Public Stem Cell Banks:

Considerations of Justice in Stem Cell Research and Therapy

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If stem cells fulfill their therapeutic promise, moving them from the laboratory into the clinic will raise several concerns about justice. One concern is that, for biological reasons alone, stem cell-based therapies might not be available for every patient who needs one. Worse, depending on how we address the problem of biological access, they might benefit primarily white Americans. We can avoid this outcome—although at a cost—by carefully selecting the stem cells we make available.

The possibility that stem cells can provide therapies for disease and illness has generated immense excitement on the part of both researchers and patients. This enthusiastic support for the notion of stem cell-based therapy is tempered by the fact that, at present, embryonic stem cells are considered technically superior to stem cells derived from other sources, such as umbilical cord blood or adult stem cells in the human body. Given this situation, policy decisions concerning stem cell research have become linked to the debate about the ethics of the creation or destruction of embryos, leaving policymakers grappling with the seemingly intractable question of the moral significance of the human embryo. This debate will continue; however, it is inevitable that research into stem cell engineering will also continue. It seems equally inevitable that as this field of research develops, additional ethics and policy questions will arise.

The forthcoming transition in the focus of stem cell research from basic science to the development of therapies raises important questions of justice. This transition is marked by increasing interest in establishing banks of stem cell lines, both to facilitate research and in anticipation of the eventual use of stem cell-derived transplants to treat such diseases as amyotrophic lateral sclerosis, Parkinson's, and diabetes.[1] The creation of stem cell banks raises questions about who stands to benefit from these banks and their research and therapeutic applications. First,

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there is a question about who, financially, will have access to stem cell-based therapies.[2] Also, given that some nations have legislated against allowing the use of embryonic stem cells, there may be a question of who legally will have access to therapies derived from banked stem cell lines, particularly those of embryonic derivation.

A final issue, and the one we will discuss in this paper, is who *biologically* will have access to cell-based therapies. As we will show, the biological properties of stem cells themselves may make them less accessible to some potential recipients than to others, a situation we term the problem of *biological access*. Unless the problem of biological access is carefully addressed, an American stem cell bank may end up benefiting primarily white Americans, to the relative exclusion of the rest of the population. We must therefore ask which of all possible ways to structure an American stem cell bank is the most just.

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The future promise of cell engineering is the ability to control cells and their functions. In the interim, however, it seems likely that cell-based treatment for disease and injury will be orchestrated through the transplantation of stem cells or their products. As with more conventional types of transplants, immune rejection is a major potential problem. Immune rejection is the principal reason that a given stem cell-based therapy for a specific disorder might be biologically less available to one patient than to another.

Immune rejection is mediated by our genetic makeup, specifically the set of genes which code for a type of protein called human leukocyte antigens (HLA). These HLA proteins are on the surface of virtually all cells in the body, including stem cells, and they play an important role in immune recognition and rejection. We have two copies of each of these genes, one inherited from each parent. There are multiple genes that code for HLA and we have two copies of each, one on each member of a chromosome pair. Some of the most important genes for the purposes of HLA-mediated immune recognition and response are HLA-A, HLA-B, and HLA-DR.

These genes are highly polymorphic, meaning they occur in variant forms, each of which is known as an allele. When an individual has two different alleles (one inherited from each parent), she is heterozygous for that allele. When, by chance, both parents pass on the same allele for a particular gene, their child is homozygous for that allele, meaning she has two identical copies of the allele.

Different methods exist for characterizing the alleles (either through

[illegible]

Allele: a variant form of a gene.

Autologous transplant: transplantation in which the eventual transplant recipient is also the donor.

Haplotype: a group of alleles that are inherited together.

Hematopoietic cells: cells that are capable of producing blood cells. Bone marrow is one source of hematopoietic cells.

Hemizygous: possessing only one allele for a gene.

Heterozygous: possessing two different alleles, one inherited from each parent, for a specific gene.

Homozygous: possessing two identical alleles, one inherited from each parent, for a specific gene.

Human leukocyte antigens (HLA): a type of protein found on the surface of cells that plays a crucial role in immune recognition and rejection.

HLA match: the donor and the recipient have matching HLA types.

HLA type: individuals normally have two HLA-A alleles, two HLA-B alleles, and two HLA-DR alleles, one from each parent. This six-allele composition is referred to as a person's HLA type.

Polymorphic: a gene is polymorphic when many alleles exist for it.

Stem cell: a cell that has the ability to divide for indefinite periods in culture and to give rise to specialized cells.

Somatic-cell nuclear transfer (SCNT): a somatic cell nucleus is extracted and inserted into an enucleated egg, which is then prompted to begin development.

[illegible]

Genetics Home Reference Glossary, U.S. National Library of Medicine: http://ghr.nlm.nih.gov/ghr/glossary/Glossary

"Genomic Medicine Glossary," *NEJM* 347, 19 (2002)

Glossary and Terms, "Stem Cells: Scientific Progress and Future Research Directions," National Institutes of Health, June 2001

National Marrow Donor Program Website: http://www.marrow.org/index.html

Talking Glossary of Genetic Terms, National Human Genome Research Institute: http://www.genome.gov/glossary.cfm

A bank composed of the most common cell lines types in the United States would favor the most populous groups in the country.

serologic or DNA methods), and the alleles are usually given numeric codes, like 0101. To find someone's HLA type is to determine which alleles she has at specific locations on the chromosome. Three locations—A, B, and DR—and thus three sets of alleles, are particularly important to HLA-mediated immune functioning. A match entails the donor and the recipient having the same HLA-A, HLA-B, and HLA-DR alleles.[3]

An individual's HLA type is linked to her ancestry; however, even within a family there is variability in HLA expression. Identical twins have identical HLA because they have received the same genetic contribution from their parents. Siblings have a roughly one in four chance of sharing an HLA type. By contrast, parents and children virtually never have identical HLA types since both parents contribute to the alleles of the child, and the chance of two parents with identical HLA types is remote.

In both bone marrow transplantation and certain types of solid organ transplantation, the match between the donor's and the recipient's HLA plays a crucial role in the acceptance or rejection of the transplant. Finding an identical match for anyone other than an identical twin is complicated by the highly polymorphic nature of HLA. The array of alleles that each person possesses is called her haplotype. If one has a relatively common HLA haplotype, finding a match may not be hard. For people with rarer haplotypes, a match may not be forthcoming. Mismatched transplants can be performed, but they are an inferior option to a matched transplant because they require increased levels of immunosuppressive drugs, which are themselves burdensome for patients and more frequently result in transplant-related complications. Some data suggest that the number of allele mismatches has a cumulative effect on negative outcomes; that is, there is a gradation of outcomes from good to poor as the number of mismatches increases. Thus, patients with more common haplotypes have a better chance of finding a match—or having biological access—and thus better odds of a successful transplant.

HLA has been demonstrated to track with geographical ancestry. For example, persons of sub-Saharan African ancestry have a greater variety of HLA types than do persons of any other geographical or ethnic grouping. A person's ancestry may significantly diminish (or increase) the odds of locating an HLA match—whether of certain solid organs, bone marrow, or stem cells.

