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NIH Stem Cell Guidelines
MSC 7997
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Ladies and Gentlemen:

Genetics Policy Institute ("GPI") is pleased to respond to the request from the National Institutes of Health ("NIH") for comments on its Draft Guidelines for Human Stem Cell Research, as published in the proposing release in the Federal Register on April 23, 2009 (the "Proposing Release").

GPI is a not-for-profit organization formed in 2003 with the mission of promoting and defending stem cell research and its application in medicine to develop therapeutics and cures for many otherwise intractable diseases and disorders. GPI seeks to catalyze and help lead a global network of influential stakeholder groups representing patient advocates, scientists, physicians and health care professionals, industrialists, bioethicists, lawyers, educators, and policy-makers. GPI pursues this mission through co-sponsorship and management of its flagship annual World Stem Cell Summit, publication of the World Stem Cell Report, special projects, speaking engagements, teaching initiatives, and strategic collaborations. Upon this base of activities and relationships, GPI serves as a communications channel, helping to build the knowledge base needed for ethical and thoughtful policy-making in support of scientifically and medically worthy research and clinical translation in the broad field of stem cells and the even broader field of developmental biology. For more information about GPI, please refer to our web site at www.genpol.org.

GPI congratulates NIH on its tireless efforts over the past 35 years to achieve a position of global leadership in the field of human embryology through both extramurally funded and intramurally conducted human embryonic stem cell ("hESC") and related medical research. These efforts by NIH underscore the central importance of knowledge in this field to achieving affordable, long-term health care. In making this point, GPI fully recognizes the gravity of the ethical responsibilities entailed by hESC and human induced pluripotent stem cell ("iPSC") research and regenerative medicine and the need for the stem cell research guidelines as adopted by NIH to fully respect and reflect these responsibilities. (We will refer to the guidelines to be adopted as the "Final Guidelines".)

In light of the historic importance of NIH's adoption of guidelines for hESC and iPSC research in furtherance of Executive Order 13505 of March 9, 2009, we expect NIH to use the preamble and explanatory note in the release that accompanies the Final Guidelines as an aid for interpretation and understanding. In this letter we use the term "Adopting Release" as the document that will contain this preamble and explanatory note. Indeed, for purposes of sound administrative procedures in accordance with the principle of the rule of law, we believe that the Adopting Release should present a detailed rationale for the Final Guidelines. Accordingly, in this letter we seek not only to comment on the Draft Guidelines but also to provide insight from a policy-making perspective to assist NIH in drafting not only the Final Guidelines, but also the Adopting Release.

Before presenting our detailed comments, we would like to highlight two threshold matters: the first focuses on Part II of the Draft Guidelines; and the second focuses on Parts III and IV of the Draft Guidelines.

Part II of the Draft Guidelines presents the requirements that must be met for hESCs to be eligible for use in research funded by NIH. Here we want to emphasize a common theme that runs through this letter: the concept that the Final Guidelines should be regarded as a "safe harbor", not as the only set of procedures by which applicants for NIH funding can establish that the derivation of hESCs proposed for use in research can meet the ethical requirements embodied in the Draft Guidelines. In support of this safe harbor approach we will offer below a five-part framework for comparing and contrasting the content of the Draft Guidelines with several other sources of guidelines and regulations for human stem cell research, including those of the International Society for Stem Cell Research ("ISSCR"), the National Academy of Science ("NAS"), and the California Institute for Regenerative Medicine ("CIRM"). Application of this framework demonstrates that in certain instances these other sources may offer means of compliance with ethical responsibilities that extend beyond the Draft Guidelines.[1] We believe a safe harbor approach also promotes the collaborative, cross-jurisdictional studies required for global progress in stem cell science and regenerative medicine.

Parts III and IV of the Draft Guidelines describe the types of stem cell and stem cell-related research that NIH proposes to be ineligible for NIH funding. We appreciate that Part IV.A simply and requisitely echoes the statutory prohibition on funding the derivation of stem cells from human embryos under Section 509 of Title V of the Consolidated Appropriations Act, 2009, Pub. L. 110-161, 3/11/09 (such statute being known as the "Dickey-Wicker Amendment"). We also understand how this statute extends to the derivation of hESCs from somatic cell nuclear transfer ("SCNT"), parthenotes, and embryos created solely for research through in vitro fertilization ("IVF"). But, for the same reason that this statute has been found not to extend to "downstream" research with hESCs derived in accordance with Part II of the Draft Guidelines, this statute should not be deemed by NIH to foreclose it from funding downstream derivatives of hESCs initially derived from the research techniques listed in Parts III.A, III.B, and IV.A. If NIH intends otherwise, this needs to be stated clearly in the Adopting Guidelines and the reasons for that decision set forth in the Adopting Release. Moreover, in setting forth ineligibility criteria of the sort in Parts III.A, III.B, and IV.B of the Draft Guidelines, it will be far more appropriate and reasonable to state that research of this type is "ineligible for funding" rather than saying that such types of research are "not allowed".

Organization of this Letter

GPI's comments in this letter comprise the following ten points.

I. Significance of Human Stem Cell Research
II. Significance of the NIH Guidelines for Stem Cell Research
III. Five Part Framework for Comparing and Contrasting hSC Research Guidelines
IV. Need to Apply the NIH Stem Cell Research Guidelines as a Safe Harbor
V. Issues relating to the Types of Research Proposed as Ineligible for NIH Funding
VI. Issues of Drafting Precision, Interpretation, and Implementation
VII. NIH's Leadership in Extending Stem Cell Research and Medicine
VIII. Addressing the Projected Growth of Stem Cell-related Clinical Trials
IX. Importance of Funding Studies of Ethical, Legal, and Social Implications in hSC Research
X. Periodic Review and Evolution of the Guidelines

[1] *See, e.g.*, Section 101(f) and (g) of the Common Rule (45 CFR 46.101). ("(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects. (g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.")

I. The Significance of Human Stem Cell Research

In a recent essay published in the peer-reviewed journal Cell,[2] Prof. Shinya Yamanaka – a world-renowned stem cell researcher who holds appointments at Kyoto University and the University of California-San Francisco – graphically illustrates that stem cell research leads to two important applications:

- the development of models of disease and assays for the discovery and development of small molecule drugs, biologics, and medical devices that can be combined with drugs, biologics, and cells; and

- the development of cell-based regenerative medicine.

While the first and second of these points have been well covered in the scientific/medical literature, the first – the value of hSCs to the discovery and development of pharmaceuticals and medical devices – has been well covered in the scientific/medical literature but not in the lay press.[3] It is absolutely vital that every stakeholder in the hSC debate understands the potential for both of these applications, as this dual-barreled potential underscores the breadth of the funding agenda on which we believe NIH must immediately focus once the Final Guidelines are in place. The Proposing Release makes note of this point. We urge NIH to continue to emphasize this point and repeat it in the Adopting Release.

