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Stem Cell Research: Federal Research Funding and Oversight

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Summary

Embryonic stem cells have the ability to develop into virtually any cell in the body, and they may have the potential to treat medical conditions such as diabetes and Parkinson's disease. In August 2001, President Bush announced that for the first time, federal funds would be used to support research on human embryonic stem cells, but funding would be limited to "existing stem cell lines." NIH has established a registry of 78 human embryonic stem cell lines that are eligible for use in federally funded research, but only 21 cell lines are currently available. Scientists are concerned about the quality and longevity of these 21 stem cell lines. NIH Director Elias Zerhouni stated before a Senate subcommittee in March 2007 that research advancement requires access to new human embryonic stem cell lines.

Some have argued that adult stem cells (from bone marrow or umbilical cord blood) should be pursued instead of embryonic stem cells because they believe the derivation of stem cells from embryos is ethically unacceptable. The NIH Director and many other scientists believe adult stem cells should not be the sole target of research because of important scientific and technical limitations. Reports issued by NIH and the Institute of Medicine state that both embryonic and adult stem cell research should be pursued. Some scientists are exploring the possibility of obtaining human embryonic stem cells that bypass the destruction of living human embryos. The President's Council on Bioethics cited four potential alternative sources of human embryonic stem cells in a May 2005 paper. A number of pro-life advocates support stem cell research; those opposed are concerned that stem cell isolation requires embryo destruction.

On January 11, 2007, the House passed H.R. 3 (DeGette) on a vote of 253 to 174. H.R. 3 would allow federal support of research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo, and thus negate the August 2001 Bush stem cell policy limitation. On April 11, 2007, the Senate passed S. 5 (Reid), which has the same text as H.R. 3 and an additional section supporting research on alternative human pluripotent stem cells. The Senate also passed S. 30 (Coleman) on April 11, 2007. Unlike H.R. 3 and S. 5, S. 30 provides support only for research on alternative human pluripotent stem cells. (The 109th Congress passed legislation identical to H.R. 3, H.R. 810 (Castle), but President Bush vetoed it, the first veto of his presidency. An attempt in the House to override the veto was unsuccessful.) On the related issue of human cloning, S. 812 (Hatch) would ban human reproductive cloning but allow for the therapeutic uses of the technique provided that a number of ethical requirements are observed. In contrast, the Weldon bill (which passed the House in the 107th and 108th Congresses) and S. 1036 (Brownback) would ban not only reproductive applications, but also research on therapeutic uses, which has implications for stem cell research. Advocates of the legislative ban say that allowing any form of human cloning research to proceed raises serious ethical issues, and will inevitably lead to the birth of a baby who is a human clone. Critics argue that the measure would curtail medical research and prevent Americans from receiving life-saving treatments created overseas. This report will be updated as needed.

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Introduction

On August 9, 2001, President Bush announced that for the first time federal funds would be used to support research on human embryonic stem cells. However, funding would be limited to stem cell lines that had been created prior to the date of the policy announcement. Research involving human embryonic stem cells raises a number of ethical issues because the stem cells are located inside the embryo, and the process of removing them destroys the embryo.[1]

A relatively small amount of federal funding has been used to support human embryonic stem cell research. The National Institutes of Health (NIH) identified 78 human embryonic stem cell lines that would be eligible for use in federally funded research, but most were found to be either unavailable or unsuitable for research. Twenty-one cell lines are currently available under the Bush policy. Scientists are concerned about the quality and longevity of these 21 stem cell lines. Many believe research advancement requires the use of new human embryonic stem cell lines.

The Director of NIH, Elias Zerhouni, stated in a hearing on March 19, 2007, before the Senate Labor, Health and Human Services (HHS), Education, and Related Agencies Appropriations Subcommittee that "It's not possible for me to see how we can continue the momentum of science and research with the stem cell lines we have at NIH that can be funded."[2] When asked if other avenues of research should be pursued instead, Dr. Zerhouni stated that "the presentations about adult stem cells holding as much or more potential than embryonic stem cells, in my view, do not hold scientific water. I think they are overstated."[3] He noted that competitors in Europe, China, and India are investing heavily in human embryonic stem cell research. "I think it is important for us not to fight with one hand tied behind our back here. I think it's time to move forward on this area. It's time for policy makers to find common ground, to make sure that NIH does not lose its historical leadership.... To sideline NIH on such an issue of importance in my view is shortsighted."[4]

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[1] For further information, see CRS Report RL33554, *Stem Cell Research: Ethical Issues*, by Judith A. Johnson and Erin D. Williams.

[2] Drew Armstrong, "NIH Chief's Opinion on Stem Cell Research Goes Afield of White House Policy," *CQ Today*, Mar. 19, 2007.

[3] Ibid.

[4] John Reichard, "Zerhouni Makes Strong Case Against Bush Policy on Stem Cells, NIH (continued...)

Several states, such as California, Connecticut, Illinois, Maryland, and New Jersey, have responded by moving forward with their own initiatives to encourage or provide funding for stem cell research, and many others are considering similar action.[5] Proponents of these state stem cell research initiatives want to remain competitive, as well as prevent the relocation of scientists and biotechnology firms to other states or overseas. However, without the central direction and coordinated research approach that the federal government can provide, many are concerned that the states' actions will result in duplication of research efforts among the states, a possible lack of oversight for ethical concerns, and ultimately a loss of U.S. preeminence in this important area of basic research.

The new majority leadership of the 110th Congress indicated that it would address the topic of stem cell research early in the first session. H.R. 3 (DeGette) was introduced on January 5, 2007, with 211 cosponsors, and passed the House on January 11, 2007. The bill would allow federal support of research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo, and thus negate the August 2001 Bush stem cell policy limitation. During the first session of the 109th Congress, the House passed identical legislation, H.R. 810 (Castle), in May 2005. In July 2006, the Senate passed H.R. 810 and President Bush immediately vetoed it, the first veto of his presidency. An attempt in the House to override the veto was unsuccessful.

Basic Research and Potential Applications

Most cells within an animal or human being are committed to fulfilling a single function within the body. In contrast, stem cells are a unique and important set of cells that are not specialized. Stem cells retain the ability to become some or all of the more than 200 different cell types in the body, and thereby play a critical role in repairing organs and body tissues throughout life. Although the term stem cells is often used in reference to these repair cells within an adult organism, a more fundamental variety of stem cells is found in the early-stage embryo. Embryonic stem cells may have a greater ability to become different types of body cells than adult stem cells.

Embryonic Stem Cells from IVF Embryos or Fetal Tissue

Embryonic stem cells were first isolated from mouse embryos in 1981 and from primate embryos in 1995. Animal embryos were the only source for research on embryonic stem cells until November 1998, when two groups of U.S. scientists announced the successful isolation of human embryonic stem cells. One group, at the University of Wisconsin, derived stem cells from five-day-old embryos produced

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[4] (...continued)
Funding," *CQ Today*, Mar. 19, 2005.

[5] For further information, see CRS Report RL33524, *Stem Cell Research: State Initiatives*, by Judith A. Johnson and Erin D. Williams.

via *in vitro* fertilization (IVF).[6] The work is controversial because the stem cells are located within the embryo and the process of removing them destroys the embryo. Many individuals who are opposed to abortion are also opposed to research involving embryos. The second group, at Johns Hopkins University, derived stem cells with very similar properties from five- to nine-week-old embryos or from fetuses obtained through elective abortion.[7] Both groups reported the human embryos or fetuses were donated for research following a process of informing one or more parents and obtaining their consent. The cells removed from embryos or fetuses were manipulated in the laboratory to create embryonic stem cell lines that may continue to divide for many months to years. The vast majority of research on human embryonic stem cells, both in the United States and overseas, utilizes cell lines derived via the University of Wisconsin method.

Embryonic Stem Cells Obtained via SCNT (Cloning)

Another potential source of embryonic stem cells is somatic cell nuclear transfer (SCNT), also referred to as cloning.[8] For certain applications, stem cells derived from cloned embryos may offer the best hope for understanding and treating disease. In SCNT the nucleus of an egg is removed and replaced by the nucleus from a mature body cell, such as a skin cell obtained from a patient. In 1996, scientists in Scotland used the SCNT procedure to produce Dolly the sheep, the first mammalian clone.[9] When SCNT is used to create another individual, such as Dolly, the process is called reproductive cloning. In contrast, scientists interested in using SCNT to create cloned stem cells would allow the cell created via SCNT to develop for a few days, and then the stem cells would be removed for research. Stem cells created via SCNT would be genetically identical to the patient, and thus would avoid any tissue rejection problems that could occur if the cells were transplanted into the patient.

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[6] The IVF embryos were originally created for the treatment of infertility. Excess embryos are often frozen for future use. A couple may elect to discard their excess embryos, donate the embryos for research, or allow another couple to adopt an embryo. The Society for Assisted Reproductive Technology and RAND conducted a survey of more than 430 infertility clinics to determine the number of frozen embryos in the United States; 340 clinics responded to the survey. Nearly 400,000 embryos have been frozen and stored since the late 1970s. The vast majority of embryos are being held to help couples have children at a later date. Patients have designated 2.8%, or about 11,000 embryos, for research. Scientists estimate these 11,000 could form up to 275 stem cell lines, perhaps much less [http://www.rand.org/pubs/research_briefs/RB9038/index1.html].