Rejection is a major research area for transplantation. The search is on for a way to allow all patients, regardless of their haplotypes, to be able to receive a transplant that will work for them. Success in this search might eventually render the concept of biological access meaningless. For now, however, the problem of immune rejection is a real obstacle to clinical success.

Since an identical match between the donor and recipient significantly reduces concerns about immune rejection, autologous grafts, in which the recipient acts as her own donor, are thought to be a promising way to avoid rejection. Unfortunately, two such autologous solutions, somatic-cell nuclear transfer and the isolation of existing stem cells from the patient's own body, are not practical at present.

In somatic-cell nuclear transfer (SCNT), a cell nucleus from the eventual transplant recipient is inserted into an oocyte from which the original nucleus has been removed, at which point the oocyte is triggered to develop. Although scientists have thus far failed to derive stem cells from human blastocysts created by SCNT, if such cells could be obtained, they would offer the recipient an exact genetic match (except for the mitochondrial genes, which do not affect HLA). Proponents of SCNT contend that this strategy could allow patients to receive customized HLA-matched therapies; however, the force of this claim is blunted by economic and logistical considerations. Although SCNT might, in theory, solve the rejection-biological access problem, it can do so only one person at a time. The amount of time and money needed to create these uniquely cloned solutions makes it unlikely that SCNT will provide a practical, widespread solution to the biological access problem. Additionally, for the foreseeable future, research in this area will continue to be overshadowed by political and moral controversy.

Some of the same limitations plague the second autologous strategy for solving the problem of rejection, that of using cells obtained directly from the patient herself through the identification and culturing of the patient's own adult stem cells.[4] Some claim that it is possible, at least in animal models, to derive adult stem cells that exhibit the same degree of developmental capacity as embryonic stem cells. From a public policy perspective, the adult sources alternative has great appeal, as it sidesteps altogether the difficult issue of embryo destruction. Whether adult sources are able to replace embryonic sources remains to be seen.[5] However, even if adult sources of stem cells are shown to be as robust as embryonic sources, using them to produce autologous stem cell-based therapies is problematic. At least for the near future, the laboratory procedures involved are extremely inefficient in generating sufficient cells. The isolation of adult stem cells yields very few cells, which are difficult to grow in culture. Like the

cloning strategy, the adult stem cell strategy is both time consuming and expensive.

There may be some circumstances in which the time and expense required to prepare customized autologous therapies are justified. For example, a stem cell-based therapy that cures a young child of a burdensome condition, thereby saving the health care system a lifetime's worth of medical expenses while providing a profound benefit to the child, might justify the time and expense of creating an autologous therapy. For most conditions, however, the costs of customized autologous therapies would be prohibitive, even for wealthy nations. Moreover, for conditions such as stroke and injury, where treatments may need to be administered quickly in order to be maximally effective, it may never be possible to prepare autologous stem cell therapies from adult (or cloned) sources within the required time constraints. Although non-autologous transplants supported by immunosuppressive therapies could in theory be used to sustain stroke and trauma patients during the time required to prepare customized, autologous stem cell therapies, here, too, the costs are likely to be prohibitive. Therefore, adult sources are not much more likely than cloned sources to provide a complete solution to the rejection-biological access problem, at least for the foreseeable future.

For the remainder of this paper, we assume that there is no "autologous fix" to the problem of biological access, at least not until the capacity to engineer cells advances to the stage where in vivo manipulation of stem cells is commonplace. In the interim, human therapies derived from stem cells will probably involve transplantation of grafts from a genetically non-identical donor. Furthermore, we assume further that, even if interventions directed at organ systems such as the brain or liver are found to be relatively unproblematic, at least some stem cell-derived therapies will create immune rejection problems.

At present, there are three main options in dealing with the problem of immune rejection: immunosuppressive drugs, clinically induced tolerance, and HLA matching.[6] Often, two or more of these techniques are used in combination. A fourth technique, genetic modification of cell lines to reduce their capacity to provoke an immune response, has no current application in clinical transplantation but perhaps could be used in future development of cell-based therapies. In theory, genetic modification could be used to create the equivalent of "universal" stem cells—cells that would not produce immune reactions in most patients.[7] From the perspective of justice, such a development would be ideal, since biological access for almost all persons would be guaranteed.[8] Animal experiments suggest avenues for pursuing the universal stem cell strategy; however, the technical barriers to defeating the multiple defenses of the immune system are formidable.[9] It may well be years, if not decades, before such engineering will be successful.

The most widely used strategy to deal with immune rejection is immunosuppression. Immunosuppressive drugs began to be widely used in the 1980s, greatly increasing the viability of HLA-mismatched organ donation. In many cases, however, transplant recipients need continual immunosuppression with drugs in order to avoid either acute or chronic rejection, even when HLA matching is available. The risks of immunosuppressive therapy are well documented and often severe. They include nephrotoxicity, diabetic and vascular complications, and an increased risk of infections.[10]

Another strategy by which to avoid rejection is the induction of immunologic tolerance. Experiments with animals have shown that various methods of reducing host immune response and promoting acceptance of grafted tissue can reduce rejection and lessen the need for ongoing immunosuppression of the graft recipient.[11] However, clinical applications for humans are still in development and are at present relatively risky. A technique for inducing tolerance called mixed chimerism is particularly intriguing in light of the potential of a single stem cell line to generate different tissue types.[12] In mixed chimerism, the host immune system is temporarily suppressed, and donor bone marrow is introduced into the recipient and allowed to engraft prior to transplant of an organ from the same donor. If the technique is successful, the recipient develops a chimeric immune system consisting of her own immune cells and the new cells engrafted from the bone marrow. This chimeric immune system should be tolerant of new tissue (for example, a transplanted organ) from the same donor. At present, few patients have undergone this procedure, mainly due to the risks involved, the uncertainty of success, and the need for a living donor who can provide both bone marrow and an organ, such as a kidney. However, data from animal experiments are promising.[13] If the same stem cell line could be induced to produce hematopoietic cells for transplant and the tissue of interest for therapy, the mixed chimerism approach could be used to provide patients with cell-based therapies from stem cells without extensive immunosuppression or the need for HLA matching.[14]

The third strategy for avoiding immune rejection is HLA matching; however, the importance of HLA matching in transplantation varies, depending on what tissue or organ is transplanted. For example, for bone marrow transplantation HLA matching is considered essential for a good clinical outcome,[15] while for liver transplantation, matching is not normally used.[16] The importance of HLA matching in transplantation also varies depending upon donor availability and disease severity. As mentioned above, while not consid-

ered optimal, mismatched transplants are performed, primarily if a match is not available.

The U.S. National Marrow Donor Program has compiled a registry of over four million donors, each of whom is typed for their HLA-A and B alleles, which are considered critical for matching. Due to the high degree of polymorphism in the relevant alleles, even with this enormous pool of donors only 50 to 60 percent of patients who need transplants can find a match.[17] Not only are the HLA alleles highly variable, but also different ethnic groups have different frequencies of specific alleles.[18] For example, the ten most common HLA-A alleles in white Americans are not the ten most common in African Americans, and vice versa.[19]

The transplant community has struggled with the issue of HLA distribution and its relation to immune rejection for years, in particular with regard to patients who are less likely to find a match due to their ethnic or racial background. This concern will extend from solid organ and bone marrow transplantation to stem cell transplants because stem cells bear the haplotype of the individual from whom the cell line was derived. Although the need for HLA matching of stem cell-derived therapies will likely vary depending on the tissue that is transplanted, matching will be critical to clinical success in at least some important therapeutic applications. As such, the disparities currently present in the field of transplantation are likely to be replicated in the emerging practice of stem cell transplantation, unless specifically guarded against.