Prof. Yamanaka's essay focuses on iPSCs and discusses, in part, their potential limitations in the context of navigating the steep, uncertain pathway from the bench to the bedside that health care products must follow. In comparison to hESCs, it is too early to believe that iPSCs are the equivalent of hESCs. In December 2007, in a paper on iPSCs published in Science, the Thomson laboratory at the University of Wisconsin-Madison cautioned that "further work is needed to determine whether human iPS cells differ in clinically important ways from ES cells."[4] While much work has been undertaken since the Yamanaka and Thomson laboratories each first announced in November 2007 the successful induction of human pluripotent stem cells from adult somatic cells, we believe much work remains to be undertaken to determine the clinically significant differences between hESCs and human iPSCs. Moreover, assuming for a moment that iPSCs prove to be the clinical equivalent of hESCs, we note that in his April 2009 essay Prof. Yamanaka advises that for purposes of the development of cell-based regenerative medicine, a new generation of progenitor cells, downstream of pluripotent stem cells, may provide greater safety than

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[2] Yamanaka, S. *A Fresh Look at iPS Cells*. Cell. Vol. 137:1. 3 April 2009. p. 13-17. The laboratories of Prof. Yamanaka at Kyoto University and Prof. James Thomson at the University of Wisconsin-Madison, were responsible for developing techniques for inducing adult cells to "dedifferentiate" back to a state in developmental biology time substantially similar, but not absolutely identical, to human embryonic stem cells. The laboratory of Prof. Rudolf Jaenisch at the Whitehead Institute at the Massachusetts Institute of Technology was instrumental, along with Prof. Yamanaka's laboratory, in laying the groundwork for human iPSCs through demonstrating the iPSC technique in the mouse model.

[3] *See, e.g.,* Chaudhary KW, et al. *Embryonic stem cells in predictive cardiotoxicity: laser capture microscopy enables assay development*. Toxicol Sci. Mar; 90(1):149-58. 2006. At The Stem Cell Summit in Boston in 2007, the value of hESCs in drug discovery was highlighted in a presentation by a co-author of this paper.

[4] Yu, Junying et al. *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*. Science. Vol. 318. 21 December 2009. p. 1920. We also note the following text from the November 2007 paper from the Yamanaka laboratory announcing that laboratory's induction of human pluripotent stem cells from fibroblast cells: "Among 32,266 genes analyzed, 5,107 genes showed more than 5-fold difference in expression between HDF and human iPS cells…, whereas 6083 genes between HDF and hES cells showed >5-fold difference in expression… . In contrast, a smaller number of genes (1,267 genes) showed >5-fold difference between human iPS cells and hES cells … . [table references omitted] Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, Cell (2007), doi: 10.1016/j.cell.2007.11.019.

iPSCs. But this strengthens the need for research with human ESCs and iPSCs, as any development of these progenitor cells to which Prof. Yamanaka refers can only take place upon the shoulders of continued hESC/iPSC research. Knowing that progress in science and medical research generally occurs along a continuum of knowledge-building that is punctuated by seminal discoveries and inventions, the Adopting Release becomes an important tool to bolster the rationale for Executive Order 13505 and NIH funding of hSC research. Simply put, in common vernacular, NIH needs to "pump up the volume" on this point. The Adopting Release offers a good place to do this.

II. The Significance of NIH Guidelines for Stem Cell Research

In promulgating guidelines for human stem cell research, NIH should in the Adopting Release review the thirty-five year history of efforts at NIH to promote the study of human embryology. We reference this span of time to explain that we need to measure in decades, not years, the loss of valuable time in this field suffered not just by the United States, but by the world, by virtue of NIH being absent from it for so long – in a manner that is wholly inconsistent with NIH's traditional leadership position in health science. Space and attention span do not permit a full recitation in this letter of the attempts by NIH stretching over four decades – from the three-quarter mark of the 20th century to the end of the first decade of the 21st century – to fund and conduct this all important area of scientific and medical research.[5] But the NIH will not be so limited in the Adopting Release, and for purposes of memorializing the important civics lessons that pertain to stem cell science and medicine, NIH needs to tell this saga in the Adopting Release. Paraphrasing George Santayana, those who are not taught the trials of history are condemned to suffer them anew. In saying this, we also take heed that the field of hESC/iPSC research and regenerative medicine touches upon many disciplines with significant ethical, legal, and social implications, a point to which we will return below in Point IX.[6]

It will be helpful for the generation that came of age at the beginning of the thirty-five year history to which we refer here to recite in the Adopting Release how it has trekked through the complex landscape of science, medicine, ethics, law, and social issues presented by the field of human embryology. This would be consistent with the principle that whenever any agency of the Executive Branch undertakes a paradigm shift of the sort that the Final Guidelines will represent, the history that led to that shift is set forth for posterity in the adopting release that effects that shift. This amounts not only to good rule of law, but to good mentorship – one of NIH's key focal points.

Proponents of human stem cell research and regenerative medicine often focus on the August 9, 2001 White House Fact Sheet on human embryonic stem cell research as the citadel that must be dissassembled in order for NIH funding of human stem cell research to proceed. While the August 9, 2001 Fact Sheet certainly presents as an important waypoint along the pathway of history that has been reversed by Executive Order 13505 of March 9, 2009, our global society needs to understand that, as a matter of executive branch decision-making in the United States, certain of the types of research made ineligible for NIH funding in the Draft Guidelines were made ineligible for federal funding years before August 9, 2001. Indeed, one of the earliest decisions on whether NIH would fund human embryonic

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[5] *See, e.g.*, Darwin, Charles. On the Origin of Species. (1859) Chapter XIV.

[6] *See, e.g.*, Dolgin, Janet L. *Embryonic Discourse: Abortion, Stem Cells, and Cloning*. 31 Fla. St. U. L. Rev. 101, 161-62 (2003) ("[T]he most important questions arising within the debate about embryonic research and therapeutic cloning (and more widely about genetic information and its uses) concern the character of the individual person in a universe with the capacity to prolong life long beyond current expectations, to alter people's minds and bodies—and perhaps their souls—through technology, and to select physical and affective traits prenatally. . . . Both the debate about abortion and that about embryonic research are also debates about social transition. The future is murky, but these conflated debates provide the analyst with a view of society contemplating itself and its most deeply held convictions.") Prof. Dolgin serves as a member of GPI's Legal Advisory Board.

research came in September 1980, in the final months of the administration of President Jimmy Carter, when the Secretary of Health, Education and Welfare (the predecessor of today's Department of Health and Human Services, the department in which NIH resides) effectively banned NIH funding of IVF research by allowing the charter of the Ethics Advisory Board to lapse.[7] This is an important part of the legal and regulatory history of stem cell science that NIH should not let us forget, as it illustrates the importance for transparency and breadth of participation in decisions of this sort.

