and rights of these individuals if we consider it conditional on the possession of specific capacities—capacities we are all prone to lack or lose in the course of a human life.

To counter the claim that the embryo is just a clump of cells deserving no respect, critics of embryonic stem cell research point to the standard position of both traditional and contemporary embryology, which is that a human life begins at fertilization.[3] Fertilization is the clearest moment of discontinuity in life: it is when a new organism, one with a unique genetic identity, exists for the first time. From fertilization and the first stages of cell cleavage, embryos exhibit a highly coordinated pattern of development in preparation for implantation in the uterus, and for further

development into an adult organism. (It is of course this very developmental potential of the human embryo that makes it such an attractive source of cells for research purposes.) Human embryos may appear to lack the characteristics of human beings, but our expanding scientific knowledge of their developmental capacities and underlying structures reveals their intricate and unique power to develop as human beings. Whether created naturally through sexual reproduction, or through IVF or other techniques such as cloning, human embryos are all human beings at a very early stage of development. Being human, regardless of one's capacities or stage of development, confers certain fundamental human rights, which are grounded in the respect we owe to the dignity and wellbeing of our fellow human beings. The most important of these rights—because it is the right necessary to secure all others—is the right to life, which demands that we do not kill other human beings.

Some people believe that the moral status of the embryo falls between the two opposing positions—that the embryo deserves "profound respect"[4] or "serious moral consideration"[5] as an early form of human life, though we need not accord to it the same rights as a fully developed person.[6] Furthermore, some argue that the moral status of human embryos may depend partly on such factors as their state of development, their origins, and the wishes of their parents. In practice, however, these intermediate ethical positions tend to justify policies that differ little from policies that assume the embryo has no special moral status.[7]

For those who see the embryo as no more than a clump of cells with similar moral status to other human tissues, the primary ethical concern with respect to harvesting ES cells from embryos would be obtaining informed consent from embryo donors, such as IVF patients. By contrast, for those who consider the embryo to be a human being with a moral status equal to that of a fully developed person, it is clear that destroying embryos for stem cell research would be a violation of the fundamental duty not to kill, which would override our duty to provide medical treatment.

The second moral claim about stem cells relates to the therapeutic promise of stem cell research—the possibility of relieving the suffering of many people afflicted by degenerative diseases and other conditions. Not only do the medical applications of stem cells offer us considerable potential benefits in terms of human health, but many claim that we are duty-bound to pursue the potential relief of human suffering. Although not everyone believes "the conservation of health…is without doubt *the primary good* and the foundation of all other goods of this life,"[8] nearly everyone would agree that health is *a good*. So there is little dispute that the potential

health benefits of stem cell research make its pursuit an important aim that ought to be carried out as far as is ethically permissible.

The third important moral claim about stem cells has to do with how studying them can contribute to our knowledge of biology. Beyond the foreseeable medical benefits that may come from stem cell therapies, scientific advances made possible by stem cell research may someday allow for as-yet-unforeseen technological and medical breakthroughs. Furthermore, the pursuit of scientific knowledge is often held to be a valuable undertaking that we should encourage for its own sake. Similarly, the freedom of scientific inquiry is a widely held principle that ought not to be constrained in the absence of overriding ethical concerns. But we must also bear in mind that, while advancing our scientific knowledge of biology is a valuable undertaking, the power this knowledge of biological development grants us may be fraught with new ethical dangers as well. Knowledge gained today for the goal of relieving suffering, or of avoiding the technical need to destroy embryos, may be used in the future for ethically questionable purposes, such as projects of human "enhancement." In this respect, our knowledge of nature can never be considered inert, neutral, or merely intrinsically valuable, as it always bears on human questions and pursuits, and, without proper guidance, has as much potential to degrade as to elevate us.

Sources of Stem Cells: An Ethical Analysis

In the following section, we examine the ethical implications of each of the techniques for obtaining stem cells. Some techniques are more problematic than others. These ethical considerations should bear on the actions of scientists and the decisions of policymakers.

Adult Stem Cells. There are a number of types of adult stem cells that can be procured from living, or recently deceased, children or adults and used for therapeutic purposes. This procedure is relatively uncontroversial, and has been carried out for decades for a variety of purposes. Acquiring adult stem cells from donors does raise such ethical issues as proper donor consent, but it does not raise the many novel ethical concerns surrounding the other sources described here. However, "adult stem cells" may also be derived from fetal tissue—the term merely denotes that they are not of embryonic origin, not that they come from fully mature adults. In fact, some kinds of adult stem cells can only be found in fetal tissue, making fetuses a possibly desirable source of tissue for some future therapies. These cells would raise somewhat similar ethical issues as those raised

by embryonic stem cells, though would likely be even more controversial given the later stage of development.