We have addressed elsewhere the issue of whether the existing stem cell lines are suitable for use in human recipients.[20] Even assuming that current stem cell lines are appropriate for human use, they are woefully inadequate from the perspective of HLA matching. The situation in the United States is particularly acute. At present there is no publicly available information about the HLA types of the embryonic stem cell lines that are approved for federally funded research in the U.S. However, given the small number of lines[21] and the fact that these stem cells were derived from embryos created by in vitro fertilization for reproductive use, the diversity of HLA types among these lines is probably extremely limited. In the near term, the unlikelihood of haplotype diversity in available stem cell lines may significantly impede the efficiency and success of first human clinical trials. Looking ahead to therapeutic use, two concerns loom large: First, many patients will not be able to find a match and therefore will face more burdensome therapeutic regimens that are less likely to be successful. Second, some groups of people may be systematically disadvantaged if their ancestral/ethnic group was not well represented in the biological material that was initially used to derive stem cells, since their haplotypes are then less likely to be included in stem cell-based therapies.

A Public Policy Response to the Problem of Biological Access

We strongly recommend that all four of these strategies for dealing with immune rejection be actively pursued. Although the capacity to induce tolerance is currently in the earliest stages of clinical application, advances in this area hold great promise, not only for stem cell-based therapies but also for transplantation in general. Continued research into immunosuppression may lead to the development of next-generation drugs that have a reduced side-effect profile. The potential to develop a universal stem cell should be explored, although the scientific obstacles are formidable. In the near term, however, HLA matching, supplemented with immunosuppression as needed, remains the principal available approach to avoiding rejection.

HLA matching and transplantation raise serious questions of public policy and justice. In the American context, there have been many attempts to address one such issue: the relative unavailability of good matches for African American transplant recipients.[22] Public policy responses to this problem have generally been restricted to appeals to the African-American community for donation and to strategies to increase overall donation.[23] In the context of stem cell-based therapies, however, the availability of HLA types need not be constrained by the vagaries of organ donation. Although we are not currently able to produce solid organs or tissues for transplantation, we are able to create stem cell lines that can be used for research and, eventually, therapies. This means that it is within our power to construct a bank of stem cell lines that includes a wide spectrum of HLA types, specifically selected to satisfy considerations of justice.

Many countries have had considerable experience with the creation and maintenance of banks of biological materials for therapeutic use. Biological banks exist for blood, sperm, corneas, and umbilical cord blood. In addition, there are systems of collection and distribution for solid organs and bone marrow. Most of these banks and systems are organized and financed by government or through

Table 1. 25 Most Common HLA-A/B Haplotype Frequencies in Five U.S. Populations[1]

	African Americans (n=252)			White Americans (n=265)			Hispanics (n=234)			Native Americans (n=187)			Asian Americans (n=358)		
	HLA-A	HLA-B	Cumul Freq	HLA-A	HLA-B	Cumul Freq	HLA-A	HLA-B	Cumul Freq	HLA-A	HLA-B	Cumul Freq	HLA-A	HLA-B	Cumul Freq
1	2301	1503	.0314	0101	0801	.0726	2902	4403	.0299	0201	0702	.0399	3303	5801	.0612
2	0101	0801	.0580	0201	4402	.1244	0201	5101	.0549	0201	3501	.0751	0207	4601	.1002
3	3001	4201	.0818	0301	0702	.1631	0301	0702	.0751	2402	1501	.1058	1101	4001	.1333
4	0205	5801	.1017	0201	0702	.1911	2402	5101	.0929	2402	4002	.1357	3303	4403	.1644
5	3601	5301	.1212	0201	4001	.2150	0101	0801	.1102	2402	3501	.1614	2402	4001	.1905
6	0301	0702	.1398	0101	5701	.2331	0201	3512	.1272	6801	5101	.1833	1101	1502	.2048
7	2301	0702	.1565	0201	0801	.2481	1101	3501	.1420	0101	0801	.2044	2402	5101	.2320
8	0201	4501	.1714	0201	1501	.2626	0201	0702	.1565	0206	2705	.2245	1101	3802	.2482
9	0201	0702	.1859	0301	3501	.2757	0201	4402	.1700	0201	5101	.2416	1101	1301	.2631
10	7401	1503	.1971	2601	3801	.2822	0201	3501	.1828	0201	1501	.2574	2402	3802	.2774
11	0201	5301	.2080	2402	4402	.2977	3301	1402	.1947	3101	5101	.2700	0203	3802	.2900
12	6802	5301	.2186	2902	4403	.3075	0201	4403	.2065	0301	0702	.2820	1101	5101	.3006
13	0301	3501	.2285	3101	4001	.3167	0201	4002	.2164	2402	4001	.2936	2402	4002	.3097
14	3402	4403	.2374	1101	3501	.3250	0201	1501	.2260	2402	2705	.3048	2402	4006	.3258
15	0201	4402	.2460	0201	5101	.3330	2402	3906	.2352	2402	4402	.3148	3001	1302	.3326
16	3402	3501	.2545	0101	0702	.3405	0301	5201	.2442	0201	3901	.3244	2402	3501	.3394
17	0201	3501	.2622	0101	5101	.3477	2402	3501	.2520	3101	4002	.3331	1101	3901	.3451
18	2301	4501	.2693	1101	5101	.3546	0201	1801	.2597	0101	5101	.3409	1101	5401	.3521
19	1101	3501	.2761	0201	5701	.3613	2402	4002	.2672	0206	1501	.3483	0201	4801	.3522
20	6802	1510	.2823	0301	4402	.3677	0201	1402	.2745	0301	2705	. 3553	0201	1501	.3582
21	2902	0702	.2893	0201	3501	.3738	0201	5001	.2818	2402	3901	.3612	3401	1521	.3635
22	3303	5301	.2950	2501	1801	.3795	0201	5701	.2881	0201	4402	.3678	2402	5201	.3687
23	0301	5701	.3005	3201	1501	.3851	1101	2705	.2953	0201	4001	.3735	2402	1501	.3736
24	6802	1503	.3059	2402	1501	.3905	0301	3501	.3012	2402	4801	.3790	1101	5502	.3786
25	0202	5301	.3100	0201	1402	.3955	2601	4002	.3066	2501	1801	.3844	1101	1501	.3831

1. Haplotypes that are within the ten most common for at least two of these ancestral/ethnic groups are shaded, demonstrating overlaps.
This table was generated by John A. Hansen and colleagues at Fred Hutchinson Cancer Research Center using data from specimens from North American volunteer donors received by the U.S. National Marrow Donor Program. HLA-A and -B haplotype frequencies were adapted from K. Cao et al., "Analysis of the Frequencies of HLA-A, B, and C Alleles and Haplotypes in the Five Major Ethnic Groups of the United States Reveals High Levels of Diversity in These Loci and Contrasting Distribution Patterns in These Populations," *Human Immunology* 62 (2001): 1009-1030. Ethnicity of the donors was established by self-report. Further information concerning this table is available at http://www.thehastingscenter.org/publications/hcr/faden.htm.

some kind of public-private partnership. Regardless of their structure, with the exception of some proprietary cord blood and sperm banks, these tissue and organ collections are considered to be public resources.