In 1993, thirteen years after the EAB lost its charter, Nobel Laureate Harold Varmus, as director of NIH, spearheaded what became an eigh-year oddyssey to bring NIH back into the field of human embryology. In 2000, the eighth year of this undertaking, NIH published final guidelines for research with human pluriptent stem cells derived from both surplus pre-implantation embryos and fetal tissue. This effort culminated in the August 9, 2001 White House Fact Sheet, intended by President George W. Bush to be a Solomonic solution to the hESC question. As an immediate consequence of this Presidential statement of policy, NIH withdrew its Final Guidelines on hESC research.

Likening these hESC guidelines of 2000 to a newly composed symphony with NIH as the composer/conductor about to conduct its debut performance, the August 9, 2001 Fact Sheet had the effect of barring the conductor from taking the conductor's stand. This left the sections of the orchestra to switch from simply tuning their instruments to performing their respective parts in the newly scored symphony at varying tempos and in different keys with their own interpretations. In some cases, sections made a complete substitution of the score with one of an opposite theme, and in other cases, sections simply departed from the concert hall. By 2004, stem cell research and related legislation had been introduced in over forty states, with enactment in 35.[8] In California, voters authorized a ten-year three billion dollar public bond program for human embryonic stem cell research, while in South Dakota, somatic cell nuclear transfer with human cells has been prohibited.[9] In addition to efforts by state legislatures, organizations such as ISSCR and NAS eventually promulgated guidelines for the conduct of research with human ESCs and iPSCs, and outside the United States, laws and regulations relating to this field were also adopted. And beyond all this, philanthropic patient advocacy organizations focused on specific diseases established their own stem cell funding programs.[10]

The resulting state of affairs from all these efforts leaves us with the proverbial patchwork of laws, regulations, guidelines, and funding programs – one that makes the U.S. Confederation of the 1780s look monolithic. To begin to address this situation, administrators from the nine states with state-funded hESC/iPSC programs formed the Interstate Alliance for Stem Cell Research ("IASCR") in 2007.[11] The formation of IASCR testifies to the fact that the current array of varying laws and regulations impedes the collaborative research across state and national borders required to advance the hESC/iPSC field. To address this, commentators are urging that we must begin to harmonize these laws, regulations and

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[7] *See* Johnson, J.A. *Human Cloning*. Congressional Research Service. RS21096. December 19, 2001.

[8] For a state-by-state survey of laws relating to human stem cell research, see http://www.ncsl.org/programs/health/Genetics/embfet.htm.

[9] South Dakota Codified Laws 34-14-27 makes "human cloning" a felony, and South Dakota Codifed Laws 34-14-26 defines "human cloning" as "human asexual reproduction accomplished by introducing the nuclear material of a human somatic cell into a fertilized or unfertilized oocyte whose nucleus has been removed or inactivated to produce a living organism, at any stage of development, with a human or predominantly human genetic constitution;"

[10] *See, e.g.*, the range of stem cell research projects funded by the Juvenile Diabetes Research Foundation. http://onlineapps.jdfcure.org/AbstractSearchResult.cfm.

[11] See www.iascr.org. *See, also,* Bulletin of the Connecticut Academy of Science and Engineering. Vol 22.4/Winter 2007.

guidelines on a global basis.[12] NIH's position as a global leader in life science and medical research thus presents with some significance here, and leads us to underscore our belief that NIH should and needs to play the role of the master composer/conductor coming back to the stand after what history will hopefully record was only a brief moment.

In his June 2007 Executive Order, President Bush expanded the human stem cell research regime resulting from the August 9, 2001 Fact Sheet to include induced pluripotent stem cells. At that point in time, Prof. Yamanaka's laboratory at Kyoto University and Prof. Jaenisch's laboratory at M.I.T.'s Whitehead Institute had already each demonstrated that mouse adult somatic cells could be reprogrammed back into an embryonic epigenetic state from which pluripotent stem cells could be produced. Five months later, in November 2007, Prof. Yamanaka's and Prof. Thomson's laboratories announced extension of this technology to human adult somatic cells. And about two weeks later the online version of the journal Science published a paper from Prof. Jaenisch's laboratory describing the use of iPSC technology to treat the human form of sickle-cell anemia in a mouse model.[13] All of this excitement over iPSCs led to the statement in the President's State of the Union Address in January 2008 that iPSCs could be used in place of hESCs to avoid the ethical questions presented by hESCs. At some point in the future, after sufficiently more experimentation, this hypothesis may prove to be scientifically correct. But as numerous scientific references state, we are not yet there, and as Prof. Yamanaka in his above-referenced essay states, iPSCs themselves may be surpassed in favor of safer and more effective tools. We believe that in setting its research agenda, NIH should take a leading role in pursuing the paths Prof. Yamanaka outlines in his essay regarding the roles of hESCs, iPSCs, and progenitor cells derived from hESCs and iPSCs.

III. A Five Part Framework for Comparing and Contrasting hSC Research Guidelines

Viewed in an integrated manner, the directions in Executive Order 13505 of March 9, 2009, the Proposing Release, and the statements of NIH during the April 17, 2009 press conference, suggest that the Final Guidelines should be drafted to work as a safe harbor cohesively alongside the Common Rule, the ISSCR and NAS guidelines, and regulations like those of CIRM. Here in this Part II we propose a five-part comparative framework for supporting this approach.

The construction of this five-part comparative framework has resulted from our undertaking to compare and contrast on a side-by-side basis a body of seven sources: (i) the Common Rule; (ii) the ISSCR guidelines for hESC research; (iii) the ISSCR guidelines for clinical translation of stem cells; (iv) the NAS guidelines for hESC and iPSC research (as amended in 2008); (v) the CIRM regulations; (vi) the NIH hESC guidelines from 2000; and (vii) the NIH Draft Guidelines under current consideration. We will refer to these seven sources in this letter as the "Seven Sources".

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[12] *See, e.g.*, Rosario M. Isasi, *Policy Interoperability in Stem Cell Research: Demistifying Harmonization*. Stem Cell Reviews and Reports. (doi:10.1007/s12015-009-9067-z) Dr. Isasi serves as a member of GPI's Legal Advisory Board.