[7] Scientists and physicians use the term "embryo" for the first eight weeks after fertilization, and "fetus" for the ninth week through birth. In contrast, the Department of Health and Human Services (HHS) regulations define "fetus" as "the product of conception from the time of implantation" (45 C.F.R. § 46.203).

[8] A somatic cell is a body cell. In contrast, a germ cell is an egg or sperm cell.

[9] Dolly was euthanized in February 2003 after developing a lung infection. Some claim her death at six years was related to being a clone, but her ailment may also have occurred because she was raised indoors (for security reasons) rather than as a pastured sheep, which often live to 12 years of age. G. Kolata, "First Mammal Clone Dies," *New York Times*, Feb. 15, 2003, p. A4.

Creating stem cells using SCNT for research purposes is often referred to as therapeutic cloning.

Charges of ethical and scientific misconduct have clouded the reputation of scientists involved in deriving stem cells from cloned human embryos. In February 2004, scientists at the Seoul National University (SNU) in South Korea announced the first isolation of stem cells from a cloned human embryo. In May 2005 they announced major advances in the efficiency of creating cloned human embryos and in isolating human stem cells from the cloned embryos. Concerns about the achievements of the SNU group arose in November 2005 when a U.S. co-author of the 2005 paper accused Hwang Woo Suk, the lead researcher of the SNU group, of ethical misconduct.[10] In December 2005 scientists in South Korea began questioning the validity of scientific evidence presented in the 2005 paper and called for an independent analysis of the data. Later that month a Korean co-author of the 2005 paper stated to the Korean media that the research was fabricated and the paper should be retracted; Hwang agreed to the retraction. On January 10, 2006, SNU stated that results of the 2004 paper were also a deliberate fabrication.[11] On July 5, Hwang was reported to have admitted full responsibility for the 2005 fabrication.[12]

Scientists at the University of Newcastle, the University of Edinburgh, Harvard University, and the University of California at San Francisco are working on deriving patient-matched stem cells from cloned human embryos.[13] The ethical and scientific misconduct developments in South Korea as well as the unsubstantiated announcement by Clonaid in December 2002 of the birth of a cloned child have contributed to the controversy over research on human embryos.[14]

Stem Cells from Adult Tissue or Umbilical Cord Blood

Stem cells obtained from adult organisms are also the focus of research. Most recently, a January 2007 report found that cells similar to embryonic stem cells can be found in amniotic fluid. However, the lead author of the report, as well as others in the field, caution that these cells are not a replacement for embryonic stem cells.[15] There have been a number of other publications on the abilities and characteristics

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[10] Gretchen Vogel, "Collaborators Split over Ethics Allegations" *Science*, Nov. 18, 2005, p. 1100.

[11] Nicholas Wade and Choe Sang-Hun, "Researcher Faked Evidence of Human Cloning, Koreans Report," *The New York Times*, Jan. 10, 2006, p. A1.

[12] Annie I. Bang, "Hwang Admits Fabricating Stem Cell Data," *The Korean Herald*, Jul. 5, 2006.

[13] Dennis Normile, Gretchen Vogel, and Constance Holden, "Cloning Researcher Says Work is Flawed but Claims Results Stand," *Science*, Dec. 23, 2005, p. 1886-1887; Carl T. Hall, "UCSF Resumes Human Embryo Stem Cell Work," *The San Francisco Chronicle*, May 6, 2006, p. A.1.

[14] For further information, see CRS Report RL31358, *Human Cloning*, by Judith A. Johnson and Erin Williams.

[15] Rick Weiss, "Scientists See Potential in Amniotic Stem Cells; They Are Highly Versatile And Readily Available," *The Washington Post*, Jan. 8, 2007, p. A1, A5.

of adult stem cells from a variety of different sources, such as bone marrow and the umbilical cord following birth. Bone marrow transplantation, a type of adult stem cell therapy, has been used for 30 years to successfully treat patients for a variety of blood-related conditions. Several private companies (such as MorphoGen, NeuralStem, Osiris Therapeutics, StemSource, ViaCell) are working on additional therapeutic uses of adult stem cells.

An opponent of embryonic stem cell research, David A. Prentice of the Family Research Council, developed a list of 72 diseases that he claimed can be treated using adult stem cells.[16] However, a letter to the online journal of Science Magazine refutes this claim, stating that "adult stem cell treatments fully tested in all required phases of clinical trials and approved by the U.S. Food and Drug Administration are available to treat only nine of the conditions on the Prentice list."[17]

Opponents of stem cell research advocate that adult instead of embryonic stem cell research should be pursued because they believe the derivation of stem cells from either IVF embryos or aborted fetuses is ethically unacceptable. Others believe that adult stem cells should not be the sole target of research because of important scientific and technical limitations. Adult stem cells may not be as long lived or capable of as many cell divisions as embryonic stem cells. Also, adult stem cells may not be as versatile in developing into various types of tissue as embryonic stem cells, and the location and rarity of the cells in the body might rule out safe and easy access. For these reasons, many scientists argue that both adult and embryonic stem cells should be the subject of research, allowing for a comparison of their various capabilities. Reports issued by the NIH and the Institute of Medicine (IoM) state that both embryonic and adult stem cell research should be pursued.[18]

In FY2004, the Consolidated Appropriations Act, 2004 (P.L. 108-199) provided $10 million to establish a National Cord Blood Stem Cell Bank within the Health Resources and Services Administration (HRSA). HRSA was directed to use $1 million to contract with the IoM to conduct a study that would recommend an optimal structure for the program. The study, *Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program*, was released in April 2005. The blood cell forming stem cells found in cord blood can be used as an alternative to bone marrow transplantation in the treatment of leukemia, lymphoma, certain types of anemia, and inherited disorders of immunity and metabolism. The IOM report provides the logistical process for establishing a national cord blood banking system, establishes uniform standards for cord blood collection and storage, and provides recommendations on ethical and legal issues associated with cord blood collection, storage and use.

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[16] [http://www.stemcellresearch.org/facts/treatments.htm] accessed on Dec. 13, 2006.

[17] Shane Smith, William Neaves and Steven Teitelbaum, "Adult Stem Cell Treatments for Diseases?" *Sciencexpress*, July 13, 2006, p. 1 [http://www.sciencexpress.org].

[18] National Institutes of Health, Department of Health and Human Services. *Stem Cells: Scientific Progress and Future Research Directions*, June 2001. The NIH report can be found at [http://stemcells.nih.gov/info/scireport/]. Institute of Medicine, *Stem Cells and the Future of Regenerative Medicine*, 2002. The IoM report can be found at [http://www.nas.edu].

On December 20, 2005, the President signed the Stem Cell Therapeutic and Research Act of 2005 (P.L. 109-129). The act provides for the collection and maintenance of human cord blood stem cells for the treatment of patients and for research. It stipulates that amounts appropriated in FY2004 or FY2005 for this purpose shall remain available until the end of FY2007, and authorizes $60 million over FY2007-FY2010. The act also reauthorizes the national bone marrow registry with $186 million over FY2006-FY2010. In addition, it creates a database to enable health care workers to search for cord blood and bone marrow matches and links all these functions under a new name, the C.W. Bill Young Cell Transplantation program.

Congress provided $9.941 million for the HRSA National Cord Blood Stem Cell Bank program for FY2005 (P.L. 108-447), and $3,957,000 for FY2006 (P.L. 109-149). For FY2007, the Administration did not request any funds for the National Cord Blood Inventory, the successor of the National Cord Blood Stem Cell Bank program. The House also did not recommend funds for FY2007, noting that "more than $22,000,000 remains available for obligation" from funds provided in prior years (H.Rept. 109-515). The Senate recommended $3.96 million for FY2007. Because Congress did not pass a Labor-HHS-Education appropriations bill for FY2007, the Continuing Appropriations Resolution, 2007 (Division B of P.L. 109-289), as amended, provides FY2007 funding for this program not to exceed the FY2006 level of funding.

Potential Applications of Stem Cell Research

Stem cells provide the opportunity to study the growth and differentiation of individual cells into tissues. Understanding these processes could provide insights into the causes of birth defects, genetic abnormalities, and other disease states. If normal development were better understood, it might be possible to prevent or correct some of these conditions. Stem cells could be used to produce large amounts of one cell type to test new drugs for effectiveness and chemicals for toxicity. Stem cells might be transplanted into the body to treat disease (diabetes, Parkinson's disease) or injury (e.g., spinal cord). The damaging side effects of medical treatments might be repaired with stem cell treatment. For example, cancer chemotherapy destroys immune cells in patients, decreasing their ability to fight off a broad range of diseases; correcting this adverse effect would be a major advance.