There are numerous ethical and political challenges to establishing a public stem cell bank. Especially in the United States, it is questionable whether in the current climate there could be any government involvement in the bank's creation, financing, or oversight. First, however, we focus on the question of how, from the perspective of justice, stem cell banks should be constructed.

We begin with a discussion of the issues that surround the creation of a bank constructed to serve therapeutic needs, then describe the distinct considerations that apply to the research context. It turns out that separate structures for research and therapy banks are desirable.

Ideally, a stem cell bank would include sufficient diversity to permit every potential recipient to receive a good match. Unfortunately, such a bank would require the creation and maintenance of a collection of enormous magnitude. As we have already noted, even with a registry of over four million donors, the U.S. Bone Marrow Donor Program provides

Society may have to choose between what it values more: ensuring that all benefit fairly from science, or protecting embryonic human life.

matches for only 50 to 60 percent of those in need. The Bone Marrow Donor Program is a registry, providing searchable information on potential donors. Given the time needed to develop stem cell lines, we assume that a registry system would not be feasible for stem cell transplants. Rather, we propose a bank, where cell lines would be maintained and stored and samples distributed to clinicians as needed. We assume that constructing a stem cell bank with hundreds of thousands or even millions of stem cell lines is out of the question, if for no other reason than the huge financial cost of creating and maintaining so many stem cell lines.

We believe that the only plausible design for a stem cell bank is to build the bank with stem cell lines that are specifically designed to be homozygous with regard to those alleles that are the most important to transplantation. In standard matching procedures, six alleles (two each of HLA-A, B, and DR) of the donor and the recipient are compared. However, a person or a cell line that is homozygous expresses only one of each allele. A bank of homozygous stem cell lines would thus provide acceptable matches for many more patients because only three of a patient's alleles would need to match the alleles of the donor, as opposed to six for heterozygous cell lines.[24]

Constructing a bank of homozygous lines will be difficult, not only because of the numerous ethical and political challenges we address later in this paper. The probability of finding homozygous spare embryos from in vitro fertilization clinics is, at best, low. A more promising but also more controversial strategy would build the bank around gamete donation. Embryos could be created from the gametes of donors who share a common haplotype; such embryos would have roughly a one in four chance of being homozygous for the relevant three alleles. If perfected, SCNT could provide a means to secure the desired stem cell lines from genetically appropriate homozygous adults. However, this procedure is even more morally and politically controversial than conventional embryo creation. It might also eventually be possible to develop the desired lines from selected cells of homozygous adults or from the cord blood of homozygous newborns, but at the moment it is still unclear whether these sources will prove sufficiently robust to completely replace the need for embryonic stem cell lines.

Although the obstacles to creating a public homozygous stem cell bank, which we discuss later, are formidable, creating such a bank is, we believe, technically feasible. Despite the increased efficiency (and thus desirability) of a homozygous bank, the number of lines needed to provide appropriate matches for all potential patients would still be prohibitively large. Identifying and soliciting female and male gametes that share a common haplotype, creating embryos from these gametes (only one in four of which will be homozygous), deriving stem cells from the selected embryo, and establishing a stem cell line is a difficult challenge. Additionally, some homozygous stem cell lines would be practically impossible to create because some haplotypes are so extraordinarily rare that finding the needed gametes or adult sources would be extremely difficult. Given these limitations, we believe that the only plausible strategy is to create a stem cell bank of limited size, containing homozygous stem cell lines chosen for development because they express some desired combination of HLA alleles.

The central ethical challenge of this proposition is determining which combination of haplotypes to include in the limited bank of homozygous cell lines intended for therapeutic use. The first step toward addressing this challenge is an assessment of the options. We think there are three main strategies, each highlighting different considerations of justice, for the selection of cell lines to be included in a limited, homozygous public stem cell bank. A straightforward maximizing approach would seek to include those cell lines from which the most matches could be made. An egalitarian approach would give all individuals who it is feasible to include in the bank an equal chance at having their haplotype represented. What we call an ethnic representation strategy would select common haplotypes within each ancestral/ethnic group so that the members of any group would have the same chance of finding a match with the banked cell lines. We consider each of these strategies and argue that the last is the most defensible.

Coverage-Maximizing Strategy

The first strategy is to seek to include those homozygous cell lines that would allow the greatest percentage of the population to find a match in the bank. This strategy recognizes that not all cell lines are alike in terms of the number of people who might benefit from them. Some haplotypes are more common than others, and a limited bank can cover more people if it includes cell lines that possess the most common haplotypes. The obvious appeal of this strategy is that it provides for the largest number of potential beneficiaries of HLA matched stem cell-based treatments.

There are, however, two significant drawbacks to this approach. First, it ensures that persons with less common haplotypes could never benefit from the bank. One might

reasonably be concerned about the fairness of such a strategy. Second, a bank composed of cell lines possessing the most common haplotypes in the United States would statistically favor white Americans simply because white Americans are the most populous group in the country.

The haplotypes that occur most commonly in white Americans overlap somewhat with the most common haplotypes of other American ancestral/ethnic groups, but significant diversity exists among the groups. (The overlap for five American ancestral/ethnic groups is illustrated in Table 1.) Even with the overlaps shown here, not all ancestral/ethnic groups share common haplotypes. The most common HLA-A/B haplotype within white Americans, A 0101 B 0801, is among the ten most common for African Americans, Hispanics, and Native Americans; however, this haplotype is not among the twenty-five most common for Asian Americans. Moreover, the haplotypes presented in Table 1 are only HLA A-A/B; if HLA-DR were included, the overlap between ancestral/ethnic groups would decrease further.

Since white Americans are more numerous than America's other ancestral/ethnic groups, the inclusion of a haplotype found in a relatively small percentage of white Americans might extend coverage to more people than the inclusion of the haplotype most common in another ancestral/ethnic group. For this reason, if a bank included homozygous lines with the fifty most common haplotypes in the United States, the de facto result would be a bank composed primarily of lines whose haplotypes are common to white Americans. While this strategy would lead to a higher number of matches than any other, the matches would be clustered within the Caucasian ancestral group, exacerbating the health discrepancies that currently exist between ethnic groups within the United States—discrepancies that track histories of oppression and social injustice.

Table 2.

Number of Homozygous Cell Lines Needed to Match U.S. White and African American Populations at HLA-A, B, and DR[1]

Number of Cell Lines[2]	*Proportion Covered: White Americans*	*Proportion Covered: African Americans*
1	.090	.038
5	.250	.106
10	.352	.177
20	.486	.287
30	.587	.382
40	.711	.466
50	.780	.540
60	.839	.606
70	.916	.663
80		.717
90		.767
100		.813
110		.856
120		.895

1. The data are from Stephen J. O'Brien and colleagues. Further information concerning this table is available at http://www.thehastingscenter.org/publications/hcr/faden.htm.
2. These calculations refer to the most common haplotypes within each ethnic group. As such, the five cell lines referred to in line two will be different lines, with different haplotypes, for white Americans than for African Americans. (See Table 1.) While it is possible that the two groups may share some common haplotypes, the divergence between the two groups is increased when HLA-DR is included in addition to HLA-A and B.