Embryos from IVF Clinics. The standard method of obtaining ES cells involves using cells extracted from the numerous embryos that are created during IVF that are not implanted and are subsequently frozen or discarded. Because the process of extracting these cells requires the destruction of the embryo, the practice is unacceptable to those who believe that human embryos have a moral status comparable to that of recognizably human beings. Even for those who accord the embryo more limited moral status, the large-scale destruction of embryos for research purposes may seem unsettling. Furthermore, obtaining informed consent from the IVF patients for whom the embryos were created represents an important ethical concern.

IVF patients who have had embryos created on their behalf, usually from their own sex cells, must face the difficult decision of the disposition of the unused embryos created during their IVF treatment. Some ethicists and scientists have argued that because these embryos are going to be discarded in any event, it would make practical and ethical sense to derive some benefit from them by using them for medical research or therapy. Others argue that these smallest human organisms deserve respect and protection, and there are programs to assist parents in donating their unused IVF embryos to other couples.[9]

Some IVF embryos go unused not because they are "surplus" but because they are deemed to be in some way deficient. A technique called preimplantation genetic diagnosis (PGD) is carried out by some IVF practitioners to test embryos for genetic conditions prior to implanting them in the patient's uterus. Embryos that are found to have genetic conditions that might reduce their viability or cause them to have an increased susceptibility to genetic diseases are not implanted; they are regarded as defective and are generally discarded.[10] Although it is unlikely that ES cells derived from embryos with genetic abnormalities would be useful in therapies, they are considered useful for the study of genetic disorders, which is one of the major medical applications of stem cell research.[11]

Non-Destructive Embryo Cell Extraction. It is possible to extract from an early stage of the embryo a single cell (blastomere), or a small number of cells, which may be able to generate a line of embryonic stem cells. Beyond the questions related to the feasibility of deriving stem cell lines from one or a very small number of biopsied cells,[12] the ethical questions related to this technique primarily concern its effect on the health of the

embryo and the possible long-term health effects of the procedure on the developing child. While embryo biopsy for PGD is a relatively common practice in IVF clinics, embryos biopsied for PGD tend to have a lower rate of implantation than ordinary IVF embryos,[13] which suggests that the procedure has a risk of killing the embryo. Furthermore, the procedure increases the risk of complications, including infant mortality, for twins and triplets.[14] Additionally, the procedure has only been used on human beings for just over twenty years, so long-term data on the health consequences of embryo biopsy are not available.[15]

Even in cases where embryo biopsy does not result in any noticeable harm to the embryo, the procedure raises ethical issues concerning the treatment of embryos as a means to another's ends. Even if no harm comes to the embryo, it is unjust to use human beings for purposes of no benefit to them without their consent (consent which, of course, the embryo cannot give). It may be argued, however, that this procedure could have benefits for the future child in the form of a line of immunologically compatible pluripotent stem cells that may be useful for future cell therapy. However, it is possible to obtain genetically matched stem cells for a newborn child from the newborn's umbilical cord blood (although it is not clear whether stem cells obtained from cord blood will have the same capacities as embryonic stem cells that could be obtained from embryo biopsy).[16]

An additional line of concern has to do with the possibility that the cells extracted from the early embryo may be totipotent, and therefore capable of developing as independent embryos. There is some uncertainty as to when during embryonic development the totipotency of individually extracted embryonic cells disappears. While there is some evidence that the cells of embryos of some mammalian species retain totipotency until the fifth division (that is, through the sixteen-cell stage),[17] scientists have not been able to isolate individual totipotent stem cells from early human embryos.[18] If it is the case that by the eight-cell stage, when the embryo biopsy would take place, the individual cells are sufficiently differentiated that they are no longer totipotent, then this procedure would avoid concerns over the destruction of early human life. On the other hand, if cells at this stage are still capable of growing as viable independent embryos, then there would be little ethical difference between this procedure and the harvesting of ES cells by destroying living embryos—though concerns over the risk to the blastocyst would remain.[19]

Organismically Dead Embryos. One alternative source of ES cells is embryos that have stopped dividing and can therefore be considered "organ-

ismically dead."[20] Just as many of the cells and organs in a person's body may continue to grow and function for a time after they have died, some of the individual cells in a dead embryo may be capable of further division if placed in a suitable environment. Harvesting ES cells from IVF embryos that have died despite best efforts to sustain their life would allow us to avoid the ethical problems associated with destroying or killing embryos in order to harvest ES cells. The paramount ethical question regarding this procedure is whether we can be certain that the embryos are in fact dead.