Before stem cells can be applied to human medical problems, substantial advances in basic cell biology and clinical technique are required. In addition, very challenging regulatory decisions will be required on any individually created tissue-based therapies resulting from stem cell research. Such decisions would likely be made by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). The potential benefits mentioned above would be likely only after many more years of research. Technical hurdles include developing the ability to control the differentiation of stem cells into a desired cell type (like a heart or nerve cell) and to ensure that uncontrolled development, such as cancer, does not occur. Some experiments may involve the creation of a chimera, an organism that contains two or more genetically distinct cell types, from the same species or

different species.[19] If stem cells are to be used for transplantation, the problem of immune rejection must also be overcome. Some scientists think that the creation of many more embryonic stem cell lines will eventually account for all the various immunological types needed for use in tissue transplantation therapy. Others envision the eventual development of a "universal donor" type of stem cell tissue, analogous to a universal blood donor.

However, if the SCNT technique, or therapeutic cloning, was employed using a cell nucleus from the patient, stem cells created via this method would be genetically identical to the patient, would presumably be recognized by the patient's immune system, and thus might avoid any tissue rejection problems that could occur in other stem cell therapeutic approaches. Because of this, many scientists believe that the SCNT technique may provide the best hope of eventually treating patients using stem cells for tissue transplantation.

Current Regulatory Landscape

The Dickey Amendment

Prior to an August 2001 Bush Administration decision (see below), no federal funds had been used to support research on stem cells derived from either human embryos or fetal tissue.[20] The work at the University of Wisconsin and Johns Hopkins University was supported by private funding from the Geron Corporation. Private funding for experiments involving embryos was required because Congress attached a rider to legislation that affected FY1996 National Institutes of Health (NIH) funding. The rider, an amendment originally introduced by Representative Jay Dickey, prohibited HHS from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. The Dickey Amendment language has been added to each of the Labor, HHS, and Education appropriations acts for FY1997 through FY2007.[21] Under the terms of the Continuing Appropriations Resolution, 2007, (Division B of P.L. 109-289) as amended, the provision (found in Section 509 of the Labor, HHS and

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[19] Chimeras have been created by scientists in a variety of different ways and have been the subject of research studies for many years. Human chimeras occur naturally when two eggs become fertilized and, instead of developing into twins, they fuse in the uterus creating a single embryo with two distinct sets of genes. For one example, see Constance Holden, "Chimera on a Bike?" *Science*, June 24, 2005, p. 1864.

[20] However, federal funds have been provided for research on both human and animal adult stem cells and animal embryonic stem cells.

[21] The rider language has not changed significantly from year to year (however there was a technical correction in P.L. 109-149). The original rider can be found in Section 128 of P.L. 104-99; it affected NIH funding for FY1996 contained in P.L. 104-91. For subsequent fiscal years, the rider is found in Title V, General Provisions, of the Labor, HHS and Education appropriations acts in the following public laws: FY1997, P.L. 104-208; FY1998, P.L. 105-78; FY1999, P.L. 105-277; FY2000, P.L. 106-113; FY2001, P.L. 106-554; FY2002, P.L. 107-116; FY2003, P.L. 108-7; FY2004, P.L. 108-199; FY2005, P.L. 108-447, FY2006, P.L. 109-149.

Education, and Related Agencies Appropriations Act, 2006) continues to control funds provided in FY2007. It states that:

> (a) None of the funds made available in this Act may be used for —
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> (1) the creation of a human embryo or embryos for research purposes; or
> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).
>
> (b) For purposes of this section, the term 'human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 [the Human Subject Protection regulations] as of the date of enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes [sperm or egg] or human diploid cells [cells that have two sets of chromosomes, such as somatic cells].

Clinton Administration Stem Cell Policy

Following the November 1998 announcement on the derivation of human embryonic stem cells, NIH requested a legal opinion from HHS on whether federal funds could be used to support research on human stem cells derived from embryos. The January 15, 1999, response from HHS General Counsel Harriet Rabb found that the Dickey Amendment would not apply to research using human stem cells "because such cells are not a human embryo within the statutory definition." The finding was based, in part, on the determination by HHS that the statutory ban on human embryo research defines an embryo as an *organism* that when implanted in the uterus is capable of becoming a human being. Human stem cells, HHS said, are not and cannot develop into an organism; they lack the capacity to become organisms even if they are transferred to a uterus. As a result, HHS maintained that NIH could support research that uses stem cells derived through private funds, but could not support research that itself, with federal funds, derives stem cells from embryos because of the federal ban in the Dickey Amendment.

Shortly after the opinion by the HHS General Counsel was released, NIH disclosed that the agency planned to fund research on stem cells derived from human embryos once appropriate guidelines were developed and an oversight committee established. NIH Director Harold Varmus appointed a working group that began drafting guidelines in April 1999. Draft guidelines were published in the *Federal Register* on December 2, 1999. About 50,000 comments were received during the public comment period, which ended February 22, 2000. On August 25, 2000, NIH published in the *Federal Register* final guidelines on the support of human embryonic stem cell research. The guidelines stated that studies utilizing "stem cells derived from human embryos may be conducted using NIH funds only if the cells were derived (without federal funds) from human embryos that were created for the purposes of fertility treatment and were in excess of the clinical need of the individuals seeking such treatment." Under the guidelines, NIH would not fund research directly involving the derivation of human stem cells from embryos; this was prohibited by the Dickey Amendment.

Other areas of research ineligible for NIH funding under the guidelines include (1) research in which human stem cells are utilized to create or contribute to a human embryo; (2) research in which human stem cells are combined with an animal embryo; (3) research in which human stem cells are used for reproductive cloning of a human; (4) research in which human stem cells are *derived* using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg; (5) research *utilizing* human stem cells that were derived using somatic cell nuclear transfer; and (6) research utilizing stem cells that were derived from human embryos created for research purposes, rather than for infertility treatment.

NIH began accepting grant applications for research projects utilizing human stem cells immediately following publication of the guidelines; the deadline for submitting a grant application was March 15, 2001. All such applications were to be reviewed by the NIH Human Pluripotent Stem Cell Review Group (HPSCRG), which was established to ensure compliance with the guidelines. James Kushner, director of the University of Utah General Clinical Research Center, served briefly as chair of the HPSCRG. Applications would also have undergone the normal NIH peer-review process.[22] The first meeting of the HPSCRG was scheduled for April 25, 2001. The HPSCRG was to conduct an ethical review of human pluripotent stem cell lines to determine whether the research groups involved had followed the NIH guidelines in deriving the cell lines. However, in mid April 2001, HHS postponed the meeting until a review of the Clinton Administration's policy decisions on stem cell research was completed by the new Bush Administration.[23] According to media sources, the 12 HPSCRG members, whose names were not made public, represented a wide range of scientific, ethical and theological expertise and opinion, as well as at least one "mainstream Catholic."[24]

The Bush Administration conducted a legal review of the policy decisions made during the Clinton Administration regarding federal support of stem cell research, as well as a scientific review, prepared by NIH, of the status of the research and its applications. The scientific review was released on July 18, 2001, at a hearing on stem cell research held by the Senate Appropriations Subcommittee on Labor, Health

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[22] According to media sources, as of April 2001 only three grant applications had been submitted to NIH, and one was subsequently withdrawn. (*Washington FAX*, Apr. 19, 2001.) Presumably, scientists were reluctant to invest the time and effort into preparing the necessary paperwork for the NIH grant application process when the prospects of receiving federal funding were uncertain under the new Bush Administration. (P. Recer, "Stem Cell Studies Said Hurt by Doubt," *AP Online*, May 2, 2001.) In a related development, one of the leading U.S. researchers on stem cells, Roger Pederson of the University of California, San Francisco, decided to move his laboratory to the United Kingdom for "the possibility of carrying out my research with human embryonic stem cells with public support." (Aaron Zitner, "Uncertainty Is Thwarting Stem Cell Researchers," *Los Angeles Times*, July 16, 2001, pp. A1, A8.) Human embryonic stem cell research was approved overwhelmingly by the House of Commons in Dec. 2000 and the House of Lords in January 2001.

[23] Rick Weiss, "Bush Administration Order Halts Stem Cell Meeting; NIH Planned Session to Review Fund Requests," *Washington Post*, Apr. 21, 2001, p. A2.

[24] Ibid.

and Human Services and Education.[25] The NIH report did not make any recommendations, but argued that both embryonic and adult stem cell research should be pursued.

Bush Administration Stem Cell Policy

On August 9, 2001, President Bush announced that for the first time federal funds would be used to support research on human embryonic stem cells, but funding would be limited to "existing stem cell lines where the life and death decision has already been made."[26] President Bush stated that the decision "allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life." The President also stated that the federal government would continue to support research involving stem cells from other sources, such as umbilical cord blood, placentas, and adult and animal tissues, "which do not involve the same moral dilemma."

Under the Bush policy, federal funds may only be used for research on existing stem cell lines that were derived: (1) with the informed consent of the donors; (2) from excess embryos created solely for reproductive purposes; and (3) without any financial inducements to the donors.[27] NIH was tasked with examining the derivation of all existing stem cell lines and creating a registry of those lines that satisfy the Bush Administration criteria. According to the White House, this will ensure that federal funds are used to support only stem cell research that is scientifically sound, legal, and ethical. Federal funds will not be used for: (1) the derivation or use of stem cell lines derived from newly destroyed embryos; (2) the creation of any human embryos for research purposes; or (3) the cloning of human embryos for any purpose.