[13] Hanna, J. et al. *Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin*. Science. Published Online Published Online December 6, 2007.

The framework comprises five major topics and varying numbers of subtopics within them, as follows:

A. Impact of hSC Derivation and Research on Donor(s)
   1. No Impact on Quality of Care
   2. Risks of Donation Procedure
   3. No Benefits to Donor
   4. No Inducement to Donor
   5. Permissible Compensation/Reimbursement
   6. Privacy Protection

B. Impact of hSC Derivation and Research on Embryos
   1, Alternative Uses of Embryo
   2. Use or Concept of "Early Embryo"
   3. Impact on Embryos

C. Nature of Research
   1. Nature of Research
   2. Duration of Stem Cell Storage
   3. Unforeseeable Uses of Stem Cells

D. Nature of Consent
   1. Voluntary
   2. Separation of Creation and Donation Decisions
   3. Timing of Initial Decision to Donate
   4. Separation of Physician and Researcher/PI
   5. No Restrictions on Transplants
   6. Limits on Research and Need for Future Consents
   7. Withdrawal Right
   8. Future Contact

E. Disclosure of Commercial Value of Research and Financial Interests of Researchers
   1. No commercial value & benefits to donor
   2. Financial Benefits to Attending Physician and Research/Investigator

In Exhibit A to this letter, we illustrate in summary tabular fashion the result of applying this array of topics and subtopics to each of the Seven Sources.[14] The abundance of checkmarks in the table illustrates substantial topical convergence between and among the Seven Sources. Nonetheless, there are also divergences between and among the Seven Sources, and these are important to the task of explaining and promulgating the Final Guidelines. (By footnote, we sound a cautionary note about the use of this preliminary table.)[15]

[14] In the electronic submission of this letter to NIH this exhibit is set forth as the ASCII "txt" form of an html file. When cut and pasted into a free-standing ".txt" file and re-extensioned as an ".htm" or ".html" file, the table can be displayed in a standard Web browser. Readers should take note of this method for transmitting graphically-oriented files in "flat" ASCII txt files.

[15] When fully cross-checked, a blank cell in the table in Exhibit A will indicate that the subtopic associated with the row in which that blank cell appears does not receive coverage in the Source associated with the column in which that cell appears. In some cases, the presence of a blank cell will make sense. For example, a Source that focuses

The divergences between and among the Seven Sources can be classified using three categories: first, differences of degree in essentially the same approach to a specific issue; second, opposite approaches to a specific issue; and third, the coverage in one or more of the Seven Sources of an approach to a specific issue that is not covered by one or more of the others. An exhaustive and systematic examination of these three types of divergence in the context of the Seven Sources goes well beyond the limits of this comment letter, but not beyond NIH's undertaking in the weeks ahead to promulgate the Final Guidelines and prepare the Adopting Release.

Using the table in Exhibit A as a map, we have performed a preliminary analysis of the divergence in the Seven Sources. This analysis yields the examples described below.

Differences of Degree in Approaching the No Restrictions on Transplants/Medical Benefits Requirement. The ISSCR hESC derivation guidelines, the ISSCR SC clinical translation guidelines, the NAS guidelines, the CIRM regulations, and the NIH Draft Guidelines all require that the informed consent include a statement that the donor understands that there can be no restrictions placed on the patients who may benefit from the use of the stem cells to be derived from the donated embryo.

- In the case of the NAS guidelines, the ISSCR hESC derivation guidelines, and the CIRM regulations, the applicable statement is that the donor understands that the donation cannot be restricted as to who may be the recipient of transplants of the cells derived, except in the case of autologous donation.

- In the case of the ISSCR SC clinical translation guidelines, the applicable statement is that "with the exception of directed altruistic donation, the donation is made without restrictions regarding the choice of the recipient of the transplanted cells".

- In the case of the Draft Guidelines, the applicable statement is that "the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the stem cells".

In these three variations, there seem to be four variables that are present or absent from each: autologous donation; directed altruistic donation; the downstream use being defined as transplantation; and the downstream use being broadly defined as providing "medical benefit". We believe that the Final Guidelines should include the exception for autologous donation and directed altruistic donation, where by "directed altruistic donation" we mean an allogeneic donation for a specific patient on whose behalf the donation may be solicited or otherwise known to the donor. And while we believe that the reference to "medical benefit from the use of the stem cells" in the Draft Guidelines is broader (and therefore better in this context) than the reference to the "recipient of the transplanted cells", the narrower scope of the ISSCR guidelines, the NAS guidelines, and the CIRM regulations should not, all other things being equal, result in a deficiency in an informed consent designed in accordance with those guidelines and regulations. This exemplifies, in part, our argument that the Final Guidelines should be viewed as a safe harbor.

Subtopics Not Covered in the Draft Guidelines. The Exhibit A table indicates that the following subtopics are not present in the Draft Guidelines: the communication to the donor that there are unforeseen uses for the stem cells to be derived from the donated embryo; the election by the donor to

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more on translational medicine may not set forth all of the guidelines that a Source that focuses on hESC or iPSC derivation. Until the table is used and fully cross-checked by many, the information in the version currently attached to this letter needs to be approached with caution, and the table should be regarded more for heuristic than definitive purposes.

limit the types of research that can be conducted with the stem cells to be derived from donated embryo and the consequent need for future consents; and the disclosure to the donor that the researcher may derive financial benefits (this concept goes beyond the concept that the research may have commercial value in which the donor will not participate, a concept covered in the Draft Guidelines). Just as the Common Rule in 45 CFR 46.101(h) allows for differences in approach in the context of cross-border collaborative studies as long as protective equivalence can be found to exist, so too should the Final Guidelines.

Finally, we observe that guidelines for derivation of cell lines from iPSCs are not within the immediate concern of NIH in the Draft Guidelines. We understand that issues relating to hESCs are more immediately pressing than those related to iPSCs. Nonetheless, we believe that research with human iPSCs present ethical issues that should at some point be addressed by NIH. Indeed, it is for this reason that iPSCs are covered in the ISSCR guidelines for clinical translation of stem cells and the NAS guidelines revised in 2008. At some point, we believe NIH will need to address this.

IV. The Need to Apply the NIH Stem Cell Research Guidelines as a Safe Harbor

In Point II above we referenced the substantial overlap between and among the Seven Sources and described certain subtopics within the five-part framework described therein where overlap is not uniform and divergences appear. We believe that the significance of the substantial overlap far outweighs the points of divergence and underpins the need for NIH to present the Final Guidelines as a "safe harbor" rather than as the only set of criteria under which eligibility for NIH funding will apply. In light of the collaborative, cross-jurisdictional studies required for global progress in stem cell science and regenerative medicine, this safe harbor approach becomes imperative.