One way of addressing the concern about fairness to individuals with less common haplotypes would be to give all haplotypes we can feasibly include in a bank, and thus all the individuals who have these haplotypes, an equal chance at being represented.[25] As a practical matter, it is effectively impossible to create homozygous stem cell lines for haplotypes that are sufficiently rare. It would be possible, however, to include in a bank many haplotypes that fall somewhere in between the rare and the common ones. The equal chances strategy seeks to promote fairness by giving all persons with haplotypes that can feasibly be represented in the bank the same chance at biological access to stem cell-based therapies. This could be accomplished by randomizing the process through which eligible haplotypes are selected for inclusion in the bank (for example, through some form of lottery in which all the relevant haplotypes are included).

While providing as many individuals as possible an equal chance of benefiting from the bank may accord with some basic intuitions about fairness, adopting the equal chances strategy has two real drawbacks. First, this strategy is not designed to address the problem of unequal access for members of different ancestral or ethnic groups. In practice, the equal chances approach might either alleviate or exacerbate these inequalities, depending on the outcome of the lottery. In either case, however, these results would be due to luck, not design, and might lead to even greater disparities between ancestral/ethnic groups than the coverage maximizing strategy. Some might argue that the ethnic inequalities that might result

from an equal chances strategy are more morally acceptable than those that would result from a coverage maximizing strategy because the process that yielded them is fair. However, those who hold that there are strong independent moral reasons to prevent further disadvantages for historically oppressed groups will not be satisfied by a process that might have this result.

Second, while a lottery might, as a matter of luck, lead to the inclusion of the same set of haplotypes as the coverage maximization strategy, the point of adopting the equal chances approach is to allow for other possibilities as well, including the possibility that most or all of the haplotypes included in the bank would be relatively uncommon. In this case, obviously, only a small number of persons would be able to benefit from the bank.

The problem that only a few might benefit from an equal chances bank becomes more acute when we consider which haplotypes we might reasonably exclude from the lottery on the grounds that they are so rare that they cannot feasibly be included. We must exclude any haplotypes that are so rare that it would be literally impossible to find donors of the gametes needed to create them. If we also excluded haplotypes on the grounds that it would not be impossible but merely extremely difficult and costly to find such donors, we would have to do so because we judged that the costs of including those haplotypes in the lottery would outweigh the benefits of doing so. But to exclude haplotypes from the lottery on this basis is inconsistent with the justification for the equal chances strategy.

That justification relies on two claims: first, that our attempts to benefit the greatest number of patients should be constrained by the requirements of justice, and second, that justice requires that we give those with uncommon haplotypes an equal chance of benefiting from the bank. If these assumptions are correct, then the fact that the equal chances strategy provides benefits to fewer patients than the coverage maximization strategy does not show that the equal chances strategy should not be adopted. By the same token, however, the fact that some haplotype is so uncommon that creating a homologous stem cell line with that haplotype would absorb most of the resources available to a bank cannot show that we should exclude it from the lottery. But if our lottery must include all such haplotypes, the number of uncommon haplotypes would be larger than one might have thought, and the probability that the bank would benefit only a very small number of people would be correspondingly greater.

We do not believe that justice requires the adoption of the equal chances strategy. In designing a bank to provide maximal coverage, we do not deprive those with uncommon haplotypes of a benefit to which they are antecedently entitled or ask them to make sacrifices from which they cannot expect to benefit. We are, instead, in a situation in which we must decide how best to allocate scarce resources. In other such situations we do not believe that the only fair way to make decisions is by lottery. For instance, those who allocate other scarce medical resources, such as ICU beds or organs, do not rely on lotteries to make their decisions, and we do not generally think that these practices are unfair. Depending on the context, allocation decisions take into account such factors as medical need or prognosis, even though this means that those who are less seriously ill or who are less likely to survive do not have an equal chance of securing the resource. Without some reason to regard the decision of which lines to include in a stem cell bank as different in kind from other decisions about the allocation of scarce resources to which no one is antecedently entitled, we should conclude that fairness does not require adoption of the equal chances strategy.

Still another reason for rejecting the equal chances strategy is that, at least for some, the primary justification for investing in stem cell research and the creation of a public bank is the advancement of human welfare, generally. From this standpoint, a process of creating the bank that yields very little benefit would be self-defeating. Whatever one thinks of the fairness of providing equal chances, we must not lose sight of the fact that in this instance we are seeking fairness within the context of advancing social welfare. If there is too little welfare or benefit, the putative fairness promoted through equal chances comes at too high a price.

[illegible]

Although we the authors do not all agree on this point,[26] most of us would prefer to select the most common haplotypes from each of the major ancestral/ethnic groups in the United States in order to make the bank useful to the same percentage of patients from each ethnic category. This strategy would be less efficient than the coverage maximizing strategy because it would take more cell lines to match the same number of patients overall. This is true for two reasons. First, the ethnic representation strategy holds that we should ex-

tend coverage to the same proportion of each ethnic group, even though a given percentage of a smaller group includes fewer people than the same percentage of a larger group. Second, different numbers of cell lines would be needed to cover the same percentage of different groups, due to the fact that some ethnic groups have more HLA diversity than others. For example, when matching for HLA-A, B, and DR, in order to ensure that roughly 50 percent of all white Americans and 50 percent of all African Americans could receive a suitable match, between sixty and eighty cell lines would be needed (Table 2). Twenty homozygous cells lines would be sufficient to match 48.6 percent of white Americans, but only 28.7 percent of African Americans. In order to cover approximately 50 percent of each group, between twenty and thirty cell lines would be needed for white Americans and between forty and fifty for African Americans.

Matching for the DR alleles in addition to the A and B alleles decreases the likelihood of finding a match and increases the number of cell lines necessary to match a given percentage of a population. In some cases it may be reasonable to match only A and B, depending on the type of tissue transplanted and the likelihood of a good clinical outcome. When matching for HLA-A and B only, in order to cover 30 percent of each of the five ancestral/ethnic groups shown in Table 1, approximately twenty-three cell lines for African Americans, twelve for white Americans, twenty-four for Hispanics, fourteen for Native Americans, and twelve for Asian Americans would need to be established, for a total of eighty-five cell lines.[27] By contrast, if the eighty-five most common haplotypes in the overall U.S. population were included (irrespective of ethnicity), white Americans would make up most of the potential matches.