Regulation of Stem Cell Research

The Common Rule (45 CFR 46, Subpart A) is a set of regulations that govern most federally funded research conducted on human beings. Its three basic requirements are aimed at protecting research subjects: the informed consent of research subjects, a review of proposed research by an Institutional Review Board (IRB), and institutional assurances of compliance with the regulations. However, ex vivo embryos (those not in a uterus) are not considered "human subjects" for these purposes, but federally funded research on human embryos is regulated by the Dickey Amendment as described above. Stem cells and stem cell lines are also not considered "human subjects," nor are they governed by the Dickey Amendment.

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[25] National Institutes of Health, Department of Health and Human Services. *Stem Cells: Scientific Progress and Future Research Directions*, June 2001. The NIH scientific report can be found at [http://stemcells.nih.gov/info/scireport/].

[26] The Aug. 9, 2001, *Remarks by the President on Stem Cell Research* can be found at [http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html].

[27] The White House, *Fact Sheet on Embryonic Stem Cell Research*, Aug. 9, 2001, found at [http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html].

Because of the current lack of federal regulation of stem cell research, the National Academies has developed voluntary guidelines for deriving, handling and using human embryonic stem cells. Two HHS agencies, FDA and NIH, regulate some aspects of stem cell research, even if research on stem cell lines is not classified as "human subjects" research. FDA, the agency that ensures the safety and efficacy of food, drugs, medical devices and cosmetics, regulates stem cell research aimed at the development of any "product" subject to its approval. NIH, the medical and behavioral research agency within HHS, regulates stem cell research that it funds in compliance with President Bush's 2001 policy. NIH has created a Human Embryonic Stem Cell Registry that lists the human embryonic stem cell lines that meet the eligibility criteria as outlined in the Bush Administration stem cell policy.

National Academies Guidelines. In July 2004 the National Academies established the committee on Guidelines for Human Embryonic Stem Cell Research to develop voluntary guidelines for deriving, handling and using human embryonic stem cells due to the current lack of federal regulation of such research. The stated position of the National Academies is that there should be a global ban on human reproductive cloning and therefore the guidelines will focus only on therapeutic and research uses of human embryonic stem cells and somatic cell nuclear transfer.

The committee released its "Guidelines for Human Embryonic Stem Cell Research" on April 26, 2005. The guidelines recommend that each institution conducting human embryonic stem cell research establish an oversight committee, including experts in the relevant areas of science, ethics and law, as well as members of the public, to review all proposed experiments. The guidelines recommend that a national panel also be established to oversee the issue in general on a continuing basis. The guidelines state that culture of any intact embryo, regardless of derivation method, for more than 14 days should not be permitted at the present time. The creation of a chimera by insertion of any embryonic stem cells into a human embryo or the insertion of human embryonic stem cells into a nonhuman primate embryo should also not be permitted. The guidelines state that chimeric animals in which human embryonic stem cells have been introduced, at any stage of development, should not be allowed to breed. The document also provides guidance on informed consent of donors and states that there should be no financial incentives in the solicitation or donation of embryos, sperm, eggs, or somatic cells for research purposes.

FDA Regulation. All of the human embryonic stem cell lines listed on the NIH Human Embryonic Stem Cell Registry (see **Table 2**) have been grown on beds of mouse "feeder" cells. The mouse cells secrete a substance that prevents the human embryonic stem cells from differentiating into more mature cell types (nerve or muscle cells). Infectious agents, such as viruses, within the mouse feeder cells could transfer into the human cells. If the human cells were transplanted into a patient, these infected human cells may cause disease in the patient which could be transmitted to close contacts of the patient and eventually to the general population. Public health officials and regulatory agencies such as the FDA are specifically concerned about retroviruses, which may remain hidden in the DNA only to cause disease many years later, as well as any unrecognized agents which may be present in the mouse cells.

The FDA defines "xenotransplantation" as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs."[28] Under FDA guidelines, transplantation therapy involving Bush approved stem cell lines, which all have been exposed to mouse feeder cells, would constitute xenotransplantation. Xenotransplantation products are subject to regulation by the FDA under Section 351 of the Public Health Service Act (42 USC 262) and the Federal Food, Drug and Cosmetic Act (21 USC 321 et seq.). FDA has developed guidance documents and the U.S. Public Health Service has developed guidelines on infectious disease issues associated with xenotransplantation.[29]

During a Senate hearing on stem cell research held by the Health, Education, Labor and Pensions Committee on September 5, 2001, the HHS Secretary stated that the FDA was overseeing 17 investigational protocols involving xenotransplantation in other areas of clinical research that involve patients. Therefore, he said, the xenotransplantation-related public health concerns over the human embryonic stem cell lines may not necessarily preclude the development of treatments for patients. While the problems presented by xenotransplantation for clinical research are neither unique to stem cell research nor insurmountable, many scientists believe it will be preferable to use sterile cell lines when attempting to treat patients via stem cell transplantation, and scientists have been successful in developing human embryonic stem cells that can be maintained without the use of mouse feeder cells.[30]

NIH Research Funding and Stem Cell Registry. The August 9, 2001, Bush Administration policy statement on stem cell research and the NIH Stem Cell Registry effectively replaced the NIH stem cell guidelines that were developed under the Clinton Administration and never fully implemented. Grant proposals for embryonic stem cell research undergo only the normal peer-review process without the added review of the HPSCRG as had been specified under the Clinton NIH stem cell guidelines. In February 2002, NIH announced the approval of the first expenditures for research on human embryonic stem cells. Funding for stem cell research by NIH is shown in **Table 1**. The NIH website provides additional information about current stem cell activities and funding opportunities.[31]

The NIH Human Embryonic Stem Cell Registry lists stem cell lines that are eligible for use in federally funded research and currently available to be shipped to

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[28] Xenotransplantation Action Plan: FDA approach to the regulation of xenotransplantation. Available at [http://www.fda.gov/cber/xap/xap.htm].

[29] These documents are available at [http://www.fda.gov/cber/xap/xap.htm].

[30] National Institutes of Health, Department of Health and Human Services, *Stem Cells: Scientific Progress and Future Research Directions*, June 2001, pp. 95-96; Susanne Rust, "UW Grows Animal-Free Stem Cell Lines," *The Milwaukee Journal Sentinel*, Jan. 2, 2006, p. A1.

[31] See [http://stemcells.nih.gov/research/funding/].

scientists.[32] As shown in **Table 2**, the NIH registry originally listed universities and companies that had derived a total of 78 human embryonic stem cell lines which were eligible for use in federally funded research under the August 2001 Bush Administration policy. However, many of these stem cell lines were found to be either unavailable or unsuitable for research. As of February 19, 2007, the NIH registry listed a total of 21 stem cell lines available from seven sources.

Table 1. National Institutes of Health Funding

($ in millions)

Stem Cell Research	FY03	FY04	FY05	FY06	FY07	FY08
Human Embryonic	20	24	40	38	37	37
Non-Human Embryonic	113	89	97	110	110	109
Human Non-Embryonic	191	203	199	206	206	205
Non-Human Non-Embryonic	192	236	273	289	288	287
Total, Stem Cell Research	**517**	**553**	**609**	**643**	**641**	**639**

Source: NIH Budget Office, February 5, 2007.

Table 2. NIH List of Human Embryonic Stem Cell Lines Eligible for Use in Federal Research

	Number of stem cell lines	
Name[a]	Eligible	Available
BresaGen, Inc., Athens, GA	4	3
Cell & Gene Therapy Institute (Pochon CHA University), Seoul, Korea	2	
Cellartis AB, Goteborg, Sweden	3	2
CyThera, Inc., San Diego, CA	9	0
ES Cell International, Melbourne, Australia	6	6
Geron Corporation, Menlo Park, CA	7	
Goteborg University, Goteborg, Sweden	16	
Karolinska Institute, Stockholm, Sweden	6	0
Maria Biotech Co. Ltd. — Maria Infertility Hospital Medical Institute, Seoul, Korea	3	
MizMedi Hospital — Seoul National University, Seoul, Korea	1	0
National Center for Biological Sciences/Tata Institute of Fundamental Research, Bangalore, India	3	
Reliance Life Sciences, Mumbai, India	7	
Technion University, Haifa, Israel	4	3
University of California, San Francisco, CA	2	2
Wisconsin Alumni Research Foundation, Madison, WI	5	5
Total	**78**	**21**

Source: [http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp].

a. Six table entries do not have stem cell lines available for shipment to U.S. researchers because of a variety of scientific, regulatory and legal reasons. The zeros entered in the "Available" column indicate that "the cells failed to expand into undifferentiated cell cultures."

[32] Information about the NIH Human Embryonic Stem Cell Registry is available at [http://stemcells.nih.gov/research/registry/index.asp].