Ordinary criteria for organismic death refer to the failure of important organs, such as the brain or heart. The largely undifferentiated embryos discussed in this proposal have not yet developed such organs, so the most obvious criteria for determining whether the embryo has died is the absence of coordinated cell division. Such developmental arrest, if irreversible, can be used as an objective diagnostic criterion for death. Much as studies of irreversible coma have allowed for a definition of brain death in developed humans, studies of IVF embryos allow doctors to determine the duration of arrest beyond which an embryo, having failed to develop further, never resumes the normal path of growth and development and ultimately begins to decompose.[21] Stem cell lines derived from live cells in dead embryos are genetically normal and express the normal markers for ES cells,[22] and several cell lines have been shown to have normal developmental potential.[23]

The harvesting of ES cells from these embryos can be seen as analogous to end-of-life organ donation. One criticism of this analogy comes from the relative indifference of IVF practitioners to the death of embryos, in contrast to the concern of physicians caring for dying patients from whom organs might be harvested. Another concern is that this method might create an incentive for IVF practitioners to create surplus embryos in the hopes that some might be used in research. But proposals for this method include the restriction that it use only embryos created for reproductive purposes that have died despite the best efforts to keep them viable.[24]

Somatic Cell Nuclear Transfer (SCNT). Creating embryos through SCNT is another possible source of ES cells; it allows for the generation of ES cells that may be more safe and efficacious for therapy than ES cells derived from IVF embryos. In 2008, scientists claimed to have successfully created cloned human embryos from adult cells, although they were not able to isolate ES cells from the embryos, which were destroyed shortly after.[25] More recently, scientists in 2011 used a modified version of the SCNT procedure, in which the egg nucleus was not removed prior to adding the somatic cell, so that the resultant embryos and embryonic

stem cells had three sets of chromosomes rather than the normal two.[26] The researchers were then able to create human embryonic stem cell lines using these embryos—the first time human ES cell lines have been created using SCNT. While this experiment represents a major breakthrough, showing that human embryos and ES cell lines can be created through SCNT, the embryos and the ES cell lines were severely genetically abnormal due to the presence of the third set of chromosomes, making them unsuitable for either research or therapy. Because this procedure would create human embryos that are destroyed in order to harvest stem cells, it raises some of the same ethical concerns as other embryo-destroying techniques. Moreover, while it could be argued that the unused embryos created by IVF for reproductive purposes were not created with their destruction in mind, the generation of embryos through SCNT involves the deliberate creation of early human life for the express purpose of destroying and using it. In addition, SCNT raises ethical concerns regarding the exploitation and endangerment of egg donors.

Furthermore, SCNT is a cloning technique: the embryos created will have a genome identical with some donor human being. It thus opens the door not only to cloned embryos but to the birth of cloned human children. This raises vexing questions about the meaning of reproduction, the relationship between the generations, and the defense of human dignity—questions that have largely led to a public consensus in opposition to cloning. Some scientists and commentators eschew the label "cloning" for SCNT, arguing that it wrongly conflates SCNT with "reproductive cloning." But the act of SCNT, at least in theory, would create a cloned embryo that could then be used for the purposes of research, therapy, or reproduction. True, no successful implantation and pregnancy using a cloned human embryo produced through SCNT has been reported and verified to date. But the use of cloning to produce children may someday follow from the use of cloning for biomedical research, especially absent any system regulating or law prohibiting cloning to produce children. (There is no federal law in the United States forbidding human cloning, although a minority of states prohibit it.[27])

Interspecies SCNT. One alternate form of SCNT that would obviate the need for human egg donors is called interspecies SCNT; it involves the transfer of a human nucleus into an enucleated animal oocyte. Some scientists have raised doubts about the technical feasibility of this procedure.[28] But some countries, including the United Kingdom, have funded research on the creation of human-animal "cybrids," or cytoplasmic hybrids, so

named because they result from the use of the interspecies SCNT procedure to combine the cytoplasm of an animal oocyte and the nucleus of a human cell.[29] While the use of interspecies SCNT to obtain pluripotent stem cells would alleviate concerns over the exploitation of egg donors, it remains a form of cloning and raises at least as many ethical concerns regarding reproduction and human dignity as does conventional SCNT.