In this letter we use the term "safe harbor" in its usual and customary regulatory sense to mean a set of rules or guidelines that when satisfied result in a particular favorable outcome – in this case, eligibility for NIH funding – but that is not meant to serve as the only set of circumstances under which that outcome can be achieved. For an example of this, we cite the equivalence concept set forth in the Common Rule, in 45 CFR 46.101(h), in the context of studies with human subjects conducted outside the United States.[16] In this regard, we believe that reasonably minded, otherwise moral, people can differ on precisely what steps to follow to assure that the derivation of hESCs satisfies ethical responsibilities. Clearly, the authors of the Common Rule evidenced this belief as well.

Our position that NIH view the Final Guidelines as a safe harbor can be moored to two important anchor points:

- the reference in Executive Order 13505 to "other widely recognized guidelines on human stem cell research, including provisions establishing ***appropriate safeguards***" *[emphasis added]*; and

- the statement in the Proposing Release noting how "[i]n developing [the] draft Guidelines, the NIH consulted its Guidelines as issued in 2000, as well as the ***thoughtful***

[16] 45 CFR 46.101(h) states in relevant part: When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. …"

> guidelines developed by other national and international committees of scientists, bioethicists, patient advocates, physicians and other stakeholders, including the U.S. National Academies, the International Society for Stem Cell Research, and others."*[emphasis added]*

In Point II above we presented the evidence for the above-quoted recognition of the thoughtfulness of the ISSCR, NAS and others in "establishing appropriate safeguards" for research with hESCs. This evidence, and the clearly stated recognition of it by NIH and the President of the United States, should lead inexorably to the conclusion that the Final Guidelines be viewed as a safe harbor, not as the only criteria to be used for determining NIH funding eligibility. With a safe harbor approach, cell lines that have been deemed to be acceptably derived under the ISSCR and NAS guidelines, the CIRM regulations, or similar guidelines or rules from donated embryos no longer needed for reproductive purposes would be deemed to be eligible for NIH funding.

We understand, based on comments from others, that exclusion of the approaches that third parties, such as ISSCR, NAS, and CIRM, have determined after very careful deliberation to be ethically acceptable derivation of hESCs could result in very valuable cell lines and research being all for nought. This potential result not only offends the senses of those who believed they were behaving in a morally upstanding manner by following the ISSCR, NAS, or CIRM guidelines or regulations, but would constitute an unwarranted multi-year setback to a field of scientific and medical research that has already suffered stagnation not for eight years, but for thirty.

In saying this, please understand that we are not suggesting a "grandfathering" approach for the previously derived cell lines to which we just made reference, but a thoughtful assessment that the manner in which those cell lines were derived meet the ethical responsibilities embodied in the Draft Guidelines. While the economic rationale of the grandfathering approach presents with some force, we note that under the Final Guidelines only those cell lines that hold up to moral scrutiny should be eligible for NIH extramurally-funded and intramurally-conducted research.

V. Issues relating to the Types of Research Proposed as Ineligible for NIH Funding

As a matter of sound administrative law, the Adopting Release must explain on a case-by-case basis the reasons for this proposed ineligibility for each of these types of research. We recognize that Part IV.A of the Draft Guidelines cites the Dickey-Wicker Amendment as the source for the ineligibility of deriving hESCs from embryos; so the explanation for funding ineligibility in this case is a rather short one. And we understand that this statute, by reason of its definition of the term "human embryo", also makes ineligible for NIH funding the creation of human embryos and derivation of hESCs from these embryos using the techniques listed in Part IV.B of the Draft Guidelines. But as we discuss below, the Adopting Release needs to explain the limits of this ineligibility.

For example, consider the type of research with chimeras described in Part III.A of the Draft Guidelines. In stating in its 2008 revised human ESC/iPSC research guidelines that the introduction of human pluripotent cells into non-human primate blastocysts should not be researched "at this time", NAS noted that this restriction was made "pending further research that will clarify the potential of such introduced cells to contribute to neural tissue or to the germ line." Assuming that as of 2009 this clarifying research has not been completed, NIH should consider repeating this clarification in the Adopting Release in order to explain the rationale for Part III.A of the Draft Guidelines. Otherwise, something appears to be fundamentally wrong with this type of research, thereby cutting off society from the potential value of this research. This point naturally raises the question as to whether funding for this clarifying research should be considered as eligible for NIH funding, and the conduct and outcome of this clarifying research exemplifies the type of research that should be systematically tracked by NIH in

accordance with our suggestions regarding the need for a state-of-the-art stem cell research database in Point X below. (We believe a similar argument pertains to the type of animal breeding research referenced in Part III.B of the Draft Guidelines.)

Turning to Part IV.A of the Draft Guidelines, again, we note that it simply echoes the statutory prohibition in the Dickey-Wicker Amendment on funding the derivation of stem cells from human embryos. As a matter of law, therefore, NIH cannot do otherwise but follow this annually renewed section in the appropriations legislation for HHS. Similarly, to the extent that the Dickey-Wicker Amendment defines "human embryo or embryos'' to include "any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells", we appreciate that NIH funds cannot be used to create embryos by these means. But, for the same reason that "downstream" research using cell lines derived from hESCs will be eligible for NIH funding if the conditions set forth in Part II of the Draft Guidelines are satisfied, logic dictates that "downstream" research using stem cells derived from the sources identified in Part IV.B of the Draft Guidelines should be similarly eligible if the conditions of scientific worthiness, ethical responsibility, and compliance with law are satisfied.

NIH should thus clarify that the research made ineligible under Part IV.B of the Draft Guidelines is only that research in which embryos are created by the three techniques listed therein and the derivation of hESCs from such embryos, not research with those cells and derivatives thereof once they exist. (Otherwise, how can downstream research with hESC cells derived in accordance with Part II of the Draft Guidelines be eligible for NIH funding?) If NIH disagrees with this logic regarding Part IV.B of the Draft Guidelines, that disagreement should be explained in the Adopting Release. By not clarifying the scope of Part IV.B in this regard and not indicating its agreement or disagreement with this logic, NIH risks confusion and possible challenge.

