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# One Chance in a Million: Altruism and the Bone Marrow Registry

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For patients who suffer from leukemia or other blood diseases, a stem cell transplant frequently offers the best chance of survival. Such a transplant is likely to be a life saving event. According to the web site of the London Health Sciences Centre [29]:

“Long-term survival may be greater than 80 per cent, . . . depending on the type of disease treated, the patient’s age, and the severity of illness. For patients with acute leukemia, long-term survival is 50-60 per cent but this is much better than 20-25 per cent survival when patients are treated with chemotherapy alone. . . . recipients eventually return to a normal lifestyle.”

The most effective treatment for many blood diseases is radiation that destroys all blood cells in the body, both diseased and healthy. The blood cells must then be replaced with healthy ones. This is accomplished by transplanting blood-forming stem cells from a healthy donor whose immune system is compatible with that of the recipient. One’s best prospect for a donor is a brother or sister. The probability that two siblings are acceptable matches is one-fourth. Those who lack a sibling donor must search among the population at large. Finding a compatible stem cell donor is vastly more difficult than finding a blood donor. The probability that two randomly selected white Americans are of matching type is less than one in ten thousand. About twenty percent of white Americans are of types that are shared by less than one person in a million. The African-American population is genetically even more diverse. The probability that two randomly selected African-Americans will match is less than one in one hundred thousand.

A remarkable set of institutions has developed for matching needy patients with compatible donors. These institutions, known as bone marrow registries, collect a list of potential volunteer stem cell donors. Those who join a registry must express their willingness to donate to any patient in need of a transplant. At the time of registration, a saliva sample is collected from the potential donor for DNA testing. The registrant’s type is stored along with the donor’s contact information. The United States National Marrow Donor Program (NMDP) began to operate in 1986 and currently maintains a registry of more than six million potential donors whose type has been determined.<sup>1</sup> The NMDP has expanded its scope internationally to include approximately 1.5 million registrants from the German bone marrow registry and smaller numbers from the registries of Sweden, Norway, the

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<sup>1</sup>See J. McCullough, H. Perkins, and J. Hansen [30] and B. Fisher [18] for discussions of the history of bone marrow registries in the United States.

Netherlands, and Israel. Other countries have national registries that are not incorporated in the NMDP, but are at least partially linked by a worldwide clearing house. There are approximately eleven million registrants in bone marrow registries throughout the world.

The existence of bone marrow registries raises interesting questions: How does the size and racial composition of the current registry compare with that of an optimal registry? What motivates people to join the registry? What financial and/or social incentives would be suitable for increasing registry size? This paper will address each of these questions.

Everyone in society faces a risk that they or a loved one will at some time need a stem cell transplant. Thus, everyone benefits from the existence of bone marrow registries. But an efficient registry would not include everyone. As the registry size increases, there is diminishing probability that adding another registrant will add an unrepresented type. Eventually, the value of marginal benefits from an additional registrant will fall below the marginal cost. This will determine the optimal size and racial composition of the registry.

We apply biologists' estimates of the probability distribution of immunity types and medical data on survival probabilities of transplant recipients to estimate the probability that an additional registrant will save a life. We then use economic estimates of the money value of a statistical life to calculate the expected value of an additional registrant. Finally, we compare this value to the marginal cost of adding an additional person to the registry.

Our estimates indicate that there is a strong case for increasing the number of registrants of all races, with the greatest net benefit coming from additional African-Americans. We estimate the size and racial make-up of an optimal registry. The current registry includes between two and three percent of the eligible U.S. population of whites, African-Americans, and Hispanics, and more than six percent of eligible Asian-Americans. An optimal registry would include approximately one-fourth of all eligible African-Americans and Asian-Americans, fourteen percent of eligible Hispanics, and seven percent of eligible whites.

The probability that a white American will fail to find a match in the current registry is less than ten percent, while for African-Americans, this probability is nearly forty percent. In an optimally constituted registry, the probability of finding no match would be about three percent for whites, nine percent for Asian-Americans and twelve percent for African-Americans. The persistence of racial differences in no-match probabilities in an optimal registry results in part from the greater genetic diversity of the Asian-American and African-American populations and in part from the fact that these pop-

ulations are smaller than the white population and hence have fewer patients seeking matches.

Those who donate stem cells bear a significant cost. Stem cells can be contributed by either of two procedures.<sup>2</sup> The more traditional method is a bone marrow transplant. Bone marrow is “harvested” from the donor’s pelvis by means of insertions of a needle that reaches the center of the bone. This operation is performed under general or regional anesthesia. A more recently developed procedure transfers stem cells collected by a filtering process from the donor’s bloodstream. This process, known as peripheral blood stem cell (PBSC) donation, requires the same type of genetic match as marrow transplants. Before the transfer, the donor is given a drug that produces a higher-than-normal number of stem cells in the bloodstream. This procedure does not require anesthesia. Both procedures impose serious inconvenience and discomfort, along with temporary side effects.<sup>3</sup> Neither procedure is likely to have long term health effects on the donor.

The biology of stem cell donations poses an unusual free-rider problem. Some who would willingly incur the costs of a donation if there were no other way to save the patient’s life might prefer to let someone else bear this cost if another donor is available. If a registrant is asked to donate, the registry may or may not contain other suitable donors for the same patient. If other matching registrants are available, the net effect of one’s own donation is simply to displace another donor. Joining the registry will be more attractive if it is likely that one will be the only available match when asked to donate.