State Laws that Restrict Stem Cell Research[33]

Many states restrict research on aborted fetuses or embryos, but research is often permitted with consent of the parent or parents. Almost half of the states also restrict the sale of fetuses or embryos. Louisiana is the only state that specifically prohibits research on in vitro fertilized (IVF) embryos. Illinois and Michigan also prohibit research on live embryos. Arkansas, Indiana, Iowa, Michigan, North Dakota and South Dakota prohibit research on cloned embryos. Virginia may also ban research on cloned embryos, but the statute may leave room for interpretation because human being is not defined. (There may be disagreement about whether human being includes blastocysts, embryos or fetuses.) California, Connecticut, Massachusetts, New Jersey and Rhode Island have laws that prohibit cloning for the purpose of initiating a pregnancy, but allow cloning for research.

Several states limit the use of state funds for cloning or stem cell research. Missouri forbids the use of state funds for reproductive cloning but not for cloning for the purpose of stem cell research, and Maryland's statutes prohibit state-funded stem cell researchers from engaging in reproductive cloning. Arizona law prohibits the use of public monies for reproductive or therapeutic cloning. Nebraska statutes limit the use of state funds for embryonic stem cell research. Restrictions only apply to state healthcare cash funds provided by tobacco settlement dollars. State funding available under Illinois Executive Order 6 (2005) may not be used for reproductive cloning or for research on fetuses from induced abortions.

Despite restrictive federal and state policies, many states are encouraging or providing funding for stem cell research (in some cases therapeutic cloning as well), as they seek to remain competitive and prevent the relocation of scientists and biotechnology firms to other states or overseas. For further information, please see CRS Report RL33524, *Stem Cell Research: State Initiatives*.

Concerns Over Access to Stem Cell Lines

Many scientists, disease advocates and others remain concerned that federally supported research on human embryonic stem cells is limited to the number of cell lines that meet the criteria of the August 9, 2001 Bush policy. As stated above, currently 21 cell lines are available for research with federal dollars. Because the pre-August 9 cell lines were developed in the early days of human stem cell research using older 1990s techniques, the cell lines not only have the problems of xenotransplantion (described in the previous section on FDA regulation), but they are harder to work with, not well characterized, and genetically unstable compared to newer stem cell lines.

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[33] The information in this section was obtained from "State Embryonic and Fetal Research Laws," National Council of State Legislatures website, at [http://www.ncsl.org/programs/health/genetics/embfet.htm], visited Mar. 30, 2007.

In reaction to the limitations imposed by the Bush policy, several U.S. research groups have decided to develop additional human embryonic stem cell lines using private funding. Some research groups are using state funds as well.[34]

In June 2004, a team of scientists at the Reproductive Genetics Institute, a private fertility clinic in Chicago, announced that they had isolated 50 new human embryonic stem cell lines from frozen embryos that were donated by patients following fertility treatment.[35] By using genetic diagnosis techniques, the Chicago team was able to create stem cell lines that carry the gene for muscular dystrophy as well as stem cell lines with the gene for six other diseases.[36] The new stem cell lines are to be used to understand the origins of disease-related symptoms and to develop and test new treatments.[37]

In March 2004, a Harvard University laboratory headed by Douglas Melton announced that using private research dollars they had isolated 17 new human embryonic stem cell lines.[38] One year later the Harvard team had increased that number to 28 new human embryonic stem cell lines.[39] In order to perform this work Harvard considered it necessary to build a new laboratory so that the group's federally funded research would be conducted separately from research on the new stem cell lines. Likewise, although the Harvard stem cell lines are available for use by other laboratories, any research using the new stem cell lines must be performed at a facility that does not receive federal support. The Harvard group intends to raise private funding to continue the work begun by Melton and his group of scientists as well as produce cloned human embryos for research studies on juvenile diabetes, Parkinson's disease, and several other diseases.[40]

In December 2002, Stanford University announced that a gift of $12 million from an anonymous donor would be used to establish an institute that will use expertise in stem cell biology and cancer biology to develop novel treatments for cancer and other diseases.[41] The Institute for Stem Cell Biology and Regenerative Medicine is headed by Dr. Irving Weissman, a professor in cancer biology at Stanford. The institute is developing new stem cell lines, some through the process

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[34] See CRS Report RL33524, *Stem Cell Research: State Initiatives*, by Judith A. Johnson and Erin D. Williams.

[35] Gareth Cook, "Clinic in U.S. Isolates 50 Lines of Stem Cells," *Boston Globe*, June 9, 2004, p. A1.

[36] The six diseases are beta thalassemia, neurofibromatosis type 1, Marfan's syndrome, myotonic dystrophy, fragile X syndrome, and Fanconi's anemia.

[37] For further information, see [http://www.reproductivegenetics.com].

[38] Rick Weiss and Justin Gillis, "New Embryonic Stem Cells Made Available," *Washington Post*, Mar. 4, 2004, p. A2.

[39] Gareth Cook, "Harvard Provost OKs Procedure," *Boston Globe*, Mar. 20, 2005, p. A29. (Hereafter cited as Cook, "Harvard Provost OKs Procedure.")

[40] For further information, see [http://www.stemcell.harvard.edu].

[41] For further information, see the Stanford University Medical Center website at [http://mednews.stanford.edu/stemcellQA.html].

of SCNT, to study the disease process of a wide range of disorders including cancer, diabetes, cardiovascular disease, autoimmune disease, allergies, and neurological disorders such as Parkinson's and Lou Gehrig's disease.[42]

In August 2002, the University of California at San Francisco established the UCSF Developmental and Stem Cell Biology Program with a $5 million matching grant from Andy Grove, the chairman of Intel Corporation. The program funds basic studies (using both animal and human cells) in stem cell biology and their translation into clinical practice with a goal of developing treatments for such diseases as diabetes, cardiovascular disease, Parkinson's disease, Alzheimer's disease and spinal cord injury. UCSF and the University of Wisconsin are the only two universities in the United States that have derived human embryonic stem cell lines that qualified for inclusion on the NIH Stem Cell Registry.

Worldwide Survey of Stem Cell Lines

A worldwide survey of laboratories conducted by the Boston Globe found that as of May 23, 2004, 128 human embryonic stem cell lines had been created since August 9, 2001; all would be ineligible for use in federally funded research under the Bush policy on stem cell research.[43] More lines are being created in laboratories overseas than in the United States, according to the survey. The survey found that 94 were created in labs outside the United States and 34 were created in this country. Of the 128 lines, 51 of the new stem cell lines are currently available for use, the remaining cell lines are not available for a variety of technical or legal reasons. For example, some cell lines have not yet been fully characterized to determine their stability or suitability for research. However, eventually their status is to be determined by using laboratory techniques. In Japan, stem cell lines are not allowed to be shipped to laboratories in other countries. In the United Kingdom, stem cell lines cannot be shipped abroad until they have been processed by the new UK Stem Cell Bank.[44]

Congressional Letters on Bush Policy

In response to concerns over access to human embryonic stem cell lines, in April 2004, a group of over 200 Members of the House of Representatives sent a letter to President Bush requesting that the Administration revise the current stem cell policy and utilize the embryos that are created in excess of need during the treatment of infertile couples.[45] The letter points out that an estimated 400,000 frozen IVF

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[42] For further information, see [http://stemcell.stanford.edu/].

[43] Gareth Cook, "94 New Cell Lines Created Abroad since Bush Decision," *Boston Globe*, May 23, 2004, p. A14.

[44] For further information on the UK Stem Cell Bank, see [http://www.ukstemcellbank.org.uk/].

[45] See [http://www.house.gov/degette/news/releases/040428.pdf].

embryos[46] "will likely be destroyed if not donated, with informed consent of the couple, for research." According to the letter,

> scientists are reporting that it is increasingly difficult to attract new scientists to this area of research because of concerns that funding restrictions will keep this research from being successful. ... We have already seen researchers move to countries like the United Kingdom, which have more supportive policies. In addition, leadership in this area of research has shifted to the United Kingdom, which sees this scientific area as the cornerstone of its biotech industry.

Under the direction of the White House, NIH Director Elias A. Zerhouni sent a letter in response to the House Members which restates the Bush Administration position against using federal funds for research involving the destruction of human embryos.[47] The letter from NIH Director Zerhouni did contain the following sentence which some observers believed in 2004 indicated a potential future policy shift: "And although it is fair to say that from a purely scientific perspective more cell lines may well speed some areas of human embryonic stem cell research, the president's position is still predicated on his belief that taxpayer funds should not 'sanction or encourage further destruction of human embryos that have at least the potential for life."[48] At the time, White House spokesperson Claire Buchan stated that the sentence did not indicate the president's position had changed. Supporters of stem cell research point out that it concedes that science could benefit from additional stem cell lines and that the president's position now rests solely on ethical arguments.

A letter signed by 58 Senators urging President Bush to expand the current federal policy concerning embryonic stem cell research was sent on June 4, 2004.[49] The letter states that "despite the fact that U.S. scientists were the first to derive human embryonic stem cells, leadership in this area of research is shifting to other countries such as the United Kingdom, Singapore, South Korea and Australia."