An explanation of the limits and rationale for Parts III.A, III.B, and IV.B of the Draft Guidelines on a de-conflated, case-by-case basis will serve four related purposes. First, this explanation will fulfill NIH's need to promulgate its hSC guidelines in accordance with the transparency required under well-established principles of administrative law. Second, if NIH currently believes that any or all of these types of research are currently not scientifically worthy or not able to be practiced in an ethically responsible manner, then NIH needs to help researchers and other members of the public understand the reasons for this. Third, this type of explanation will allow NIH to begin to meet the directive in Executive Order 13505, as repeated in the Proposing Release, that requires it to "review and update these Guidelines periodically, as appropriate". In this respect, tracking the evolution of stem cell science in terms of its worthiness, ability to be practiced in an ethically responsible manner, and in compliance with law constitute the subject matter to be included in the linked data database that we propose in Point X below. And fourth, we believe that only through offering explanations of this type can NIH reclaim and maintain a respected position of globally-minded and self-consistent policy-making leadership in the field of human stem cell research.

VI. Issues of Drafting Precision, Interpretation, and Implementation

We focus here on three aspects that are generally common to the drafting of any kind of rules or guidelines, whether at the legislative or the executive branch levels of government: the need for as much precision as reasonably possible in the rules or guidelines; the need to address uncertainties of interpretation that can hinder their successful implementation; and the need to avoid practical problems that can also hinder their successful implementation.

As a starting point, we urge NIH to include a glossary in the Final Guidelines. Inclusion of a glossary would follow the usual and customary convention of setting forth definitions for terms used in rules and guidelines promulgated by an agency of the executive branch of government. As the character of regulations and guidelines most often depends significantly on the specific definitions ascribed to terms of art therein, without a glossary in the Final Guidelines or Adopting Release, NIH risks substantive uncertainties in applying the Final Guidelines and the increased administrative expense entailed by the need to address these uncertainties on a case-by-case basis. In Exhibit B to this letter we present a list of several terms or their correlatives that appear in the Draft Guidelines and the Proposing Release for which definitions may prove helpful.

A key term in the Final Guidelines, of course, will be the definition of "human embryonic stem cells". As described in the Draft Guidelines, "human embryonic stem cells are cells that are derived from human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers." In its 2008 Guidelines, NAS defines the term "embryonic stem (ES) cells" as "primitive (undifferentiated) cells derived from the early embryo that have the potential to become a wide variety of specialized cell types." While there is a high degree of correspondence between these two definitions, the NAS definition includes a time component in referring to the "early embryo". This time component takes on significance when one realizes that the definition of "embryo" in scientific terms and the definition of "fetus" set forth in the Common Rule have a time overlap.[17] The NIH's draft guidelines in 2000 contained the word "early", but NIH deleted the word from the final 2000 guidelines noting in the preamble to those guidelines that "the Guidelines make it clear that NIH funding of research using hPSCs derived in the private sector from human embryos can involve only embryos that have not reached the stage at which the mesoderm is formed." Instead of a mesoderm-based reference, the Draft Guidelines uses an even more subtle approach in the phrase "known to develop into cells and tissues of the three primary germ layers." We believe that this may be too subtle for the lay reader, and that also using the term "early embryo" may have educational value for readers of the Adopting Release and Final Guidelines.

Further to this centrally important point about defining the class of human embryos that can give rise to stem cells that can, in turn, be used in research eligible for NIH funding, we note the scholarship of Louis M. Guenin, Lecturer on Ethics in Science in the Department of Microbiology and Molecular Genetics at Harvard Medical School. In his seminal work The Morality of Embryo Use, Guenin presents a compelling argument for the morality of using embryos that are donated to medicine, subject to a prohibition by their respective donors of intrauterine transfer. Guenin uses the term "epidosembryo" for such an embryo.[18] Guenin illustrates that the combination of the prohibition of intrauterine transfer with the scientific fact that development of the embryo requires implantation results in the epidosembryo having no embryonic development potential, thus forming the basis for the morality of using the epidosembryo for medical research. We note that while the 2000 NIH Final Guidelines contained a

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[17] 45 CFR 202(c): "Fetus means the product of conception from implantation until delivery." NAS in the Glossary of its Guidelines for hESC research (rev. 2008) states: "Embryo—An animal in the early stages of growth and differentiation that are characterized by cleavage, laying down of fundamental tissues, and the formation of primitive organs and organ systems; especially the developing human individual from the time of implantation to the end of the eighth week after conception, after which stage it becomes known as a fetus."

[18] Guenin, Louis M. The Morality of Embryo Use (2008), p. 27. ("After the Greek epidosis, for an Athenian's beneficence to the common weal, I define the following: Epidosembryo. An epidosembryo is a human embryo as to which the following obtain: (a) The embryo was created outside the human body, and (b) the progenitors who contributed the gametes or other cells from which to form the embryo have donated the embryo, as of or after its creation, on the condition, set forth in written instructions accepted by the recipient, that (i) the recipient shall use the embryo solely in medical research or therapy, and (ii) never may the embryo or any totipotent cell taken from the embryo be transferred into a woman or into an artificial uterus.")

prohibition of intrauterine transfer of embryos, the Draft Guidelines does not. We also note that there may be other areas of life science research in addition to medicine where an epidosembryo approach to substantiating the morality of using hESCs/iPSCs has relevance – one such example being the use of hESCs for determining the toxicity of substances in the field of environmental health assessments.[19]

Part II.B.1 of the Draft Guidelines requires that "All options pertaining to use of embryos no longer needed for reproductive purposes were explained to the potential donor(s)." The word "all" in this context poses a problem. First, what is meant by "all options"? Is it possible that a new option could emerge? And if a new option does emerge, it is virtually certain that, as Thomas Kuhn pointed out in his seminal work on the structure of scientific revolution forty-seven years ago, some will know about this new option before others. As drafted, Part II.B.1 thus imposes a speed of information transfer that is impossible to achieve. Moreover, if new uses of hESCs fall into the category of "all options pertaining to use of embryos", the problem here is clearly exacerbated.

Part II.B.2 of the Draft Guidelines states that there can be no financial inducements for the donation of embryos. In view of the vast potential for differing views as to what constitutes "financial inducement" in the context of embryo donation, we believe NIH must carefully distinguish the term "financial inducement" from the types of permissible compensation and reimbursement permitted under the Common Rule, ISSCR guidelines, the NAS guidelines, the CIRM regulations, and the NIH 2000 Final Guidelines.[20] The provision of this type of permissible compensation and reimbursement to embryo donors should not render hESCs derived therefrom as ineligible for NIH funding.[21] The points here echo our safe harbor comment made above.

Part II.B.4 of the Draft Guidelines states that there must have been "a clear separation between the prospective donor(s)'s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes." In this context, what does "clear separation" mean? Imagine that during an introductory meeting with a well-intentioned IVF professional, a prospective embryo donor asks questions about both the creation and the donation of embryos? Would a well-intentioned response from the IVF professional that describes the creation process and then the donation process violate the "clear separation" requirement? Some guidance and examples on this topic in the Adopting Release would be helpful.