The probability, conditional on being asked to donate, that one is the only match for the patient depends on one’s race and on the number of persons of each race who are currently in the registry. With the existing registry, this probability is about eight percent for whites and almost eighty percent for African-Americans. In an optimal registry these percentages would fall to about three percent for whites and twenty percent for African-Americans.

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<sup>2</sup>A third source of stem cells is umbilical cord blood collected from newborns’ placentas at delivery. Cord blood storage is unlikely to replace the bone marrow registry on a large scale because it is dramatically more expensive to store frozen cord blood than to store data about potential donors. The number of cord blood units stored is less than one percent of the number of persons in the registry.

<sup>3</sup>According to the NMDP web site, “Marrow donors can expect to feel some soreness in their lower back for a few days or longer... Some may take two to three weeks before they feel completely recovered.” The web site reports that PBSC donors often experience bone pain and flu-like symptoms, as well as occasional insomnia, headaches, fatigue, nausea, and vomiting.

Not only would an optimal registry have to attract more volunteers of all races than the current registry, but it would have to attract them despite the fact that in an optimal registry, a donor will be less likely to be the only available match for the recipient. It is therefore unclear whether a large enough registry can be obtained solely from unpaid volunteers. We consider the incentive problems that are likely to attend alternative forms of financial and social inducements and we suggest that payments to donors are more likely to be effective than payments to new registrants.

## Some Genetic Background

The body's immune system uses proteins known as human leukocyte antigens (HLA) to distinguish cells that belong to the body from those that do not. A stem cell transplant is likely to be successful only if the donor's HLA type is sufficiently close to that of the recipient. A person's HLA type is determined by genes located on chromosome 6, one copy of which is inherited from each parent. Until recently, the medical standard for an HLA match compared the specific contents, or *alleles*, of the three genes HLA-A, HLA-B, and HLA-DRB1 at a low level of resolution. Using this standard, there are about twenty million HLA-types.<sup>4</sup>

Two siblings have matching HLA types with probability one-fourth, since they match only if they both inherit the same version of chromosome 6 from each parent. A specific combination of alleles for HLA-A, HLA-B, and HLA-DRB1 on one chromosome is known as a *haplotype*. An individual's HLA compatibility is determined by the full list of six alleles on her two copies of chromosome 6. This is known as her *phenotype*. We obtained data on the population distribution of HLA types from a study by Motomi Mori *et al* [34], which is based on a sample of about 400,000 individuals who were registered with the National Marrow Donor Program in 1995 and whose HLA-A,-B,-DR phenotypes were recorded. The distribution of HLA types is markedly different across races, and sample observations have accordingly been partitioned into five racial groups: whites, African-Americans, Asian-Americans, Hispanics, and Native Americans.

Because the sample is small relative to the number of possible phenotypes, direct estimation of the population distribution of phenotypes would not be effective. However, with an elegant application of statistics and ge-

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<sup>4</sup>Recent research indicates that outcomes are improved by using higher resolution matching and by considering at least one additional gene from chromosome 6. We will discuss the effect of more refined matching later in this paper.

Table 1: Probability of HLA Match by Race

	White	African-Am	Asian-Am	Hispanic	Native Am
White	1/11,000				
African-Am	1/113,000	1/98,000			
Asian-Am	1/223,000	1/1,310,000	1/29,000		
Hispanic	1/44,000	1/259,000	1/254,000	1/34,000	
Native Am	1/13,000	1/116,000	1/173,000	1/36,000	1/11,000

*Notes:* Probabilities are calculated with Matlab, using our construction of phenotype distribution for each race, based on the Mori estimates [34] of haplotype distribution.

netic theory, geneticists are able to exploit this data much more powerfully. Mori *et al* [34] assume that within racial groups, mating is random with respect to HLA type. Based on this assumption, they use the observed distribution of phenotypes to construct a maximum likelihood distribution of haplotypes for each of the five racial groups. This process assigns positive estimated frequencies to about eleven thousand haplotypes. With this estimate of haplotype frequencies and the assumption of random mating within races, it is possible to estimate the frequency distributions of genetic types that are not directly observed in the sample. We use the haplotype distribution published by Mori *et al* to construct such an estimate of the distribution of phenotypes in each group.<sup>5</sup> This process assigns positive probabilities to more than ten million distinct phenotypes.

Table 1 shows the probabilities by race that two randomly selected persons would have matching HLA types. Although two people are more likely to match if they are of the same race, the probability of matches across races is not negligible. The distribution of types is far from uniform. Some types are relatively common and some are extremely rare. The probability is about one in eleven thousand that two randomly selected white Americans are of matching types. But about half of the white population are of types that occur with frequency less than one in one hundred thousand, and about one-fifth are in groups with frequency less than one in a million. The African-American population is even more heterogeneous. The probability

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<sup>5</sup>An individual's phenotype is determined by the contents of his or her two haplotypes. The distribution of phenotypes is not the same as that of haplotype pairs (genotypes) because phenotypes do not distinguish how alleles are divided between the two chromosomes.

that two randomly selected African-Americans have matching types is about one tenth of the corresponding probability for two whites.

## Benefit-Cost Analysis

The welfare economics of the bone marrow registry is simplified and symmetrized by a “veil of ignorance” that shrouds knowledge of our medical futures. Nobody knows whether they or their loved ones will ever need a stem cell transplant. Hardly anyone knows whether they have a rare or a common HLA type. Additions to the registry are public goods that benefit everyone by increasing the probability of finding a donor if one is needed. Although the HLA type of registrants is not known until after they are enrolled and tested, the frequency distribution of types is known to differ by race. Thus we treat the number of registrants of each race as a distinct public good. We estimate the summed willingness-to-pay of persons of each race for adding an additional person of any specified race to the registry.