Since white Americans constitute 75 percent of the overall population,[28] the haplotypes most common in this group are the most common in the U.S. population overall. If the ten most common haplotypes among white Americans (Table 1) were chosen for the stem cell bank, only three would overlap with the ten most common haplotypes for African Americans and Native Americans; there would be four overlaps with Hispanics, and none with Asian Americans. Thus, such a bank would provide matches for a much higher proportion of white Americans than of any other ancestral/ethnic group.[29]

On our proposal, fewer patients would have access to stem cell therapies than would otherwise be the case. We do not take lightly the idea of designing a bank in such a way that fewer patients will be able to benefit from it. Nonetheless, we believe that the ethnic representation strategy should be adopted. In the United States, ancestral/ethnic groups other than white Americans are the only groups of persons that share two traits: first, they would be systematically underrepresented in a bank constructed according to the coverage maximization strategy, and second, they have endured a history of discrimination within American society. The coverage maximization strategy would both mimic this discrimination and exacerbate its effects, which in our view argues against its adoption.

As members of societies that have a history of ethnic discrimination, we have an obligation to reduce ethnic disparities in life expectancy and other indicators of health. Insofar as these disparities are understood as present injustices, at the very least, public policy should not be formulated in ways that make them worse.[30] Insofar as they are the result of past injustices, as members of the society that produced them, we have an affirmative obligation to take steps to ameliorate them. For these reasons, it would be wrong to adopt policies that exacerbate the effects of discrimination, even if the factors that would serve to widen the disparity—for example, a higher rate of polymorphisms in one group as compared to another—are themselves unrelated to any historical or current social injustices.

Moreover, providing equal ethnic representation in a stem cell bank would prevent the expressive harm that would result from unequal representation. If we followed the coverage maximizing strategy, the resulting stem cell bank would ensure access to stem cell-based therapies for a much greater percentage of white Americans than other groups. For example, if the twenty-five most common haplotypes among all Americans were selected, due to the fact that white Americans are the most numerous group, all twenty-five haplotypes would be those common to white Americans. Thus, in the pool of twenty-five cell lines, approximately 40 percent of white Americans could find a match, while 7.8 percent of African Americans could be matched by this pool of cell lines, 19 percent of Hispanics, 21 percent of Native Americans, and 3.6 percent of Asian Americans.[31] The justification for adopting this strategy is based solely on a commitment to maximizing medical benefits, without regard to the implications for different ethnic groups. Indeed, had the population genetics worked out differently, the coverage maximizing strategy could have affected ethnic groups quite differently. Nevertheless, if a bank made the benefits of stem cell therapy avail-

The resulting human embryonic stem cell lines will not be matched to

allow for equitable biological access.

able almost exclusively to white Americans, members of minority ancestral/ethnic groups might well wonder whether their interests had been taken seriously by those who decided which lines to include. Given the history of American race relations, and of the medical profession's treatment of non-white Americans, this concern cannot be dismissed as unreasonable.[32] The need to avoid giving some persons reasonable grounds for concern about whether they are regarded as full and equal citizens whose interests are taken seriously, especially when those concerns have often been well founded, is a further reason to reject the coverage maximizing strategy.

While the ethnic representation approach is not maximally efficient, it does ensure that the greatest amount of benefit is produced consistent with an expression of respect for the fundamental equality of members of at least the major ancestral/ethnic groups in the United States.[33] Given the country's history of oppression of a number of minority groups and the continued fragility of race relations, a policy that allowed further privileging of white Americans over other groups would signal a failure to acknowledge the equal worth of persons of all ethnic groups.

A Stem Cell Bank for Clinical Research

We now turn to the question of how a research bank should be constructed. The goals of clinical research are distinct from the goals of clinical medicine, and so too are the relevant moral considerations. Everyone has an interest in research yielding its results as efficiently as possible and thus everyone has an interest in investigators being able to find appropriate human subjects quickly and easily. In contexts where HLA matching is thought to be important, it will be much easier to find eligible research subjects if the stem cell line from which the intervention is developed has a common haplotype. Thus in a research bank, as opposed to a therapeutic bank, the arguments favoring the equal chances strategy have no force. The arguments in favor of the ethnic representation strategy may also seem less persuasive, since the primary concern is to establish quickly whether a particular experimental treatment is indeed "safe and effective" and thus worth distributing to all.

We agree that a research bank should be designed to fit the needs of the research enterprise and thus that it should be comprosed primarily of homozygous stem cell lines for the most common haplotypes in the American population. However, there is a powerful argument for including at least several homozygous lines that are common in particular ancestral/ethnic groups. Without such lines, it is possible that researchers will be both less able and less likely to pursue the promise of stem cell science for diseases that occur disproportionately or present differently in different ethnic groups. If this were to occur, then it would not be possible for all to benefit fairly from society's investment in stem cell research. Assuming that there are good arguments for keeping the number of lines in a research bank to a minimum, a research bank of homozygous stem cell lines could likely function effectively with as few as fourteen lines—the six most common haplotypes of the population, which would match approximately 25 percent of all Americans (most of whom would be white Americans), as well as the two most common haplotypes in African Americans, Hispanics, Native Americans, and Asian Americans, which would match between 5 and 10 percent of the population in each of these ethnic groups (Table 1).

Global Justice

In this paper, we focus on research and therapy banks for the United States, and our analysis of how to construct these banks justly is specific to the American context. In stem cell banks designed for other countries or for multi-national banks, considerations of justice may well be specified differently and thus different patterns of haplotypes may be required.

A particularly important worry from the perspective of justice is how fairly to accommodate the world's population as stem cell medicine progresses. Data from the population genetics literature indicates that populations in different regions are likely to have significantly different HLA frequencies—both different from each other and different from the U.S. population—thus potentially confounding efforts to make therapies widely available on a global scale. For example, sub-Saharan African populations exhibit the highest degree of genetic diversity globally,[34] and this diversity is not well represented in groups in other world regions. Economic considerations would clearly come into play for countries in the global South, whose health care and health research budgets are already severely constrained—but again, this topic merits a separate analysis and is not the focus of our efforts. We assume that relatively rich countries will develop stem cell-based therapies and that eventually these products will be made financially available to those in poorer countries. To achieve biological access on a worldwide level, concerted effort and collaboration will be needed among developed nations pursuing stem cell-based therapies in order to consider genetic diversity in sufficiently broad terms to meet the needs of patients in resource-poor, as well as resource-rich, countries.

Moral and Political Challenges

There are several significant challenges to creating patterned stem cell banks in the manner we have proposed. Assuming for the time being that the cell lines will be derived from embryonic sources, the first challenge will be the solicitation of gametes. Many people will need to be HLA typed in order to identify donors who have the desired haplotypes. Female donors will have to undergo the bur-

densome process of ovarian hyperstimulation and oocyte retrieval, the risks and discomforts of which are not trivial. The acceptability of these risks turns in part on how they compare to the risks and discomforts of donating bone marrow or of being a living kidney or liver donor. Like these other transplantation donors, gamete donors to a stem cell bank should not be paid, thereby sharply distinguishing the banks from the practices of infertility programs. The burdens of ensuring a just system of access to stem cell therapies will fall disproportionately on women relative to men (for whom gamete donation is, by comparison, inconsequential). Whether women will be willing to become egg donors in the absence of financial compensation is unclear, although based on experience with the donation of bone marrow, kidneys, and livers, many people appear willing to assume medical burdens for the benefit of others. It is also possible that laboratory procedures will be developed to drive differentiation of human embryonic stem cells into oocytes,[35] obviating the need for egg donations from individual women. This technology has not yet been fully worked out, and thus cannot yet be counted on for establishing a stem cell repository.