Altered Nuclear Transfer (ANT). ANT involves the creation of "biological artifacts" through a modified version of the technique of nuclear transfer.[30] In ANT, the starting materials used in the technique (the adult cell nucleus and/or the cytoplasm of the oocyte) are altered before being combined so that the product of the procedure is not capable of establishing the integrated unity that characterizes an embryo. Because these "artifacts" contain pluripotent but not totipotent cells, they are not capable of developing as embryos, and therefore, proponents of this method argue, harvesting stem cells from them does not raise the same ethical issues surrounding the harvesting of stem cells from human embryos. The central ethical question related to this proposal is whether we ought to consider these biological artifacts to be non-organismal and therefore non-human entities, or whether there is a kind of similarity to natural embryos such that they have intrinsic moral value. Proponents of ANT argue that since the modifications made to the nucleus (or the cytoplasm of the egg) to prevent embryogenesis are made *before* it is transferred to the oocyte, and since the artifact created by the procedure has cells that are not totipotent, at no point is the newly created artifact ever an embryo.[31] But if, as some critics contend, ANT actually creates altered but disordered embryos, then it raises questions both about the ethics of destroying human embryos and about the ethics of intentionally creating defective embryos. Also, like SCNT, ANT depends on human egg donors, raising ethical concerns about their possible exploitation and endangerment.[32]

In the version of ANT known as the ANT-Cdx2 procedure, the expression of the gene Cdx2 is preemptively altered. In natural embryogenesis, the expression of Cdx2 is an early indicator of integrated development and orderly cell differentiation, and Cdx2 is an important factor in the formation of the trophectoderm—a structure essential for normal embryonic development and implantation.[33] When Cdx2 is "silenced," or interfered with in such a way that it is not expressed by the cell, it becomes impossible for the "biological artifact" to develop in the manner of a natural embryo. Whether the entity created by the ANT-Cdx2 procedure can be considered a kind of defective embryo, or rather is simply a mass of pluripotent stem cells,

depends on a number of complex philosophical and scientific questions. For instance, the precise role of the Cdx2 gene in embryonic development is still subject to some controversy: while it is clear that Cdx2 is essential for the proper functioning of the trophectoderm and for the specification of the axial body plan in the early embryo,[34] there remains some dispute over the extent to which Cdx2 is responsible for directing the organization of early embryonic cells.[35] Furthermore, some philosophers have raised questions as to whether or not the entities created by procedures like ANT-Cdx2 are sufficiently disorganized to be considered non-embryonic entities.[36] More scientific research in animal models may help to clarify certain issues, such as those related to the precise biological role of genes like Cdx2, including the potential reversibility or irreversibility of the intervention.[37] But to some extent, there are conceptual questions—what do we consider an embryo to be?—that will call for continued debate.

In another version of the procedure, Altered Nuclear Transfer with Oocyte-Assisted Reprogramming (ANT-OAR), rather than silencing or removing from the nucleus the genetic elements that are associated with totipotency, factors associated with pluripotency are *added* to the nucleus. In this way, the procedure aims at directly reprogramming the cell to a pluripotent state. In essence, instead of suppressing some factors required for totipotency, this procedure expresses only the factors required for pluripotency. While the ANT-Cdx2 technique may be thought of as an alternative version of SCNT where the artifact created is not an embryo, ANT-OAR is more similar to other techniques for reprogramming adult cells to a pluripotent state. The moral status of the artifact produced by ANT-OAR would arguably be very similar to an induced pluripotent stem cell, as there is no dispute that the cells produced would never have any of the characteristics of embryos (see below for an ethical analysis of induced pluripotent stem cells).

Regardless of the particular techniques that already exist, ANT is a broad conceptual proposal and is not tied to any specific candidate genes or factors. As knowledge of developmental biology increases, it may be that a number of genes or gene combinations will provide reliable and effective intervention, together with solid evidence for the kind of preemptive alteration envisioned in the ethical argument in support of ANT.