### Estimating Probabilities of Finding a Match

Our first step in measuring benefits is to estimate the effect of an additional registrant of specified race on the probability that individuals who seek transplants will find a match in the registry. We estimate this effect using probability distributions of HLA types by race that we constructed from the Mori estimates of haplotype distribution. Since about ten million types have non-zero probabilities, the estimated probability distributions of HLA types are vectors with ten million components. This calculation is made possible by the remarkable computational power of Matlab.

A significant fraction of those listed in the bone marrow registry are not available to donate when called upon. Some have moved without leaving forwarding addresses, some have health conditions that prevent them from donating, and some are no longer willing to contribute. To estimate probabilities of finding a match, we use “effective” registry sizes, which are expected numbers of registrants who are available to donate if called. Table 2 reports, by race, the number of persons in the registry, the fraction available, the effective number in the registry, and the probability that a randomly selected person lacks an HLA-match in the registry.<sup>6</sup>

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<sup>6</sup>The estimated fractions of registrants available when asked are based on NMDP experience as reported by Craig Kollman *et al* [25].



Table 2: Registry size and probability of no match, by race, in 2006

Race	Number in Registry	Fraction Available	Effective No. in Registry	Probability of No Match
White	4,444,335	.65	2,888,818	.08
African-Am	485,791	.34	165,169	.38
Asian-Am	432,293	.44	190,209	.21
Hispanic	594,801	.47	279,556	.16
Native Am	70,781	.48	33,975	.11

*Notes:* Registration statistics are obtained from NMDP Registry and Transplant Statistics [37]. The published table includes 1.5 million registrants of “unknown” race. According to the NMDP, almost all of these are recruited through international registries in Germany, the Netherlands, Sweden, Norway, and Israel, which do not collect information on race. Since the racial composition of these countries is almost entirely white, we count all of the unknowns as white. After 2002, the NMDP began to ask those listed as Hispanic to specify whether they were white, African-American, Asian-American, or Native American. We treat Hispanic as a racial group because our data on HLA distributions does so. This requires an imputation to avoid double-counting of registrants as being both Hispanic and a member of one of our other racial groups.

We calculate the probability that a person of specified race will find a match as follows. Let  $R$  be a vector listing the effective number of persons of each of the five races, white, African-American, Asian-American, Hispanic, and Native American, in the registry. For each race  $x$ ,  $R_x$  is the number of persons of race  $x$  in the registry. Let  $p_i^x$  be the fraction of the population of race  $x$  that is of HLA type  $i$ . We assume that within races, a person’s HLA type does not influence the probability of joining the registry. The probability that no type  $i$ ’s are found among registrants of race  $x$  is the probability that no type  $i$ ’s are selected in  $R_x$  random draws from the population of race  $x$ . This probability is

$$(1 - p_i^x)^{R_x}. \tag{1}$$

A registry with enrollment vector  $R$  contains no persons of type  $i$  if there are no type  $i$ ’s among registrants of any race. Therefore, when  $R$  is the vector of registrants by race, the probability that a person of type  $i$  has no match of any race in the registry is

$$p_i^0(R) = \prod_x (1 - p_i^x)^{R_x}. \tag{2}$$

The probability that a person of race  $x$  has no match in the registry is therefore

$$\sum_i p_i^x p_i^0(R). \quad (3)$$

Let us define  $G_{xy}(R)$  to be the increase in the probability that a random member of race  $y$  has a match in the registry if one adds one registrant of race  $x$  to a registry of composition  $R$ . The probability that someone of race  $y$  is of type  $i$  and has no match in the registry is  $p_i^y p_i^0(R)$ , and the probability that a new registrant of race  $x$  is of type  $i$  is  $p_i^x$ . Therefore the probability that a person of race  $y$  is of type  $i$ , has no match in the current registry, and will have a match if an additional person of race  $x$  is added to the registry is  $p_i^x p_i^y p_i^0(R)$ . Summing these probabilities over the types, we have

$$G_{xy}(R) = \sum_i p_i^y p_i^x p_i^0(R). \quad (4)$$

It is interesting to see that  $G_{xy}(R)$  is symmetric in  $x$  and  $y$ . Thus the effect of adding a registrant of race  $x$  on the probability that a person of race  $y$  will find a match is the same as that of adding a registrant of race  $y$  on the probability that a person of race  $x$  will find a match. Since we have estimated the type frequencies,  $p_i^x$  and  $p_i^y$ , for any two races  $x$  and  $y$  and the probabilities  $p_i^0(R)$  that a member of type  $i$  will have no match, we can calculate the effects  $G_{xy}(R)$  for any pair of races. Table 3 shows the increased probability of finding a registered match by race of the registrant and of the recipient.

Table 3: Gain in match probability from adding one registrant (Figures in table must be multiplied by  $10^{-7}$ )

Gain to a member of this Race	Race of Added registrant				
	White	African-Am	Asian-Am	Hispanic	Native Am
White	0.143	0.136	0.094	0.146	0.132
African-Am	0.136	6.043	0.154	0.547	0.287
Asian-Am	0.094	0.154	3.727	0.212	0.207
Hispanic	0.146	0.547	0.212	1.124	0.305
Native Am	0.132	0.287	0.207	0.305	1.012

*Notes:* Entries are calculated with Matlab using Equations 3 and 4 above, with estimated frequency distribution of phenotypes based on Mori's haplotype distribution [34]. Numbers reported in table are  $10^7$  times actual effects of one person.