A related challenge will be securing sufficient gamete donations from minority populations and, in particular, from African Americans. The whole point of the ethnic representation strategy is to ensure that minorities are not systematically disadvantaged in access to stem cell therapies. At the same time, however, the African American community is distrustful of the medical and scientific establishment. This distrust manifests itself in many ways, including reluctance to consent to organ donation and reluctance to participate in medical research. Since constructing the banks as proposed will be impossible if African Americans and other minority groups do not participate in it, securing their trust and commitment will be essential.

The most obvious, and most formidable, challenge to creating stem cell banks in the United States is the widespread disagreement about the moral status of early human life. It is certain that a significant portion of the population will be opposed to the creation of such banks solely because they necessitate the creation and destruction of embryos. It may be difficult for politicians or governmental entities to support the idea of a patterned stem cell bank because of the amount of controversy surrounding this very contentious issue.

At least in the near term, creating the desired pattern of homozygous cell lines will require deriving lines from new embryonic sources. Developing a just system of access to the benefits of stem cell therapies would thus appear to require the instrumental creation and destruction of embryonic life.[36] Therefore, we believe that it is morally desirable to delay creation of the therapy bank until there is solid evidence from early clinical trials that stem cell-based therapies will work. In the interim, we should examine the progress that is being made with non-embryonic sources of stem cells and with immunosuppression and tolerance-inducing techniques. If any of these approaches are significantly advanced by the time stem cell therapies are approaching clinical utility, it might render a therapy bank created through the destruction of embryos unnecessary.

At the same time, however, it is essential to establish a research stem cell bank in order to justly and safely proceed with human clinical investigation. Several avenues of research in stem cell science are approaching first human experiments. Elsewhere, we argue that the embryonic stem cell lines currently approved for federal funding are not appropriate for use in human beings.[37] Unless adult sources of stem cells can, in the very near term, be determined to produce robust stem cell lines, it is likely that the transition from the laboratory to clinical investigation will require the destruction of additional human embryos. A patterned research bank constructed of homozygous lines of common haplotypes may actually minimize this use of embryos. Possibly as few as fourteen lines would provide a sufficiently broad base for clinical research, including the investigation of applications of particular interest to minority communities.

Another challenge will be identifying a structure for the research bank that will allow it to function as a public good and thus to fulfill its social purpose. A complicated web of proprietary interests has made it very difficult for researchers to effectively use existing stem cell lines. It is unclear whether a research bank could be constructed that could avoid this morass, particularly if it is not established or regulated by the federal government. Since federal involvement in a research bank is unlikely, funding will need to come from the private sector. Philanthropic support would be more likely to ensure that the bank operates as a true public good than would a consortium of commercial interests. By the time a therapy bank needs to be constructed, government involvement may be possible. For example, public values may shift, should the clinical utility of embryonic stem cell lines be established. Alternatively, non-embryonic cells might become reliable sources of stem cell lines, allowing the therapy bank to be constructed without the use of embryos.

Although there is encouraging progress in research on adult sources, we are not optimistic that there will be a technical fix for the moral and public policy quandaries posed here. It seems most likely to us that evidence of therapeutic value will be at hand before alternatives to embryonic sources will be found to be practical. Although we strongly support continued research into better immunosuppressive therapies and tolerance induction and believe that advances will be made in this area, it also seems unlikely to us that they will render the clinical advantages of HLA matching moot. Thus, we believe that society

may well have to choose what it values more—ensuring that all benefit fairly from advances in stem cell science or protecting embryonic human life. If society decides to create a therapy bank, then every effort should be made to coordinate with similar efforts in other countries, in order to minimize the numbers of embryos that must be destroyed. The United Kingdom recently announced that it has already embarked on the creation of a stem cell bank of its own.[38] It is not known at this writing whether the U.K. bank is being designed to address considerations of justice. It is also not clear what kind of HLA distribution is represented in the U.K. bank or whether immunologic matching would be possible for some proportion of the U.S. population.

Current and future policies concerning scientific research need to be responsive to the concerns about equitable biological access addressed in this paper. The existing human embryonic stem cell lines in the United States on which federally funded research is allowed will be insufficient to meet this goal. Federal restrictions on stem cell research will need to be re-evaluated, along with policies regarding funding priorities, patent protections, and incentives to the research community in order to ensure that justice concerns are adequately addressed as scientific research progresses. Although the process will be controversial, the need for equitable biological access to new therapies must be balanced with respect for early human life. Thoughtful discussion among scientists, policymakers, and the public about these challenging issues will help ensure that new therapies are developed fairly and responsibly.

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1. See G. Vogel, "Pioneering Stem Cell Bank Will Soon Be Open for Deposits," Science 297 (2002): 1784; "China Approves Stem Cell Bank," BBC News World Edition, 11 December 2002.

2. It seems inevitable, and of serious moral concern, that there will be significant economic barriers to access to new therapies utilizing stem cells or other cell-based preparations. New technologies are usually expensive and thus the earliest (and sometimes only) beneficiaries of medical advances are the economically privileged, both within and between nations. While economic constraints with regard to access to stem cell therapies are troubling, they are but a special case of a general set of deep moral challenges about justice and health policy that are beyond our focus here. See World Health Organization, Advisory Committee on Human Health Research, Justice and Resource Allocation: Implications for the Post-Genomic Era. (Geneva: WHO, 2002).

3. In the clinical context, what is considered a match does not entirely negate concerns about compatibility because, in addition to the six alleles matched (two each for HLA-A, B and DR), there are additional alleles relevant to immune response. For example, there are differences in outcomes between HLA matched siblings and unrelated HLA matched donors, indicating that additional HLA alleles (apart from the six matched ones) or non-HLA antigens also play a role in clinical outcome. Therefore, even when a complete (6/6) match is identified for a transplant, some immunosuppression is normally required.

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6. See J.A. Bradley, E.M. Bolton, and R.A. Pedersen, "Stem Cell Medicine Encounters the Immune System," Nature Reviews: Immunology 2 (2002): 859-71. A novel approach to reducing, not eliminating, the cell lines' capacity to provoke an immune response would be to "knock out" or inactivate one copy of the alleles principally implicated in rejection (for example, HLA-A, -B and -DR). This technique would render the cell line hemizygous for those alleles; in other words, one allele would be present for each of these genes rather than two. This would greatly simplify the statistical challenge of HLA matching while enabling the cell to retain critically important functions of these molecules. There are technical challenges to creating knockouts that presumably could be overcome with sufficient time and resources. This strategy would not completely solve the problem of immune rejection but would facilitate matching strategies. In the interim, the principal approaches for dealing with rejection remain traditional HLA matching, immunosuppressive drugs, and tolerance.