On July 14, 2004, HHS Secretary Thompson announced in a letter to Speaker of the House Dennis Hastert that NIH would establish Centers of Excellence in Translational Stem Cell Research.[50] The new centers are to investigate how stem cells can be used to treat a variety of diseases. A National Embryonic Stem Cell Bank is to collect in one location many of the stem cell lines that are eligible for federal research funding. In the letter to Speaker Hastert, Secretary Thompson stated

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[46] A survey conducted in 2002 and published in 2003 by the Society for Assisted Reproductive Technology and RAND determined that nearly 400,000 frozen embryos are stored in the United States, but most are currently targeted for patient use. See David I. Hoffman et al., "Cryopreserved Embryos in the United States and Their Availability for Research," *Fertility and Sterility*, vol. 79, May 2003, pp. 1063-1069.

[47] Rick Weiss, "Bush's Stem Cell Policy Reiterated, but Some See Shift," *The Washington Post*, May 16, 2004, p. A18.

[48] Letter from Elias A. Zerhouni, Director, National Institutes of Health, to The Honorable Diana DeGette and The Honorable Michael Castle, May 14, 2004.

[49] See [http://feinstein.senate.gov/04Releases/r-stemcell-ltr.pdf].

[50] Andrew J. Hawkins, "NIH Stem Cell Bank, Centers of Excellence Will Fast-Track Translational Research, Says Thompson," *Washington FAX*, July 15, 2004.

that "before anyone can successfully argue the stem cell policy should be broadened, we must first exhaust the potential of the stem cell lines made available with the policy."[51] In reaction to the announcement, the President of the Coalition for the Advancement of Medical Research stated that "creating a bank to house stem cell lines created before August 2001 does nothing to increase the wholly inadequate supply of stem cell lines for research."[52] On October 3, 2005, NIH announced that it had awarded $16.1 million over four years to the WiCell Research Institute in Wisconsin to fund the National Stem Cell Bank.[53] NIH also awarded $9.6 million over four years to fund two new Centers of Excellence in Translational Human Stem Cell Research, one at the University of California, Davis and the other at Northwestern University.

Alternative Sources of Human Embryonic Stem Cells

Most scientists involved in human embryonic stem cell research are focused on using stem cells derived from human embryos via the methods developed by scientists at the University of Wisconsin. However, a small number of scientists have begun to explore ways of obtaining human embryonic stem cells that bypass the destruction of living human embryos and, therefore, may be less troubling to those who object to the research on moral and ethical grounds. The President's Council on Bioethics identified four potential methods in a paper released in May 2005.[54] The four alternative methods would require additional research to determine whether human embryonic stem cells could be generated.

Some council members, however, expressed concern that work on alternative sources is a "diversion from the simple task at hand which is to move forward with the established laboratory techniques ... for studying embryonic stem cell research and biomedical cloning" and that the four proposals would "use financial resources that would be better devoted to proposals that are likely to be more productive."[55] Laurie Zoloth, professor of Medical Humanities and Bioethics, and of Religion at Northwestern University's Feinberg School of Medicine, maintains that public funding should not be used to satisfy the moral qualms of a minority and proposes that private religious groups should consider funding research on alternative sources

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[51] Ibid.

[52] Ibid.

[53] NIH Press Office, "NIH Awards a National Stem Cell Bank and New Centers of Excellence in Translational Human Stem Cell Research," Oct. 3, 2005, [http://www.nih.gov/news/pr/oct2005/od-03.htm]. The website for WiCell and the National Stem Cell Bank can be found at [http://www.wicell.org/].

[54] The President's Council on Bioethics, *White Paper: Alternative Sources of Human Pluripotent Stem Cells*, May 2005, at [http://www.bioethics.gov/reports/white_paper/index.html].

[55] Ibid., Personal Statement of Michael S. Gazzaniga, p. 76 and Personal Statement of Dr. Janet D. Rowley, p. 90.

of human embryonic stem cells just as Jehovah's Witnesses supported efforts to develop blood-saving surgical techniques to avoid transfusions.[56]

Dead Embryos

One possible method under discussion is deriving human embryonic stem cells from dead embryos. Early embryos frequently fail to develop in naturally occurring conceptions.

> Slightly fewer than a third of all conceptions lead to a fetus that has a chance of developing. In other words, if you were to choose [an embryo] at random and follow it through the first week of development, the chances are less than one in three that it would still be there at full term, even though there has been no human intervention. Nature, it seems, performs abortions at a much higher rate than human society. It is simply not true that most [embryos], if undisturbed, will produce a human being. The probability that a conception will result in a live birth is actually quite low. Note that since we have assumed that all conceptions lead to cell division, we have almost surely overestimated the true success rate.[57]

As many as 60% of IVF embryos produced by infertility clinics are judged to be incapable of developing to live birth, according to IVF clinics, due to abnormal appearance or failure to divide appropriately, and are not used by the infertile couple. Although failure to divide is often caused by genetic abnormalities and might seem to eliminate any prospect of using these embryos even for research, several studies suggest that some normal cells may be obtained from such organismically dead embryos and may be useful in creating stem cell lines.

The possibility that normal cells removed from dead embryos could potentially develop into an embryo (and if transferred into a uterus — a child) would be disturbing to some individuals. In addition, such a possibility would likely preclude federal funding for producing stem cell lines from such cells because of restrictions contained in the Dickey Amendment (see subsection, below, *Embryo Biopsy*). Research studies to determine the precise criteria for embryonic organismic death would be needed; however, such "natural history" studies could not be conducted with federal dollars. Federal funding of any type of research involving human embryos, starting with IVF then later cloning and the creation of stem cell lines from embryos, has been blocked by various policy decisions dating back more than 25 years and is currently controlled by the Dickey Amendment (see section, above, *The Dickey Amendment*).

The President's Council points out that this method of obtaining stem cells from dead embryos may not be acceptable to scientists because they understandably want to work only with the best materials. Why would scientists want to use cells derived from dead embryos, which may be abnormal, asks the council, or even bother trying

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[56] Molly Laas, "Alternative Stem Cell Derivation Methods Should Be Funded By Private Religious Groups," *Research Policy Alert*, Nov. 10, 2005.

[57] Harold J. Morowitz and James S. Trefil, *The Facts of Life: Science and the Abortion Controversy* (Oxford University Press, 1992), p. 51.

to create these cell lines when they can use existing cell lines or derive new ones from IVF embryos? The only advantage may be eligibility for federal funding. One Council member points out that the proposal entails thawing out embryos to follow the natural history of dead embryos, and because it is unknown "which embryos will not divide and which will, some portion (about half) will continue to divide and will be healthy embryos. What happens to these healthy embryos? ... [I]t would be strange, while allowing large numbers of unwanted but otherwise normal and viable IVF embryos to die, to ask scientists to make strenuous efforts to rescue cells, potentially abnormal, only from those thawed embryos that have spontaneously stopped dividing.... This seems to me to be the height of folly."[58]

Embryo Biopsy

A second method of obtaining embryonic stem cells without destroying the embryo employs a technique used by IVF clinics that offer pre-implantation genetic diagnosis (PGD). At the 6-8 cell stage, one or two cells are removed from the embryo created via IVF; these cells are then screened for genetic or chromosomal abnormalities before the embryo is transferred to a woman's uterus. According to the American Society for Reproductive Medicine, more than 2,000 children have been born in the United States following PGD, though it is still unclear whether subtle or late onset injuries may occur in children born following PGD.[59]

In August 2006, researchers at Advanced Cell Technology (ACT) in Worcester, Massachusetts, reported that they had created human embryonic stem cell lines using individual cells obtained from 8-cell-stage embryos that were produced via IVF for fertility treatment purposes.[60] This work builds on ACT's prior success, announced in October 2005, in deriving mouse embryonic stem cells by removing one cell from an eight-cell mouse embryo.[61] Following implantation into a surrogate mouse mother, the seven-cell embryos developed into healthy mice at the same rate as embryos that had not been biopsied. Creation of the mouse stem cell lines was much less efficient than when a later-stage embryo was used.

Skeptics of this new method point out that although it is understandable that couples who are at risk of having a child with a genetic disease may willingly agree to the potential added risk of PGD, couples may not agree to such a procedure for the sole purpose of creating stem cell lines for research when the emotional and financial stakes of in vitro fertilization and PGD are so very high. Research studies to

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[58] The President's Council on Bioethics, *White Paper: Alternative Sources of Human Pluripotent Stem Cells*, May 2005, p. 21 and p. 89.

[59] Nicholas Wade, "In New Method for Stem Cells, Viable Embryos," *The New York Times*, Aug. 24, 2006.

[60] Irina Klimanskaya et al., "Human Embryonic Stem Cell Lines Derived from Single Blastomeres," *Nature*, published online Aug. 23, 2006; and Press Release, "Advanced Cell Technology Announces Technique to Generate Human Embryonic Stem Cells the Maintains Developmental Potential of Embryo," Aug. 23, 2006, [http://www.advancedcell.com/].