## Estimating the Number of Lives Saved

To estimate the number of lives saved by an additional registrant, we first estimate the number of patients of each race who seek transplants. We then calculate the expected increased probabilities of finding a compatible donor that result from adding one more donor of a given race. Finally, we multiply the increased probabilities of finding a compatible donor by the increase in long term survival probability that results from obtaining a transplant.

The first column of Table 4 reports the number of persons of each race who received transplants in 2006. The second column estimates the numbers who would have obtained transplants had a match been available, but who were unable to find a match. The third column estimates the total number of persons seeking transplants.

Table 4: Numbers of Actual and Potential Transplants (2006)

Race	Actual Transplants	Number with No Match	Potential Transplants
White	2394	203	2597
African-Am	120	72	192
Asian-Am	83	22	105
Hispanic	191	38	229
Native Am	12	1	13
All Races	2800	336	3136

*Notes:* The NMDP report *Number of Allogenic Transplants Performed* [38], shows that in 2006, approximately 2,800 patients received transplants through the NMDP, either from bone marrow or peripheral stem cell donations. We apply the proportions of all transplants performed since 1987 by race, as reported in the *2004 Biennial Report of the NMDP* [35], to estimate numbers of patients of each race in 2006. To estimate the number of potential transplants of each race, we divide the number of actual transplants by the probability that someone of that race finds a match in the registry. The probability of finding a match is just one minus the “probability of no match” reported in table 2.

We next estimate the expected annual increase in the number of transplants to persons of race  $y$  that would result from an additional registrant of race  $x$ . To obtain this estimate, we multiply the number of potential transplants to persons of race  $y$  found in Table 4 by the estimate in Table 3 of the increased match probability for persons of race  $y$  resulting from an additional registrant of race  $x$ . In Table 5, we report the expected number

of additional transplants that result from adding 1,000 new registrants of each specified race.

Not every transplant saves a life. With some probability, the recipient will die shortly after receiving the transplant. With some probability, a patient would survive without a transplant. To obtain the effect of an additional registrant on the expected number of lives saved, we need to multiply the increase in the expected number of transplants by the probability that a transplant saves an additional life. The biennial report of the NMDP ([35], page 3-37), reports that the probability that a transplant recipient survives for at least ten years after a transplant is about thirty percent. Survival probabilities of patients who do and do not receive transplants depend on the medical condition for which they are treated. We have surveyed the medical literature on each of the most common conditions treated by stem cell transplants. Appendix B of this paper reports for each condition an estimate of the long term survival probability of those who receive transplants and of those who receive the next best available treatment. We estimate that the availability of an HLA compatible donor increases long term survival probability of a patient seeking a transplant by an average of twenty-one percentage points. Therefore we calculate the expected number of lives saved by an additional registrant as twenty-one percent of the probability that the additional registrant is a match for a patient who had no other match in the registry. Table 5 reports the expected number of lives saved by adding 1,000 new registrants of each specified race.

Table 5: Expected annual additional transplants and lives saved by adding 1,000 effective registrants

Race of New Registrants	Expected Annual Transplants Added	Expected Annual Lives Saved
White	0.044	0.009
African-Am	0.166	0.035
Asian-Am	0.072	0.015
Hispanic	0.077	0.016
Native Am	0.050	0.010

## Valuing Lives Saved

The benefits of the bone marrow registry are well suited to measurement using the value of statistical life approach. This method was introduced by E.J. Mishan [32], and further developed for analysis of public projects by Theodore Bergstrom [6] and Pierre Dehez and Jacques Drèze [13]. The underlying theory and its empirical implications are lucidly explained in a survey by Kip Viscusi and Joseph Aldy [49]. An individual’s “value of statistical life” (VSL) is her marginal rate of substitution between survival probability and wealth—the rate at which she is willing to make exchanges between monetary wealth and small changes in survival probability. For example, someone who would pay \$1000 to eliminate a one-time fatality risk of .0001 would have a value of statistical life of approximately  $\$1000 \div .0001 = \$10,000,000$ . A larger registry benefits each person in society by contributing a small increment to the survival probability of each. The marginal rate of substitution of an individual between this public good and private consumption is the product of the effect on her survival probability times her value of statistical life. The Samuelson condition for efficient provision of a public good compares the sum of individual marginal rates of substitution between the public good and private goods to the marginal cost of the public good relative to private goods. If individuals’ values of statistical life are uncorrelated with their gains in survival probability from a larger registry, then the sum of marginal rates of substitution is equal to the average VSL times the expected number of lives saved.

Many efforts have been made to estimate the value of a statistical life using a wide variety of methods, including ingeniously designed surveys (Michael Jones-Lee, M. Hammerton and P. R. Philips [24] and Magnus Johannesson, Per-Olav Johanson, and Karl-Gustav Löfgren [23]), studies of market wage premiums for dangerous work, consumer decisions about purchasing consumer safety devices, health care decisions, and decision rules used by government agencies. Viscusi and Aldy [49] review a large number of these studies. Estimated valuations vary widely across studies and methodologies, but according to Viscusi and Aldy, are mainly concentrated in the range from four to nine million U.S. dollars. We assume a value of statistical life of \$6.5 million, the midpoint of this range. This is consistent with the policies of the U.S. Environmental Protection Agency, as reported in their publication “Guidelines for Preparing Economic Analyses” [48], which recommends a VSL equivalent to 6.75 million 2004 dollars.

After joining the registry, potential donors can remain in the registry until they reach age 61. According to the NMDP 2004 biennial report [35]

Table 2-1, page 2-24, the median age of new registrants is 35 years. We therefore assume that new registrants will remain in the registry for 25 years and we discount the annual flow of benefits at a rate of 2 percent per year. Table 6 reports our estimate of the present value of an additional (effective) registrant under these assumptions.