Embryonic Stem Cell Fusion. Researchers have found that fusing an ES cell with an ordinary adult (somatic) cell can transform the adult cell into a cell that will be pluripotent, just like an ES cell.[38] While this procedure does require the use of ES cells, it could allow for the creation of a limitless

number of new pluripotent stem cell lines without using or destroying any more human embryos—since the procedure could, in theory, rely on existing stem cell lines alone. However, this proposal faces difficult technical challenges—namely, the fact that the resulting cells have an abnormal number of chromosomes, which makes them infeasible for clinical use. Still, the knowledge gained through these cell-fusion experiments helped to make possible the creation of induced pluripotent stem cells, discussed below.

Induced Pluripotent Stem (iPS) Cells. Induced pluripotent stem cells are perhaps the most prominent alternative source of stem cells proposed for therapy and research.[39] Derived from many forms of adult cells (although cells derived from fetal tissue have so far been most effective), iPS cells can be easily procured without risk to the donor, and without generating or destroying any human embryos. Unlike ordinary adult stem cells, induced pluripotent stem cells may very well have the same efficacy as embryonic stem cells. And like SCNT-created cells, and in contrast to ES cells extracted from unused IVF embryos, iPS cells derived from a patient's own cells would in principle be fully compatible with the patient's immune system. But unlike SCNT, the procedure for creating iPS cells does not require the generation of embryos, and unlike either SCNT or ANT, the procedure would not require the procurement of human egg cells.

While the use of iPS cells may sidestep many of the questions related to the moral status of the human embryo, other important ethical concerns remain. For instance, pluripotent stem cells can be used in a cloning technique known as "tetraploid complementation" (the technical details of which we describe in Appendix B). The relative ease with which researchers can introduce genetic modifications to embryonic stem cells has made the creation of genetically engineered mice from embryonic stem cells using tetraploid complementation a common practice among molecular biologists.[40] If iPS cell technology can make cells that are equivalent to embryonic stem cells, tetraploid complementation may prove to be an efficient way not only to perform human cloning, but also human genetic engineering.[41] Moreover, creating genetically identical individuals from pluripotent stem cells falls outside a number of current laws that prohibit reproductive cloning but define cloning only in terms of SCNT.[42]

An additional reproductive technology that may be enabled by iPS cells is the generation of sex cells (sperm and eggs) for treating infertility.[43] One advantage of this technique would be that it could reduce the reliance of many infertility-treatment patients on donated sex cells, the use of which raises its own set of ethical concerns.[44] On the other hand,

the development of this technology would raise ethical concerns related to the consequences and risks for embryos and children created using stem cell-derived sex cells. Given the uncertainties surrounding the long-term consequences of reproduction using stem cell-derived sex cells, by employing this technology we are inevitably subjecting future offspring to risks that they obviously had no chance to consent to. Furthermore, research on deriving sex cells from stem cells would require the creation of embryos from the derived sex cells in order to test their functionality.[45] In both its final form as a technology for assisting reproduction and in the process of developing this technology, deriving sex cells from stem cells will essentially involve performing experiments on human organisms without their consent, which is deeply ethically troubling.[46]

Conclusion

A wide range of ethical complications has come to light since interest first arose in the medical applications of stem cells. These problems have chiefly related to the means of procuring stem cells, especially techniques involving the destruction of human embryos. Other ethical problems have included the possibility of human cloning and the potential exploitation of embryo and egg donors, as well as the questions raised by the new alternative techniques for obtaining stem cells.

The ethical acceptability of a particular research technique or medical procedure is not a matter for science alone to decide—it is not only a matter of empirical fact but also of moral judgment. Such moral judgments are not the exclusive domain of scientists or of experts in bioethics. Insofar as these matters impinge on public policy and on questions of the human future, they are deserving of public consideration and they rightly become matters not just of private conscience but of political deliberation. In the next appendix, we turn to matters of public policy and law.

Notes

1. We are indebted to Chapter 3 of the President's Council on Bioethics (PCBE) report *Monitoring Stem Cell Research*, Washington, D.C., 2004, for its analysis of the moral claims related to embryonic stem cell research that helped lay the foundations of our thinking on this question.

2. See, for example, Michael S. Gazzaniga, *The Ethical Brain: The Science of Our Moral Dilemmas*, 2nd ed. (New York: Harper Perennial, 2006).

3. William J. Larsen *et al.*, *Human Embryology*, 3rd ed. (New York: Churchill Livingstone, 2001). See also, Neil A. Campbell and Jane B. Reece, *Biology*, 7th ed. (San

Francisco: Pearson, 2005), 987-1000.

4. Department of Health, Education, and Welfare, Ethics Advisory Board, "Report of the Ethics Advisory Board," *Fed. Reg.* 44 (June 18, 1979): 35,056.