[61] Nicholas Wade, "Stem Cell Test Tried on Mice Saves Embryo," *The New York Times*, Oct. 17, 2005.

determine if there is a risk of harm to a human embryo by the cell biopsy procedure probably would not be funded with federal dollars due to, as mentioned above, longstanding opposition to federal support for any type of research involving human embryos. Furthermore, research suggests, a single cell from a sheep or rabbit 4- or 8-cell embryo is potentially capable of developing into a normal sheep or rabbit. The possibility that a biopsied human cell may have "the potential to develop into an embryo and a child on its own" could preclude federal funding for producing stem cell lines from such cells because of restrictions contained in the Dickey Amendment (see section, above, *The Dickey Amendment*).[62]

Biological Artifacts — Altered Nuclear Transfer

A third possible method involves using the techniques of genetic engineering and SCNT (cloning) to obtain embryonic stem cells from embryo-like groups of cells which are not, in the strict sense, human embryos. In this approach, called altered nuclear transfer (ANT), a gene in the nucleus of the somatic cell is altered, so that normal embryo development is not possible, before the nucleus is placed within an enucleated egg. In October 2005, scientists at the Massachusetts Institute of Technology reported success in generating mouse embryonic stem cells utilizing the ANT approach.[63] A gene was disabled that allows for embryo implantation; gene function can be restored later so the stem cell line is unaffected. As is the case with SCNT, if the ANT approach is ever used to generate human embryonic stem cells a major obstacle would be obtaining an adequate supply of human eggs. This is the subject of intense scientific research. Researchers are trying to develop methods of obtaining human eggs without resorting to superovulation of female patients, an expensive procedure that some find morally questionable.

Some researchers believe ANT might serve as a temporary bridge until other technologies are developed, such as dedifferentiation of somatic cells. Until then, if federal support is provided, its proponents believe ANT would allow embryonic stem cell research collaboration on a national level without the ethical concerns involved in using leftover IVF embryos. Others believe that the procedures involved in ANT are more complex than deriving human embryonic stem cells from normal embryos, and many scientists "would be reluctant to attempt such challenging feats with no rational purpose other than to satisfy the ethical objections of others."[64]

Critics are concerned over the questionable morality of creating a biological artifact with a built in genetic defect, or what might be considered as the deliberate creation of a doomed or disabled human embryo. "Some find it aesthetically repulsive and ethically suspect to be *creating* such neither-living-nor-nonliving, near-human artifacts, a practice they regard as ethically no improvement over *destroying*

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[62] The President's Council on Bioethics, *White Paper: Alternative Sources of Human Pluripotent Stem Cells*, p. 29.

[63] Nicholas Wade, "Stem Cell Test Tried on Mice Saves Embryo," *The New York Times*, Oct. 17, 2005.

[64] Ibid., p. 47.

early embryos."[65] Proponents of the ANT approach argue that "such an entity would be a 'biological artifact,' not an organism. Removal of cells from, or even disaggregation of, this artifact would not be killing or harming, for there is no living being here to be killed or harmed."[66] Given the ethical uncertainties, it is unclear whether or not research involving ANT to generate human embryonic stem cells could be supported with federal funds.

Dedifferentation of Somatic Cells

The fourth method identified by the President's Council on Bioethics involves the dedifferentiation of somatic cells, literally reprogramming or winding back the clock on cell development to produce cells with the capabilities of embryonic stem cells. In August 2005, researchers at Harvard announced qualified success at producing a hybrid cell that has some of the characteristics of an embryonic stem cell.[67] The Harvard group fused human skin cells with human embryonic stem cells, but the process is very inefficient — 50 million skin cells and 50 million embryonic stem cells yielded only 10 to 20 fused cells — and all the hybrid cells have twice the normal amount of DNA. However, Yuri Verlinski and his team at the Reproductive Genetics Institute in Chicago claim to have created 10 patient-matched embryonic stem cell lines, called stembrids, with the normal amount of DNA. First the nucleus, which contains the DNA, is removed from the human embryonic stem cells and then these enucleated cells are fused with cells from a patient.[68] Alan Trounson at Monash University in Melbourne, Australia, is working on a similar method involving cell fusion.[69]

Because embryos are not involved, federal funding for research on this method would presumably not be blocked by the Dickey Amendment. However, the President's Council on Bioethics expresses some concern that dedifferentiation might proceed too far, resulting in a cell that has the capability of developing into an embryo. This possibility would raise serious ethical issues for some, and presumably the Dickey Amendment may again preclude the use of this method in the production of human embryonic stem cells for research. Moreover, such an embryo would be a clone of the individual who donated the somatic cell and any attempt to "save" such an embryo through the implantation in a woman's uterus would raise additional moral and ethical questions.

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[65] The President's Council on Bioethics, *White Paper*, p. 41.

[66] Ibid., p. 37.

[67] Rick Weiss, "Skin Cells Converted to Stem Cells," *The Washington Post*, Aug. 22, 2005, p. A1.

[68] Michael LePage and Rowan Hooper, "Double Triumph in Stem Cell Quest," *New Scientist*, May 28, 2005, p. 8.

[69] Rick Weiss, "Stem Cell Advances May Make Moral Issue Moot," *The Washington Post*, June 6, 2005, p. A7.

Congressional Actions

Stem Cell Research

Members of the 110th Congress indicated weeks prior to the start of the new Congress that they would address the topic of stem cell research early in the first session. This prediction was fulfilled; stem cell research was one of the topics addressed in the first 100 hours of the 110th Congress.

H.R. 3 (DeGette), the Stem Cell Research Enhancement Act of 2007, was introduced on January 5, 2007, with 211 cosponsors. The House passed H.R. 3 on a vote of 253 to 174 on January 11, 2007. The text of H.R. 3 is identical to legislation introduced in the 109th Congress, H.R. 810 (Castle). It would amend the Public Health Service Act by adding a new Section 498D, "Human Embryonic Stem Cell Research." The new section would direct the Secretary of HHS to conduct and support research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo. Stem cell lines derived after enactment must meet ethical guidelines established by the NIH. Only embryos that were originally created for fertility treatment purposes and in excess of clinical need are eligible for stem cell derivation. Only embryos that the individuals seeking fertility treatments have determined will not be implanted in a woman, and will be discarded, are eligible for stem cell derivation. Written consent is required for embryo donation. The Secretary, in consultation with the Director of NIH, shall promulgate guidelines 60 days after enactment. No federal funds shall be used to conduct research on unapproved stem cell lines. The Secretary shall annually report to Congress about stem cell research.

A companion bill, S. 5 (Reid), was introduced on January 4, 2007, with 30 cosponsors. A star print of S. 5 was ordered on March 29, 2007,[70] and the measure laid before Senate by unanimous consent on April 10, 2007. On April 11, 2007, the Senate passed S. 5 (Reid) on a vote of 63 to 34, and (Coleman) on a vote of 70 to 28. The text of S. 5 is the same as H.R. 3, except that the Senate bill contains an added provision that would direct the Secretary of HHS to conduct and support research on alternative human pluripotent stem cells. This added provision is very similar to H.R. 322 and portions of S. 30 (see below). S. 5 would amend the Public Health Service Act by adding a new Section 498E, "Alternative Human Pluripotent Stem Cell Research." S. 5 would require the Secretary of HHS to develop techniques for the isolation, derivation, production, and testing of stem cells that are capable of producing all or almost all of the cell types of a developing body, and may result in improved understanding of treatments for diseases and other adverse health conditions, but that are not derived from a human embryo. Within 90 days of enactment, the Secretary, after consulting with the Director of NIH, would be required to (1) provide guidance concerning the next steps required for additional research, including the extent to which additional basic or animal research is required; (2) prioritize research that holds the greatest potential for near-term clinical benefit; and (3) take into account techniques outlined by the President's Council on

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[70] The star print of S. 5 is identical to S. 997 (Harkin). S. 997 (Harkin) was introduced on March 27, 2007.

Bioethics and any other appropriate techniques and research. The Secretary would be required to prepare and submit to the appropriate committees of Congress an annual report describing the activities and research conducted. The only difference between the added provision in S. 5 and H.R. 322 is the definition of the term human embryo. S. 5 would define "human embryo" as having the same meaning as found within the applicable appropriations act with respect to the fiscal year in which research is to be supported. S. 5 authorizes such sums as may be necessary for FY2008 through FY2010.

S. 30 (Coleman), the Hope Offered through Principled and Ethical Stem Cell Research Act, or HOPE Act, was introduced on March 29, 2007. On April 11, 2007, the Senate passed S. 30 (Coleman) on a vote of 70 to 28 and S. 5 (Reid) on a vote of 63 to 34. Parts of S. 30 are similar to H.R. 322 (and therefore similar to parts of S. 5 as well). S. 30 would amend the Public Health Service Act by adding a new Section 498D, "Human Pluripotent Stem Cell Research." The bill would require the Secretary of HHS to develop techniques for the isolation, derivation, production, or testing of stem cells that have the flexibility of embryonic stem cells and that may result in improved understanding of treatments for diseases and other adverse health conditions. Such work will not involve the creation of a human embryo for research purposes or the destruction or discarding of, or risk of injury to, a human embryo other than those that are naturally dead. Naturally dead is defined as having naturally and irreversibly lost the capacity for integrated cellular division, growth, and differentiation that is characteristic of an organism, even if some cells of the former organism may be alive in a disorganized state. Within 90 days of enactment, the Secretary, after consulting with the Director of NIH, would be required to (1) provide guidance concerning the next steps required for additional research, including the extent to which additional animal research is required; (2) prioritize research that holds the greatest potential for near-term clinical benefit; (3) take into account techniques outlined by the President's Council on Bioethics and any other appropriate techniques and research; and (4) in the case of stem cells from a naturally dead embryo, require certain assurances from the researchers. The Secretary would be required to prepare and submit to the appropriate committees of Congress an annual report describing the activities and research conducted. The bill authorizes such sums as may be necessary to carry out Section 498D. Lastly, S. 30 would direct the Secretary of HHS to contract with the Institute of Medicine (IOM) to conduct a study to recommend an optimal structure for an amniotic and placental stem cell bank program. The IOM is to complete the study and submit a report to HHS and Congress no later than 180 days after enactment.