Table 6: Present value of an additional effective registrant

<b>Total present value to this group</b>	<b>Race of the additional effective registrant</b>				
	White	African-Am	Asian-Am	Hispanic	Native Am
White	\$1012	\$961	\$664	\$1,028	\$928
African-Am	\$71	\$3155	\$81	\$285	\$150
Asian-Am	\$27	\$44	\$1,063	\$60	\$59
Hispanic	\$91	\$341	\$132	\$701	\$190
Native Am	\$5	\$10	\$8	\$11	\$37
Total Value	\$1,206	\$4,512	\$1,947	\$2,085	\$1,364

The entries in the first row show that the white population benefits substantially from additional registrants of other races. This is true mainly because there is a large population of whites who are potential beneficiaries.

### Costs of An Additional Registrant

The NMDP web-site reports a cost of \$52 for tissue-typing an additional registrant in 2007. Personal communication with sources at the NMDP indicates that the total cost of obtaining sample material, tissue-typing, and maintaining a record of a new potential donor's contact information is approximately \$105. We have calculated benefits for an additional *effective* registrant—one who is able and willing to make a donation if called upon. Since not all registrants are available when called upon, our cost estimates must include the cost of registering more than one person per effective registrant. Kollman *et al* [25] report that, based on NMDP experience, the fractions of recent registrants who can be located, pass the physical examination, and who consent to make a donation are .70 for white registrants, .42 for African-Americans, .50 for Asian-Americans, and .52 for Hispanics.<sup>7</sup>

<sup>7</sup>These fractions are larger for recent registrants than for earlier registrants because HLA types were misclassified for a significant number of earlier registrants. Current DNA

Increasing the number of registrants increases the expected number of transplants and hence the expected total hospital and physician costs of performing these transplants. We estimate total hospital and physician costs for a transplant at about \$166,000.<sup>8</sup> Multiplying this cost by the expected number of additional transplants resulting from an additional registrant (see Table 5), we find that the expected annual hospitalization costs resulting from adding a registrant range from about \$7 for whites to about \$28 for African-American registrants.

### Comparing Benefits and Costs

Table 7 shows estimated marginal benefits and costs from adding an effective registrant to the bone marrow registry. Marginal benefits exceed costs for all races and the benefit-cost ratio is highest for African-Americans. The 2004 Biennial Report of the NMDP [35] announced that the NMDP has “changed its strategy in recent years to focus more on recruiting minority volunteer donors and less on recruiting Caucasian volunteers” (page 2.27). The report shows that the number of new white registrants diminished by about twenty five percent from 1996 until 2004, while the number of new registrants from minority groups was roughly constant. The NMDP’s emphasis on recruiting African-American donors, particularly given a fixed budget, is consistent with our estimates of benefit-cost ratios. However, our results indicate that there is a strong case for increasing the total budget of the NMDP to allow increased recruitment of registrants from all races.

Table 7: Benefit-cost comparison for an additional registrant

	<b>Race of the additional registrant</b>				
	White	African-Am	Asian-Am	Hispanic	Native Am
Benefit	\$1206	\$4,512	\$1,947	\$2,078	\$1364
Total Cost	\$297	\$800	\$446	\$455	\$359
B/C Ratio	4.1	5.6	4.4	4.6	3.8

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testing methods have largely eliminated this problem for new registrants.

<sup>8</sup>This estimate is based on a survey of costs in 2001 by Alberto Redaelli et al [41] and converted to 2007 dollars.

## Optimal Registry Size and Composition

We have seen that the expected present value of benefits exceeds the cost of adding registrants to the current NMDP registry. We next investigate the size and racial composition of an optimal registry—one that maximizes the difference between total benefits and total costs. Our task is made more complex by the differences in type distribution across races and by the fact that a significant number of matches occur across races. Fortunately, it turns out that the difference between total benefits and total costs is a strictly concave function of the vector of numbers of registrants of each race. (We prove this in Appendix A.) Therefore a local optimum is also a unique global optimum and so we can use straightforward numerical methods to find the number of persons of each race in an optimal registry. Table 8 reports the number of persons of each race<sup>9</sup> in an optimal registry and compares it to the existing registry size<sup>10</sup> By our calculations, the optimal registry size is more than two-and-a-half times as large as the current registry for all races, and nearly ten times as large for African-Americans.

Table 8: Actual and optimal registry size (in millions)

Race	Number in registry	Optimal number in registry	Ratio optimal to actual
White	4.44	12.11	2.72
African-Am	0.49	4.73	9.75
Asian-Am	0.43	1.76	4.07
Hispanic	0.59	2.93	4.93

The bone marrow registry is less than twenty years old, and registrants remain eligible on average for about twenty-five years after joining. Therefore, the registry has continued to grow, although the number of new registrants has diminished in recent years.<sup>11</sup> Current registration rates, however, do not appear to be sufficient to achieve the optimal registry size, even in the long run. If registrants remain in the registry for an average of 25 years,

<sup>9</sup>We omit estimates for Native Americans. The distribution of HLA types of Native Americans is very similar to that of whites. As a result, the calculation of the optimal number of Native American registrants is volatile.

<sup>10</sup>The figures reported are total registry sizes, not effective registry sizes.

<sup>11</sup>The number of new registrants was 630,000 in 1996 and was approximately 500,000 in 2004. In 2004, approximately 85,000 registrants turned 61 and were removed from the registry.



then in long run equilibrium, the number of new registrants per year would have to be about four percent of the optimal registry size. Table 9 compares current registration rates with steady state optimal rates for each race.