5. National Institutes of Health, *Report of the Human Embryo Research Panel* (Bethesda, Md.: NIH, 1994), available at http://bioethics.georgetown.edu/pcbe/reports/past_commissions/.

6. See, for example, Michael Sandel, "Statement of Professor Sandel," in PCBE, *Human Cloning and Human Dignity: An Ethical Inquiry*, Washington, D.C., 2002, available at http://bioethics.georgetown.edu/pcbe/reports/cloningreport/appendix.html; and Michael J. Sandel, "Embryo Ethics—The Moral Logic of Stem-Cell Research," *New England Journal of Medicine* 351, no. 3 (2004): 207-209.

7. PCBE, *Monitoring Stem Cell Research*, Washington, D.C., 2004, 83-84, available at http://bioethics.georgetown.edu/pcbe/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.

8. René Descartes, *Discourse on Method*, trans. Richard Kennington (Newburyport, Mass.: Focus Publishing, 2007), 49 (emphasis added).

9. John Harris, "Stem Cells, Sex and Procreation," *Cambridge Quarterly of Healthcare Ethics* 12, no. 4 (2003): 353-371. See also Jacqueline Pfeffer Merrill, "Embryos in Limbo," *The New Atlantis*, no. 24, Spring 2009, 18-28, http://www.thenewatlantis.com/publications/embryos-in-limbo.

10. For a review of the technical and ethical issues surrounding the practice of PGD, see PCBE, *Reproduction and Responsibility*, Washington, D.C., 2004, Chapter 3, available at http://bioethics.georgetown.edu/pcbe/reports/reproductionandresponsibility/chapter3.html.

11. For a review of the scientific applications of ES cells derived from embryos found to have genetic disorders by PGD, see D. Ben-Yosef, M. Malcov, and R. Eiges, "PGD-Derived Human Embryonic Stem Cell Lines as a Powerful Tool for the Study of Human Genetic Disorders," *Molecular and Cellular Endocrinology* 282, no. 1-2 (2008): 153-158.

12. Scientists from Advanced Cell Technologies have published a protocol for deriving human ES cells from single blastomeres. See Irina Klimanskaya *et al.*, "Derivation of Human Embryonic Stem Cells from Single Blastomeres," *Nature Protocols* 2, no. 8 (2007): 1963-1972.

13. Claire Basille *et al.*, "Preimplantation Genetic Diagnosis: State of the Art," *European Journal of Obstetrics & Gynecology and Reproductive Biology* 145, no. 1 (2009): 9-13.

14. I. Liebaers *et al.*, "Report on a Consecutive Series of 581 Children Born After Blastomere Biopsy for Preimplantation Diagnosis," *Human Reproduction* 25, no. 1 (2009): 275-282.

15. The first human pregnancies using embryos biopsied for PGD were reported in A. H. Handyside *et al.*, "Pregnancies from Biopsied Human Preimplantation Embryos

Sexed by Y-Specific DNA Amplification," *Nature* 344, no. 6268 (1990): 7680-770. See also Liebaers *et al.*, "Report on a Consecutive Series of 581 Children," 275-282.

16. PCBE, *Alternative Sources of Pluripotent Stem Cells*, Washington, D.C., 2005, Section II, available at http://bioethics.georgetown.edu/pcbe/reports/white_paper/alternative_sources_white_paper.pdf.

17. Aneta Swuinska *et al.*, "Blastomeres of the Mouse Embryo Lose Totipotency after the Fifth Cleavage Division: Expression of *Cdx2* and *Oct4* and Developmental Potential of Inner and Outer Blastomeres of 16- and 32-Cell Embryos," *Developmental Biology* 322, no. 1 (2008): 133-144.

18. Douglas A. Melton and Chad Cowen, "'Stemness': Definitions, Criteria, and Standards," in *Essentials of Stem Cell Biology*, 2nd ed., ed. Robert Lanza *et al.* (Burlington, Mass.: Elsevier Academic Press, 2009), xxiii.

19. PCBE, *Alternative Sources of Pluripotent Stem Cells*, 29.

20. For a discussion of the scientific details of this procedure, first proposed by Witherspoon Council chairman Donald W. Landry and his Columbia University colleague Howard A. Zucker, see PCBE, *Alternative Sources of Pluripotent Stem Cells*, 8-23. See also Donald W. Landry and Howard A. Zucker, "Embryonic Death and the Creation of Human Embryonic Stem Cells," *The Journal of Clinical Investigation* 114, no. 9 (2004): 1184-1186.