Part II.B.5 of the Draft Guidelines states that in connection with the timing of the consent to donation and any withdrawal thereof that donor(s) be "informed that they [retain] the right to withdraw consent until the embryos [are] actually used for research." In this context, what does "actually used for research" mean? At what step does "actual use" occur? We understand that a commonly adopted policy in other nations has the consent withdrawal right end at the time an hESC line is derived from the donated embryo. To extend this withdrawal right past this point would be difficult to administer and borders on irrationality. It would be good if the Final Guidelines address this point.

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[19] See, e.g., CIRM. *Stem Cells in Predictive Toxicology*. CIRM Workshop Report July 7-8, 2008. ("Chapter 4. Stem Cells And Predictive Toxicology In Environmental Health Assessment.")

[20] Section II.A.1(e) of the NIH 2000 Final Guidelines permitted payments to embryo donors that "do not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells."

[21] For a general discussion of this subject see Chapter 7 ("Buying and Selling Human Tissues") in Korobkin, Russell with Munzer, Stephen R. Stem Cell Century: Law and Policy for a Breakthrough Technology. Yale University Press. 2007. For a specific example of how this subject is treated in the United Kingdom, Prof. Korobkin cites Braid, Mary. *The Price of Eggs*. Independent on Sunday. (London), Mar. 26, 2006, at 58 (citing the Human Fertilisation and Embryology Authority). Prof. Korobkin serves as a member of GPI's Legal Advisory Board.

Part II.B.6 of the Draft Guidelines states that "decisions related to the creation of human embryos for reproductive purposes [should be] made free from the influence of researchers proposing to derive or utilize human embryonic stem cells in research. Whenever it [is] practicable, the attending physician responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize human embryonic stem cells should not have been the same person." We understand that, for good reason, the policy in many nations recognizes the ethical value of separating the creation decision for reproductive purposes from the donative decision, which both Part II.B.4 and Part II.B.6 address. But as in the example we describe above in the context of Part II.B.4, here in the case of Part II.B.6 we can foresee the case of a brilliant, thoroughly moral IVF physician who has ideas for improving IVF that he or she wants to pursue through research with hESC cells derived from his or her patients. If this situation and others exemplify when it is not practical for physician and researcher to be different persons, then the Adopting Release should provide these as examples.

VII. NIH's Leadership in Extending Stem Cell Research and Medicine

Executive Order 13505 mandates NIH to "review and update [the Final] Guidelines periodically, as appropriate". We believe that in addition to this periodic review and updating, NIH must as well take a global proactive leadership position in funding the research necessary to extend the frontiers of human stem cell science and medicine, including research that may potentially lead to ethically sound ways of practicing the research techniques that are ineligible for funding under the Draft Guidelines. A case in point is the need for NIH to help fund the research necessary to address the questions about SCNT described in Point V above.

VIII. Projected Growth of Stem Cell-related Clinical Trials

A search on May 22, 2009 on the clinicaltrials.gov database with the search string "stem cell" in the "intervention" search field called forth 1,918 studies – all of which we believe have been based on adult stem cell interventions. Of the 1,918 studies, 1,880 had specified start dates, and of these 1,880 studies, 1,798 had start dates ranging from 1988 through the end of 2008. The compound annual growth rate (CAGR) in the number of these clinical trials beginning in or before 2008 over the 1988-2008 period was 26.2% - resulting from a CAGR of 40.3% for the period 1988-2000 and, not surprisingly, a CAGR of 7.8% for the 2000-2008 period. A preponderance of these trials related to hematopoietic stem cell transplants, one of the earliest medical therapies based on stem cell research.[22] In light of the historic step about to be taken by NIH in adopting the human stem cell research guidelines, we believe that in the coming years the combination of adult stem cell trials with the potential for interventional studies based on hESCs/iPSCs and their downstream derivatives could easily result in the growth of stem cell and stem cell-related interventional studies returning to, if not exceeding, the pre-2000 CAGR. Indeed, we understand that some states are focusing on the steps required to ready their clinical trial infrastructures for this potential. We believe that, consistent with its historic mission as a global leader in advancing the state-of-the-art in medical care, NIH must immediately begin to play a role in this aspect of stem cell research and medicine.

[22] In response to a request with "stem cell" in the intervention field, the internal logic of clinicaltrials.gov returns all studies with "stem cell" in the intervention field or in the title of the study. Of the 1,918 studies, only 921 have "stem cell" in the intervention field, and of these, approximately 600 presented with terms such as "peripheral blood", "hematopoietic", "bone marrow" in the intervention field. Of the 1,918 studies, 765 have been funded by NIH, with 636 of these funded by the National Cancer Institute.

IX. The Importance of Funding Ethical, Legal and Social Implications Studies

During the last 22 years, beginning in 1987 with the establishment of the public side of the Human Genome Project, and then in 2005 with the establishment of the Cancer Genome Atlas (originally called the Human Cancer Genome Project), NIH has allocated a small but meaningful percentage of the budget for large-scale research programs to the study of the ethical, legal, and social implications (commonly referred to as "ELSI") entailed by those programs.[23] We believe that this practice should be followed for hSC research, particularly in light of the need described above for NIH to continually revisit the ineligibility of certain techniques identified in Parts III and IV of the Draft Guidelines. This point takes on added significance in view of the far-reaching ethical, legal, and social implications of stem cell research and regenerative medicine.[24]

X. Periodic Review and Evolution of the Guidelines

The Proposing Release reiterates the President's directive in Executive Order 13505 that NIH must "review and update [the hSC guidelines] periodically, as appropriate." Some stakeholders have focused on the word "periodically" to suggest that this means NIH should at punctuated, predesignated times review and update the guidelines, while other stakeholders have focused on the phrase "as appropriate" to suggest that NIH must continually monitor developments in human stem cell research and revise the Final Guidelines, and any revisions thereof, as the need arises based on underlying advances in the relevant science and technology. Our position is that the best policy lies in the middle of these two suggestions.

To achieve this middle ground we propose the following steps:

1. NIH should establish or participate in establishing a global interactive database for tracking, monitoring, and analyzing advances in the field of stem cell research and regenerative medicine. By "field" here we mean a landscape that includes science, medicine, healthcare, ethics, law, and social implications. This database should be constructed with state-of-the-art advances in the Semantic Web Technology/Linked Data systems.[25] The purpose of this database is to support the information needs of NIH in administering and setting policy for its extramural funding and intramural conduct of hSC research.[26]

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[23] See Nass, Sharyl J and Stillman, Bruce W. (editors). Large-Scale Biomedical Science – Exploring Strategies for Future Research. Institute of Medicine of the National Academies and Division on Earth and Life Studies, National Research Council. 2003 (In discussing Dr. Watson's commitment to devote five percent of the HGP budget to the study of the project's ethical, legal, and social implications, the editors note on page 35: "This commitment of NIH funds to ethical debate was unprecedented, as was making bioethics an integral part of an NIH-biological research program.")