Table 9: Current and steady state optimal registrations per year

Race	Current annual new registrants	Annual registrants for optimal steady state	Ratio optimal to current
White	340,000	480,000	1.4
African-Am	30,000	189,000	6.3
Asian-Am	40,000	70,000	1.8
Hispanic	45,000	117,000	2.6

*Notes:* Current annual new registrants is estimated by the average number of new registrants in 2003 and 2004, as reported in the NMDP Biennial Report [35], Table 2.19. Annual registrants for optimal steady state is calculated as four percent of the optimal registry size reported in Table 8.

Table 10 shows for each race the percentage of the population of eligible age who are enrolled in the current registry and who would be enrolled in an optimal registry. We see that current enrollments are between two and three percent for whites, African-Americans and Asian-Americans and larger for Asian-Americans. An optimal registry would have more than seven percent of all whites, fourteen percent of Hispanics, and nearly twenty-five percent of all African-Americans and Asian-Americans. This table also shows the probability that a patient seeking a transplant will fail to find a match in the current registry and in an optimal registry. Although an optimal registry includes larger fractions of the African-American and Asian-American populations, they would still be less likely to find a match in the optimal registry than would whites. This discrepancy arises because the African-American and Asian-American populations are both smaller and more genetically diverse than the white population. We have calculated that even if all eligible African-Americans were added to the registry and the number of whites left unchanged, the probability of finding a match in the registry would be lower for an African-American patient than for a white.

Table 10: Percent of population in registry and probability of no match

Race	Pct of eligible population in actual registry	Pct of eligible population in optimal registry	Prob no match in actual registry	Prob no match in optimal registry
White	2.7	7.1	.08	.03
African-Am	2.4	23.8	.38	.12
Asian-Am	6.5	26.5	.21	.09
Hispanic	2.9	14.3	.11	.06

*Notes:* Figures in the first and second columns represent the ratio of U.S. registrations in the NMDP to U.S. population aged 18-61, by race.

### Sensitivity to Quantitative Assumptions

Our benefit-cost comparisons are sensitive to two quantitative estimates about which there must be much uncertainty. The first of these is prediction of future medical technology. The expected benefit from an additional registrant depends critically on the number of patients seeking transplants over the next twenty-five years. But how medical innovations will affect the demand for transplants over this period? We have assumed that the number of transplants will remain constant at 2006 levels. This assumption seems conservative. Over the past decade, the number of transplants facilitated by the NMDP has grown steadily, and has increased by almost ten percent per year in the years, 2005-2007. The NMDP attributes much of this growth to the availability of improved techniques that make transplants feasible for more patients [39]. If the number of patients seeking transplants were to continue to grow at ten percent annually, the present value of expected benefits from an additional registrant would be nearly four times as large as our estimates. If this number were to grow at five percent per year, this number would be twice our estimate. It is also possible that future medical discoveries will reduce the need for stem cell transplants or make it possible for patients to accept transplants from donors who are less closely matched. Benefits from adding new registrants to the current registry would continue to exceed costs so long as the rate of decrease in number of patients is less than thirty percent per year.

Another critical assumption about which there is significant room for disagreement is the value attributed to saving a statistical life. According to Viscusi and Aldy [49] estimates of the VSL vary over the range from

\$4-\$9 million. We used the middle of this range, \$6.5 million. Changing the valuation to the lower or upper end of this range would reduce or increase benefits by about forty percent. Even with a forty percent reduction in the VSL, benefits would exceed costs for adding registrants of all races.

Our estimates treat the population served by the NMDP as a closed system. We do not account for the possibility that patients in the countries served by the NMDP may get transplants from other registries or that residents of other countries may obtain transplants from the NMDP. If the world clearing house for registrants operated entirely smoothly, the number of available registrants would be almost twice the number in the NMDP, but the population served and hence the number of patients seeking transplants would also be much larger. We do not have data on the number of persons receiving or seeking transplants from non-NMDP countries, nor on the racial composition of these populations and registries. We have made crude estimates of expected benefits, assuming that the ratio of the number of registrants to the number of persons seeking transplants in the non-NMDP countries is the same as for the NMDP. With these assumptions, the present value of benefits remains more than three times the present value of costs for all races and more than five times that of costs for those of African ancestry.

### **Finer Classification**

The traditional medical standard for an HLA match focused on whether the alleles of the genes HLA-A, HLA-B, and HLA-DRB1 were similar at a “low” resolution. Recent research has suggested that outcomes are improved by also matching the gene HLA-C and possibly HLA-DQB1 and HLA-DRB1 (Bronwen E. Shaw *et al* [46], Stephanie J. Lee *et al* [27], and Pascale Loiseau *et al* [28]). There also appears to be benefit to matching alleles at higher genetic resolution than was done previously (Neal Flomenberg *et al* [19]). Our study uses the traditional matching standard. We do so because the best publicly available data on the population distribution of HLA types is compatible with this standard and because most studies that have evaluated the effectiveness of stem cell transplants relative to other treatment options were carried out using the traditional standard. As more rigorous matching standards are applied, the benefits from a larger registry are likely to be greater than those that we have calculated. When more comprehensive data on the population distribution of higher resolution HLA types and on the incremental effectiveness of closer matches become available, it will be useful to recalculate these benefits. In the mean time, our estimates serve as a useful lower bound for the value of an increased registry.