H.R. 322 (Bartlett), the Alternative Pluripotent Stem Cell Therapies Enhancement Act of 2007, was introduced on January 9, 2007. The text of H.R. 322 is similar to legislation introduced in the 109th Congress, H.R. 5526 (Bartlett) and S. 2754 (Santorum). H.R. 322 would amend the Public Health Service Act by adding a new Section 409J, "Alternative Human Pluripotent Stem Cell Research." The bill would require the Secretary of HHS to develop techniques for the isolation, derivation, production, and testing of stem cells that are capable of producing all or almost all of the cell types of a developing body, and may result in improved understanding of treatments for diseases and other adverse health conditions, but that are not derived from a human embryo. Within 90 days of enactment, the Secretary, after consulting with the Director of NIH, would be required to (1) provide guidance

concerning the next steps required for additional research; (2) prioritize research that holds the greatest potential for near-term clinical benefit; and (3) take into account techniques outlined by the President's Council on Bioethics and any other appropriate techniques and research. The Secretary would be required to prepare and submit to the appropriate committees of Congress an annual report describing the activities and research conducted. The bill would define term human embryo as any organism not protected as a human subject under part 46 of title 45, Code of Federal Regulations, as of the bill's date of enactment, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. The bill authorizes such sums as may be necessary for FY2008 through FY2010. H.R. 322 was referred to the House Committee on Energy and Commerce.

H.R. 457 (Paul), the Cures Can Be Found Act of 2007, was introduced on January 12, 2007. It amends the Internal Revenue Code to allow tax credits for (1) an amount equal to the contribution paid by the taxpayer within the tax year to stem cell research or storage facilities; (2) $2,000 for each umbilical cord blood donation made by the taxpayer within the tax year. The bill allows credits only for donations to facilities that do not engage in research on stem cells derived from human embryos. H.R. 457 allows a business tax credit for stem cell research and storage expenses. The bill was referred to the House Ways and Means Committee.

H.R. 1892 (Lipinski), was introduced on April 17, 2007. The bill would direct the Secretary of HHS to provide for the establishment and maintenance of a National Amniotic and Placental Stem Cell Bank.

S. 51 (Isakson), the Pluripotent Stem Cell Therapy Enhancement Act of 2007, was introduced on January 4, 2007. It would amend the Public Health Service Act requiring the Secretary of HHS to develop techniques for the isolation, derivation, production, or testing of pluripotent stem cells that have the flexibility of embryonic stem cells for the improved understanding of, or treatments for, diseases and other adverse health conditions. Such techniques must not involve (1) the creation of a viable human embryo for research purposes; or (2) the destruction or discarding of a human embryo or embryos; or (3) knowingly subjecting a human embryo or embryos to risk of injury or death greater than that allowed for federal research on fetuses in utero under current law. The bill would require the Secretary to (1) provide guidance concerning the next steps required for additional research; (2) prioritize research with the greatest potential for near-term clinical benefit; and (3) take into account techniques outlined by the President's Council on Bioethics and any other appropriate techniques and research. S. 51 was referred to the Senate HELP Committee.

S. 362 (Coleman), the Stem Cell Research Expansion Act, was introduced on January 23, 2007. The bill states that HHS may provide funding for research on embryonic stem cell lines created prior to January 23, 2006, that does not result in the use of federal funding to destroy an embryo or embryos. S. 362 was referred to the Senate Health, Education, Labor, and Pensions Committee.

S. 363 (Coleman), the Hope Offered through Principled, Ethically-Sound Stem Cell Research Act, was introduced on January 23, 2007. The bill directs the

Secretary of HHS to conduct research to develop techniques for the isolation, derivation, production, and testing of pluripotent stem cells that have the flexibility of embryonic stem cells. Such research will not involve the creation of human embryos for research purposes or the destruction or discarding of human embryos. Research may include methods that use cells derived from altered nuclear transfer or cells derived from organismically dead embryos; adult stem cells from various sources; the direct reprogramming of adult cells; and the derivation of stem cells from human germ cells and other methods that do not harm or destroy human embryos. Within 90 days of enactment, the Secretary will issue final guidelines that provide the next steps required for additional research, prioritize research, and take into account techniques outlined by the President's Council on Bioethics and any other appropriate techniques and research. The bill establishes a National Stem Cell Research Review Board, which will monitor research, prioritize research, and ensure fair consideration of both embryonic stem cell and adult stem cell research for funding. The bill also contains provisions on informed consent, privacy of individually identifiable information, and a prohibition on profiteering from commerce involving human embryos. The bill authorizes $5 billion for research for FY2008 through FY2017. S. 363 was referred to the Senate Health, Education, Labor, and Pensions Committee.

S. 957 (Burr), the Amniotic Fluid and Placental Stem Cell Banking Act of 2007, was introduced on March 22, 2007. The bill provides for the collection and maintenance of amniotic fluid and placental stem cells for the treatment of patients and research. S. 957 was referred to the Senate Health, Education, Labor, and Pensions Committee.

Cloning

S. 812 (Hatch), the Human Cloning Ban and Stem Cell Research Protection Act of 2007, was introduced on March 8, 2007. The text of S. 812 is identical to legislation introduced in the 109th Congress, S. 876 (Hatch). S. 812 would amend Title 18 of the United States Code to ban human reproductive cloning but allow cloning for medical research purposes, including stem cell research. S. 812 includes a criminal penalty of imprisonment of not more than 10 years and a civil penalty of not less than $1 million. S. 812 would require the Comptroller General to prepare a series of four reports within one year of enactment. The first report describes the actions taken by the Attorney General to enforce the prohibition on human reproductive cloning, the personnel and resources used to enforce the prohibition, and a list of any violations of the prohibition. A second report describes similar state laws that prohibit human cloning and actions taken by the state attorneys general to enforce the provisions of any similar state law along with a list of violations. A third report describes the coordination of enforcement actions among the federal, state and local governments. A fourth report describes laws adopted by foreign countries related to human cloning.

S. 812 would amend the Public Health Service Act by requiring that human SCNT be conducted in accordance with the ethical requirements (such as informed consent, examination by an Institutional Review Board, and protections for safety

and privacy) contained in subpart A of 45 C.F.R. Part 46,[71] or Parts 50 and 56 of 21 C.F.R.[72] S. 812 would prohibit conducting SCNT on fertilized human eggs (oocytes), and would implement a "Fourteen-Day Rule" that an "unfertilized blastocyst shall not be maintained after more than 14 days from its first cell division, aside from storage at temperatures less that zero degrees centigrade." S. 812 stipulates that a human egg may not be used in SCNT research unless the egg is donated voluntarily with the informed consent of the woman donating the egg. The bill also specifies that human eggs or unfertilized blastocysts may not be acquired, received or otherwise transferred for valuable consideration if the transfer affects interstate commerce. In addition, SCNT may not be conducted in a laboratory in which human eggs are subject to assisted reproductive technology treatments or procedures, such as in vitro fertilization for the treatment of infertility. Violation of the provisions in S. 812 regarding ethical requirements would result in a civil penalty of not more than $250,000. S. 812 was referred to the Senate Judiciary Committee.

S. 1036 (Brownback), the Human Cloning Prohibition Act of 2007, was introduced on March 29, 2007. The text of S. 1036 is identical to legislation introduced in the 109th Congress, S. 658 (Brownback). It would amend Title 4 of the Public Health Service Act (42 U.S.C. §§ 289 et seq.) and ban the process of human cloning as well as the importation of any product derived from an embryo created via cloning. Under this measure, cloning could not be used for reproductive purposes or for research on therapeutic purposes, which would have implications for stem cell research. S. 1036 includes a criminal penalty of imprisonment of not more than 10 years and a civil penalty of not less than $1 million. It would require the Government Accountability Office (GAO) to conduct a study to assess the need (if any) for any changes in the prohibition on cloning in light of new developments in medical technology, the need for SCNT to produce medical advances, current public attitudes and prevailing ethical views on the use of SCNT, and potential legal implications of research in SCNT. The study is to be completed within four years of enactment. S. 1036 has been referred to the Senate Health, Education, Labor, and Pensions Committee.

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[71] This provision specifies protections due to human beings who participate in research conducted or supported by HHS and many other departments.

[72] This provision specifies protections due to human beings who participate in research involved in testing a drug or medical device for FDA approval.