[24] For an exploration of the ELSI ramifications of stem cell research and regenerative medicine, *see* Korobkin, *supra*.

[25] Sir Tim Berners-Lee, the scientist who conceived the World Wide Web in the late 1980s, has been championing this technology since the mid-1990s; and other executive branches of the U.S. government have been adopting this technology, the most notable recent example of which is the adoption by the United States Securities and Exchange Commission of its XBRL/Interactive Data system. (See SEC Releases 33-9002 and 9006.) Sir Tim himself presented a good example of the power of this technology in the field of drug discovery at the annual 2009 TED Conference in Long Beach, California. *See* Berners-Lee, Sir Tim. *Linked Data*. http://www.w3.org/2009/Talks/0204-ted-tbl/#(1), Slides 17 through 20.

[26] GPI is grateful to Alan L. Jakimo, a Partner in the New York office of Sidley Austin LLP, for his suggestion about the construction of this database and his overall assistance in drafting this letter. Mr. Jakimo is an Adjunct Professor of Law at Hofstra University and serves as a member of the GPI Legal Advisory Board.

2. An office within NIH, using the database described in Step 1 above, would actively monitor the field of human stem cell research for discoveries and developments. This office would prepare an annual public report on the state of the field and anticipated developments in the following twelve months.

3. On a bi-annual basis, NIH would invite public comment on the need to revise the then existing Final Guidelines, and, as appropriate, propose revisions to the Final Guidelines.

4. In the case of each seminal discovery, NIH would promptly convene a task force outside the bi-annual review process to determine the need for revising the Final Guidelines.

We believe that both the rapid pace of development in human stem cell research and its significance to life science, medical science, and health care warrant this formal but flexible approach to relevant knowledge-building and the evolution of thoughtful and appropriate guidelines.

* * *

GPI appreciates the opportunity to have presented the above comments relating to NIH's Draft Guidelines for Human Stem Cell Research and would be pleased to answer any questions or comments that NIH may address to us.

Returning to our introductory remarks, GPI underscores its gratitude to the President of the United States and NIH for undertaking the effort to move ahead with a set of guidelines under which human stem cell research will be eligible for NIH extramural funding and intramural programs. We know this process will be difficult. This said, a significant piece of the future of worldwide health relies on NIH's success in coming back as a beacon in the field of human stem cell research and medicine. GPI wishes NIH much success in this endeavor.

Respectfully submitted,

/s/ Bernard Siegel

Bernard Siegel
Executive Director
Genetics Policy Institute

Exhibit A

A Preliminary Illustrative Analysis – Subject to Review and Correction

(see note below)

	Concept	Common Rule	ISSCR – hESC deriv.	ISSCR-SC clinical transla.	NAS	CIRM	NIH 2000	NIH 2009
Impact on Donor	No impact on quality of care	(1)	√	√	√	√		√
	Risks	√	√	√	√	√		(1)
	No Benefits	√	√	√	√	√	√	√
	No Inducement	√	√	√	√	√	√	√
	Permissible Compensation/ Reimbursement	√	√	√	√	√	√	
	Privacy	√	√	√	√	√	√	√
	# of Subjects	√						
Impact on Embryo	Alternative Uses		√	N/A		√		√
	Use or concept of "Early Embryo"	DWA(2)	√	N/A	√	√	√(3)	√(4)
	Impact on Embryo	DWA(2) Definition of fetus(5)	√	N/A	√	√	√	√
	Intrauterine Transfer of Embryo/hESCs Prohibited		√		√	√	√	

(1) See discussion in the letter to which this Exhibit A is attached under Point III.

(2) See cross reference to 45 CFR 46.204(b) in Dickey-Wicker Amendment, Section (a)(2).

(3) See discussion in the letter to which this Exhibit A is attached under Point VI.

(4) See definition of "human embryonic stem cells" in Part I of Draft Guidelines.

(5) See definition of fetus in 45 CFR 46.202(c).

NOTE: When fully cross-checked, a blank cell in this table will indicate that the subtopic associated with the row in which that blank cell appears does not receive coverage in the Source associated with the column in which that cell appears. In some cases, the presence of blank cell will make sense. For example, the ISSCR and NAS guidelines and the CIRM regulations are not limited to embryos that were created for reproductive purposes. Thus, under those guidelines and regulations there is a need that the informed consent in cases of oocyte donation disclose the risks that attend oocyte donation. Until a fully cross-checked, peer-reviewed table exists, the blank cells in this table need to be approached with caution and this table should be regarded for illustrative, not definitive purposes.

EXHIBIT A (continued)

	Concept	Common Rule	ISSCR – hSC deriv.	ISSCR-SC clinical transla.	NAS	CIRM	NIH 2000	NIH 2009
Nature of Re-search	Nature of Research	√	√	√	√	√	√	√
	Duration of cell storage		√	√	√	√	√	√
	Unforeseeable Uses		√	√		√		
Nature of Consent	Voluntary	√	√	√	√	√	√	√
	Separation of Decisions						√(1)	√
	Timing of Initial Consent for Donation						√	√
	Separation of Physician from Researcher/PI						√	√
	No Restrictions on Transplants		√(2)	√(3)	√(2)	√(2)	√	√
	Limits on Research / Need for Future Consents		√	√		√		
	Withdrawal Right	√	√	√	√	CR applies		√
	Future Contact				√			
Com-mercial & Finan-cial Value	No commercial value & benefits to donor		√	√	√	√	√	√
	Financial Benefits to Attending Physician/PI		√	√		√		

(1) Implicit from timing and separation of physician from researcher/PI.

(2) Except for autologous administration.

(3) Except for altruistic donation.

EXHIBIT B
PROPOSED LIST OF TERMS FOR GLOSSARY

(These are terms used in the Draft Guidelines. Additional terms may be warranted based on the content of the Final Guidelines and the Adopting Release.)

blastocysts
breeding
cell
coded
cord
culture
derive (and its correlatives)
differentiate (and its correlatives)
dividing (and its correlatives)
donor
embryo (and its derivatives)
embryonic stem cell
fertilization
germ
identifiable
induced pluripotent stem cell
inducements
IVF
nuclear
organs
parthenogenesis
pluripotent
reproductive
"research involving"
"research in which"
somatic
stem cell
transplant (and its correlatives)