Frédèrick Fève and Jean-Pierre Florens [17] consider the possibility of a two-step testing process involving a cheap genetic “pretest.” The pretest would be only partially informative about a volunteer’s HLA type. Volunteers could then be selected for full testing and introduction into the registry depending on the results of the pretest.<sup>12</sup> A simple implementation of a pretest would be to determine volunteers’ national and regional origins on a finer basis than is currently done. A recent report by the NMDP [36] states that “preliminary findings indicate that HLA distribution may vary considerably by region and reinforces the value of focusing our recruitment efforts on minority racial and ethnic communities.” For ideological reasons, the major European bone marrow registries do not collect data on race. Nevertheless, each country supplies separate statistics on registration by its own nationals and the distribution of HLA phenotypes within European countries is known [8].

Although HLA distributions differ between countries, patients needing transplants are quite likely to find their only match in the registry of another country. In 2004, approximately thirty five percent of all stem cell donations were from donors in one country to recipients in another [50]. For small countries, international transfers are especially important. Approximately ninety percent of the donations received by Swiss patients come from outside Switzerland and ninety percent of the donations made by Swiss residents are received by non-Swiss [33].

The methods that we have developed for dealing with differing HLA type distributions across races are well-suited to the study of regional and national differences. Our benefit-cost estimates include the benefits of adding a registrant of any race to persons of any other race. This method, as applied to national registries, can be used to estimate the probability that a new registrant in one country will be the only match for a patient in another. Thus we can study the effects of national registry sizes on the export and import of stem cells between nations and regions. This in turn permits an analysis of the incentive problems that arise in the interaction between national bone marrow registries.

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<sup>12</sup>In a related paper [16], the authors evaluate the optimality of a proposed recruitment plan for the French registry, assuming that there is no sharing of stem cells across national boundaries, and assuming that the registry can draw donors from an optimized distribution of types.

## What Motivates Potential Donors?

Those who join the bone marrow registry are told that if called upon to donate, they will bear risk, inconvenience and discomfort, they will receive no monetary reward, and the beneficiary will almost certainly be a stranger. Yet millions of people have voluntarily joined bone marrow registries. Why have they done so?

The decision faced by stem cell donors is qualitatively different from that in standard Nash equilibrium models of private provision of public goods (see Bergstrom, Larry Blume and Hal Varian [7]). In these models, potential contributors care only about the sum of individual contributions. Thus one person's donation is a perfect substitute for that of another. The biology of immune systems ensures that stem cell contributions by two people of different HLA types can not be substituted for each other.<sup>13</sup> For someone who is the only representative of an HLA type in the registry, a donation will critically determine the survival of a patient of this type. However if there are others of the same type in the registry, one's own donation is not essential, since another equally suitable donor is available.

The number of patients needing transplants is small relative to the number of persons in the registry and hence the probability that a registrant will ever be asked to donate is small. The lifetime probability for a white person who remains in the registry for twenty five years is only about one percent. For other races this probability is even lower. If the bone marrow registry contains more than one HLA match for a patient, only one donor will be needed. If there is no one else of a person's HLA type in the registry, we define a registrant as *pivotal*. In Appendix A, we show how to calculate the conditional probability that a donor of specified race will be pivotal.

For each race, Table 11 reports the probability  $\pi$  that a registrant will be asked to donate and the probability  $h$  that a registrant is pivotal, conditional on being asked to donate. We see that  $h$  is about eight percent for a white registrant, thirty percent for an Asian-American and almost eighty percent for an African-American. If the registry size were increased to optimal levels, the conditional probabilities of being pivotal would be much lower for members of all races but would remain larger for other races than for whites.

Blood donors and kidney donors also face free-rider problems, though these differ from the free-rider problem that arises with stem cell donation.

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<sup>13</sup>Although the standard public goods model does not apply well to donation of stem cells, it does apply to financial support of costs of operating the bone marrow registry.

Table 11: Probabilities of being asked and of being pivotal if asked

Race	Current Registry		Optimal Registry	
	$P(\text{Asked} \text{Reg})$ $\pi$	$P(\text{Pivotal} \text{Asked})$ $h$	$P(\text{Asked} \text{Reg})$ $\pi$	$P(\text{Pivotal} \text{Asked})$ $h$
White	.013	.08	.004	.03
African-Am	.005	.78	.001	.19
Asian-Am	.006	.30	.002	.11
Hispanic	.008	.22	.003	.08

While blood donation is much less traumatic than stem cell donation, blood donors encounter a more standard free-rider problem. There are millions of other potential donors whose blood is a perfect substitute for one’s own. The blood type with the fewest compatible donors (O negative) can accept transfusions from about seven percent of the population. Kidney donations require the same compatibility as blood donations, with a few additional complications, but the cost of donating a kidney is much greater than that of donating blood.<sup>14</sup> The waiting list for kidney transplants is currently more than three times as large as the number of transplants that are annually performed. Therefore, kidney donors, unlike stem cell or blood donors, can be certain that their donation will increase the number of transplants performed and not simply displace the contribution of another suitable donor.

### Meditations of a Consequentialist Altruist

At present, those who join the registry can not be expected to know the probability  $h$  of being pivotal. Perhaps many donors would not be interested in this number if they were told. Nevertheless, it is likely that more people would be willing to join the registry if the likelihood that a donor is pivotal in saving a life is higher. It is therefore useful to consider the decision problem faced by a potential donor who is aware of the relevant probabilities.