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21. As of October 14, 2003, 12 lines were available for shipping. NIH Human Embryonic Stem Cell Registry. http://stemcells.nih.gov/registry/index.asp

22. B. Barger, T.W. Shroyer, S.L. Hudson, M.H. Deierhoi, W.H. Barber, J.J. Curtis, M.G. Phillips, B.A. Julian, R.S. Gaston, and D.A. Laskow, et al., "The Impact of the UNOS Mandatory Sharing Policy on Recipients of the Black and White Races—Experience at a Single Renal Transplant Center," Transplantation 53 (1992): 770-74; D.E. Butkus, E.E. Meydrech, and S.S. Raju, "Racial Differences in the Survival of Cadaveric Renal Allografts. Overriding Effects of HLA Matching and Socioeconomic Factors," NEJM 327 (1992): 840-5; M.H. Park, D.E. Tolman, and P.M. Kimball, "Disproportionate HLA Matching May Contribute to Racial Disparity in Patient Survival Following Cardiac Transplantation," Clinical Transplantation 10 (1996): 625-28.

23. In our present system, the supply of solid organs and tissues available for transplantation in the United States is restricted to donations, from either living or cadaveric sources. As such, the supply is finite and insufficient to provide for every individual in need of a transplant. There is ongoing discussion as to how the supply of organs and tissues may best be increased, including the proposal to adopt a presumed consent system in which all potential cadaver donors are considered for organ and tissue harvesting, unless they have explicitly stated that this is against their wishes. However, even if such a policy were adopted, it is likely that demand would still overwhelm supply and that organs and tissues would continue to be allocated within the context of scarcity.

24. While homozygous cell lines would be effective in providing tissue for transplant that could be recognized as "self" by T cells and antibodies in the recipient, a potential problem could arise with regard to natural killer (NK) cells, another cell population of the immune system that can interfere with engraftment of certain kinds of tissue grafts. Basically, T cells and B cells recognize foreign targets and thereby become activated to reject foreign tissue. In contrast, NK cells recognize familiar ("self") targets and become quiescent, appropriately failing to attack cells. Therefore, the absence of self molecules on transplanted tissue could cause a problem. While homozygous cells would express one set of matched HLA antigens, they would not express both. Thus, NK cells could potentially become activated due to a failure to achieve the normal shut-off mechanism that occurs when self molecules are recognized.

On the other hand, NK cells are much less potent as a cause of rejection than are T cells, and their importance would vary markedly depending on the type of tissue being transplanted. Since a given stem cell line could, in theory, be used to produce a variety of tissue types, in some cases NK reactivity might cause a problem; in other cases, not. For example, NK cells do not appear to cause rejection of solid organ transplants. They can cause rejection of bone marrow cell transplants and have been found responsible for the phenomenon known as hybrid resistance by which F1 hybrid mice reject bone marrow transplants from parental inbred strains. See I. Nakamura, K. Nakano, and G. Cudkowicz, "Target Determinants for F1 Hybrid Anti-Parental H-2d Cell-Mediated Lympholysis: Self Antigens Controlled by the D End," Journal of Immunology 130 (1983): 2429-33. However, even in this case, rejection can be overcome by use of greater numbers of donor cells so that NK-mediated resistance is relative rather than absolute. See R.M. Rembecki, V. Kumar, C.S. David, and M. Bennett, "Polymorphism of Hh-1, the Mouse Hemopoietic Histocompatibility Locus," Immunogenetics 28 (1988): 158-70.

25. Nicholas Rescher discusses a variation on this strategy in his article, "The Allocation of Exotic Medical Lifesaving Therapy," Ethics 79(1969): 173-86.

26. LeRoy Walters, Dan Brock, and Mark Greene do not endorse this position.

27. In fact, somewhat fewer than 85 cell lines would be needed overall because of the partial overlap of common haplotypes among ancestral/ethnic groups. The point we are emphasizing here is that different numbers of cell lines would be needed to cover the same percentage of each group.

28. "Overview of Race and Hispanic Origin: US Census Brief," U.S. Census Bureau. Issued March 2001. http://www.census.gov/prod/2001pubs/c2kbr01-1.pdf.

29. It is important to emphasize again two points about using ethnic categories to describe biological phenomena such as HLA diversity. First, the socially defined categories lack precision in terms of ancestry. For example, a person who self-identifies as Hispanic may have ancestors from one or more of four major world regions: North America, South America, Africa, and Europe. Second, a related point: all population subgroups in the United States have some degree of admixture, that is, mixing of groups with different ancestral origins, and this is particularly evident in African American and Hispanic populations. Because of the complex history of human migration, population growth, and mixing, there is no clear way to predict what genetic similarities might exist in different populations. Therefore an empirical approach is needed, exemplified by the tables we have included here.

30. Increases in health disparities do not necessarily result in injustice. If, for example, allowing greater health disparities made the worse-off groups better off than they would otherwise be, such disparities would arguably be consistent with principles of justice. Similarly, if a medical advance can only benefit some, but not all, any subsequent increase in health disparities is not necessarily unjust. The presumption against widening the gap is thus in principle a defeasible one. However, we do not see any considerations that would defeat the presumption in favor of reducing health disparities in the present context.

31. This calculation is based upon the data in Table 1, matching only HLA-A/B.

32. That this concern is reasonable is an important part of this argument. We are not arguing that a stem cell bank should be designed to avoid any possible suspicion that those who decided which cell lines to include discounted some people's interests. This demand would be unreasonable: there is no policy so obviously noble that no one could conceivably misinterpret the motives behind its adoption. However, the creation of a stem cell bank that covers most white Americans and few non-white Americans is not just a policy that someone might possibly misinterpret as reflecting a complete disregard for the interests of non-white Americans. It is a policy that plainly invites that interpretation, especially in light of America's history of discrimination against members of minority ancestral/ethnic groups. See V.N. Gamble, "Under the Shadow of Tuskegee: African Americans and Health Care," American Journal of Public Health 87 (1997): 1773-78. Moreover, it would, in our judgment, be difficult to allay the suspicion that those who chose to design a stem cell bank in such a way that virtually no non-white Americans could benefit from it had failed to take the interests of non-white Americans seriously.

33. Ideally, the bank should include stem cell lines that are representative of all ethnic groups that have distinctive HLA patterns, including Native Americans. Whether this will be possible is unclear, both in terms of practical feasibility and in terms of resources.

34. A. Sanchez-Mazas, "African Diversity from the HLA Point of View: Influence of Genetic Drift, Geography, Linguistics, and Natural Selection," Human Immunology 62 (2001): 937-48.

35. K. Hübner, G. Fuhrmann, L.K. Christenson, J. Kehler, R. Reinbold, R. De La Fuente, J. Wood, J.F. Strauss III, M. Boiani, and H.R. Schöler, "Derivation of Oocytes from Mouse Embryonic Stem Cells," Science 300 (2003): 1251-56.

36. Although many countries currently rohibit the creation of a bank that necessitates the creation and destruction of human embryos, there are several countries in which such activity would be legally permissible. Furthermore, those countries that have criminalized this process might be more apt to revise their laws once the clinical applications of stem cell-based therapies leave the realm of speculation and enter that of observable reality.

37. Forthcoming, L. Dawson et al., "Safety Issues in Cell-Based Intervention Trials," Fertility and Sterility 80 (2003): 1077-85.

38. National Institute for Biological Standards and Control. The UK Stem Cell Bank. 6 January 2003. http://www.nibsc.ac.uk/divisions/cbi/stemcell.html.