21. Donald W. Landry *et al.*, "Hypocellularity and Absence of Compaction as Criteria for Embryonic Death," *Regenerative Medicine* 1, no. 3 (2006): 367-371.

22. Svetlana Gavrilov *et al.*, "Derivation of Two New Human Embryonic Stem Cell Lines from Nonviable Human Embryos," *Stem Cells International* 2011, article ID 765378.

23. Xin Zhang *et al.*, "Derivation of Human Embryonic Stem Cells from Developing and Arrested Embryos," *Stem Cells* 24, no. 12 (2006): 2669-2676.

24. PCBE, *Alternative Sources of Pluripotent Stem Cells*, 14.

25. The first successful attempt to clone human embryos using SCNT was reported in Andrew J. French *et al.*, "Development of Human Cloned Blastocysts Following Somatic Cell Nuclear Transfer with Adult Fibroblasts," *Stem Cells* 26, no. 2 (2008): 485-493. While the authors did manage to successfully create a human embryo, they were unable to derive an embryonic stem cell line from it. Previously, Hwang Woo Suk had claimed to have derived patient-specific ES cells from cloned blastocysts, but it was later shown that he had fabricated his results. Hwang Woo Suk *et al.*, "Patient-specific Embryonic Stem Cells Derived from Human SCNT Blastocysts," *Science* 308, no. 5729 (2005): 1777-1783.

26. Scott Noggle *et al.*, "Human Oocytes Reprogram Somatic Cells to a Pluripotent State," *Nature* 478, no. 7367 (2011): 70-77.

27. National Conference of State Legislators, "Human Cloning Laws," http://www.ncsl.org/IssuesResearch/Health/HumanCloningLaws/tabid/14284/Default.aspx.

28. Young Chung *et al.*, "Reprogramming of Human Somatic Cells Using Human and Animal Oocytes," *Cloning and Stem Cells* 11, no. 2 (2009): 213-223. See Appendix A for more details on the technical feasibility of this procedure.

29. United Kingdom, Parliament, Human Fertilization and Embryology Act (2008), c. 22, http://www.legislation.gov.uk/ukpga/2008/22/contents.

30. A detailed review of the scientific issues surrounding ANT appears in Appendix A.

31. PCBE, *Alternative Sources of Pluripotent Stem Cells*, 36-50.

32. William Hurlbut, member of the Witherspoon Council and the author of the ANT proposal, opposes the use of potentially dangerous superovulation techniques to procure human egg cells for the sole and specific objective of obtaining eggs for research purposes, arguing for the use of alternative sources of human egg cells. See William B. Hurlbut, "Framing the Future: Embryonic Stem Cells, Ethics and the Emerging Era of Developmental Biology," *Pediatric Research* 59, no. 4 (2006): 4R-12R.

33. Hathaitip Sritanaudomchai *et al.*, "CDX2 in the Formation of the Trophectoderm Lineage in Primate Embryos," *Developmental Biology* 335 (2009): 179-187.

34. Kallayanee Chawengsaksophak *et al.*, "Cdx2 is essential for axial elongation in mouse development," *Proceedings of the National Academy of Sciences* 101, no. 20 (2004).

35. Guangming Wu *et al.*, "Initiation of Trophectoderm Lineage Specification in Mouse Embryos is Independent of Cdx2," *Development* 137, no. 24 (2010): 4159-4169. According to this paper, Cdx2 has a very important role, but is not absolutely necessary for the differentiation of the trophectoderm, suggesting that Cdx2-deficient embryos do retain some of the important developmental capacities that are characteristic of normal embryos. A 2006 paper published in *Science* claimed that Cdx2 was responsible for specifying trophectoderm cells from the 2-cell stage, but the lead author of the study, Kaushik Deb, was later found to have fabricated data, leading to the retraction of the paper. Kaushik Deb *et al.*, "Cdx2 Gene Expression and Trophectoderm Lineage Specification in Mouse Embryos," *Science* 311, no. 5763 (2006): 992-996.

36. See the 2005 *Communio* debate on ANT, available at http://www.communio-icr.com/ant.htm. See in particular Adrian J. Walker, "Altered Nuclear Transfer: A Philosophical Critique," *Communio* 31, Winter 2004, http://communio-icr.com/articles/PDF/walker31-4.pdf; and David L. Schindler, "*Veritatis Splendor* and the Foundations of Bioethics: Notes Towards an Assessment of Altered Nuclear Transfer and Embryonic (Pluripotent) Stem Cell Research," *Communio* 32, Spring 2005, http://communio-icr.com/articles/PDF/DLS32-1.pdf.

37. In theory, some of the gene-knockdown techniques used for ANT might be reversible through various kinds of "rescue-experiments." A recent paper describing the role of Cdx2 in early cellular differentiation found that by co-injecting both the anti-sense Cdx2 along with synthetic Cdx2 mRNA into the zygote, the embryo would develop normally. It is not clear whether or not an "embryo" with *maternal* Cdx2 knocked down prior to fertilization could be rescued in this way, although it is a very important question that has surprisingly not received much scientific attention. The PCBE White Paper asks whether the procedure is reversible, as does bioethicist Søren Holm in a

2008 article (Søren Holm, "'New Embryos'—New Challenges for the Ethics of Stem Cell Research," *Cells Tissues Organs* 187 (2008): 257-262). Agnieszka Jedrusik *et al.*, "Maternally and Zygotically Provided Cdx2 Have Novel and Critical Roles for Early Development of the Mouse Embryo," *Developmental Biology* 344, no. 1 (2010): 66-78.

38. Chad A. Cowan *et al.*, "Nuclear Reprogramming of Somatic Cells After Fusion with Human Embryonic Stem Cells," *Science* 309, no. 5739 (2005): 1369-1373.

39. A detailed review of the scientific issues surrounding iPS cells appears in Appendix A.

40. Anthony J. F. Griffiths, Susan R. Wessler, Richard C. Lewontin, and Sean B. Carroll, *Introduction to Genetic Analysis* 9th ed. (New York: W. H. Freeman and Company, 2008), 748-750.

41. Hans-Werner Denker, "Human Embryonic Stem Cells: The Real Challenge for Research as Well as for Bioethics Is Still Ahead of Us," *Cells Tissues Organs* 187 (2008): 250-257. Some ethicists have even argued that the ability of embryonic stem cells to be "reconstituted" into viable embryos through the tetraploid complementation technique shows that the harvesting of embryonic stem cells does not really destroy any embryos, since the technique allows the stem cells to be restored into embryos. Regardless of whether the "reconstituted embryo" would really be the same individual as the original, this technique also requires the destruction of the tetraploid embryo in order to work. See Katrien Devolder and Christopher M. Ward, "Rescuing Human Embryonic Stem Cell Research: The Possibility of Embryo Reconstitution After Stem Cell Derivation," *Metaphilosophy* 38, no. 2-3 (2007): 245-263.

42. Bernard Lo *et al.*, "Cloning Mice and Men: Prohibiting the Use of iPS Cells for Human Reproductive Cloning," *Cell Stem Cell* 6, no. 1 (2010): 16-20.

43. ES cells may also be used to generate sex cells that could then be used to treat infertility, but iPS cells would allow for infertility patients to have sex cells generated that would be genetically equivalent to their own sex cells. Given the relative availability of donated sex cells and embryos, the advantage of generating sex cells from iPS cells would be the ability for a patient to have sex cells that are genetically equivalent to his or her own natural sex cells, rather than relying on donated sex cells.

44. For a review of the ethical concerns raised by creating donor-conceived offspring, see Cheryl Miller, "Donated Generation," *The New Atlantis*, no. 21, Summer 2008, 27-44, http://www.thenewatlantis.com/publications/donated-generation; and Elizabeth Marquardt, Norval D. Glenn, and Karen Clark, *My Daddy's Name Is Donor*, Commission on Parenthood's Future (New York: Institute for American Values, 2010), http://familyscholars.org/my-daddys-name-is-donor-2/.

45. Debra J. H. Matthews *et al.*, "Pluripotent Stem Cell-Derived Gametes: Truth and (Potential) Consequences," *Cell Stem Cell* 5, no. 1 (2009): 11-14.

46. For a discussion of some of the ethical issues surrounding reproductive technologies and iPS cells, see Matthew Hoberg, "The Moral Frontiers of Stem Cell Research," *The Public Discourse*, December 6, 2010, http://www.thepublicdiscourse.com/2010/12/2035; as well as Bernard Lo *et al.* "Cloning Mice and Men: Prohibiting the Use of iPS Cells For Reproductive Cloning," 16-20.