We will consider a rational potential donor whose choices are consistent with a von Neumann Morgenstern utility function. Let us assume that this person is a “consequentialist altruist,” who values actions only by their

<sup>14</sup>People are much more likely to be willing to sacrifice a kidney for a loved one than for a stranger. Alvin Roth, Tayfun Sönmez, and M. Utku Ünver [42] devised exchange networks to facilitate multilateral kidney trades that allow people to donate kidneys for the benefit of specific patients with whom they are not themselves donor-compatible.

results.<sup>15</sup> Three distinct possible states of the world are of concern to the decision-maker. One possibility is that she is never asked to donate. A second is that she is asked to donate and is the only person of her type in the registry. The third possibility is that she is asked to donate and the registry contains at least one other person of her type. Let  $\pi_i$  be the probability  $i$  will be asked to donate if registered, and let  $h_i$  be  $i$ 's perceived probability that if asked to donate, she is the only registrant of her type.<sup>16</sup>

Assume that signing up to join the registry is costless. Then a consequentialist altruist will assign the same utility  $U_{0i}$  to joining the registry and not being asked to donate as to not joining the registry. Suppose that  $i$  assigns a utility cost  $C_i$  to the risk, pain, and inconvenience of making a donation and that making a pivotal donation adds  $B_i$  to  $i$ 's utility, where  $B_i > C_i$ . Then  $i$  attaches a utility of  $U_{0i} + B_i - C_i > U_{0i}$  to making a pivotal donation. If  $i$  makes a donation when there is at least one other willing registrant of her type, then  $i$ 's participation has no effect on the patient's survival probability, but simply saves another registrant the cost of donating. Let  $V_i$  be the utility that  $i$  attaches to saving someone else the trouble of donating and suppose that  $V_i < C_i$ . Then in the event that there is another compatible donor in the registry,  $i$  would prefer not to donate since  $U_{0i} + V_i - C_i < U_{0i}$ .

The NMDP asks registrants to promise that they are "willing to donate to any person in need," though there is no contractual obligation to do so. A consequentialist altruist would join only if she intended to donate if asked. The expected utility of  $i$  for joining the registry is

$$(1 - \pi_i)U_{0i} + \pi_i(h_i(U_{0i} + B_i - C_i) + (1 - h_i)(U_{0i} + V_i - C_i)), \quad (5)$$

and  $i$  will prefer to join the registry if and only if the utility in Expression 5 exceeds  $U_{0i}$ . This is the case if and only if

$$h_i(B_i - C_i) + (1 - h_i)(V_i - C_i) > 0. \quad (6)$$

Let us simplify by assuming that  $V_i = 0$ . Then Condition 6 becomes

$$\frac{B_i}{C_i} > \frac{1}{h_i}. \quad (7)$$

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<sup>15</sup>The *Stanford Encyclopedia of Philosophy* [52] defines consequentialism as "the view that normative properties depend only on consequences."

<sup>16</sup>The NMDP does not reveal to potential donors whether they are the only person of their HLA type in the registry. Although we have estimated the probability  $h$  for persons of each race, no such estimates have been publicly available, and perceptions about this probability are likely to vary widely.

As shown in Table 11, we estimate that the probability  $h$  of being pivotal is .08 for white Americans. If this were the probability perceived by all potential donors, then Condition 7 tells us that those who join the registry must have benefit-cost ratios  $B_i/C_i > 12.5$ . According to Table 10, about 2.7 percent of the eligible white population is enrolled in the registry. This means that the current registry of white Americans can be supported by motives of consequentialist altruism if 2.7 percent of the population have benefit-cost ratios exceeding 12.5 for making a pivotal stem cell donation to a stranger. An African-American who is asked to donate is much more likely to be pivotal than a white. For African-Americans, the current African-American enrollment could be maintained if 2.4 percent of the population have personal benefit-cost ratios exceeding 1.25. For Asian-Americans, maintaining the current registry would require 6.5 percent of the population to have benefit-cost ratios of at least 3.3, and for Hispanics, this would require 2.9 percent to have benefit-cost ratios of at least 5.

An optimal registry of well-informed consequentialist altruists would require much more intense and widespread altruism than is needed to maintain the current registry. According to Table 8, an optimal registry would have about twice as many whites, about four times as many Hispanics and Asian-Americans, and almost ten times as many African-Americans as the current registry. Not only would the registry have to be much larger, but we see from Table 11 that with the optimal registry, each person's probability of being pivotal would be less than half of what it is in the current registry. These considerations suggest that to achieve an optimal registry with a population of consequentialist altruists, it may be necessary to offer additional inducements for potential registrants.

## More Complex Motivations

Economists, whose usual fare is the study of rational, selfish agents, are less experienced with predicting behavior of those who act with generosity. Some useful insights can be captured by upgrading the sensibilities of our familiar workhorse, *homo economicus*, to those of a consequentialist altruist. But this modest upgrade is unlikely to capture the full variety of motives that underlie much of altruistic behavior.

In recent years, economists have developed models and experiments that explore alternative motives for altruistic behavior. Bergstrom, Blume, and Varian [7] and James Andreoni [2] proposed that people feel a “warm glow” that depends on the size of their own gift, independent of the ultimate stock of public goods. Brian Duncan [14] introduced the notion of “impact phi-



lanthropy,” where people take pleasure in the difference made by their own actions. Roland Benabou and Jean Tirole [4] suggested that “people perform good deeds and refrain from selfish ones because of social pressure and norms that attach honor to the former and shame to the latter.” Benabou and Tirole show that to determine motives from actions requires a somewhat subtle signal extraction model where good actions may or may not impress others. As Tore Ellingsen and Magnus Johannesson [15] put it, “some people are generous, but everyone wants to appear generous.” Benabou and Tirole also suggest that people perform prosocial acts in order to improve their own self-image, using concrete actions to signal to their future selves the kind of person that they really are.

A series of papers by Jason D. Dana, Roberto A. Weber, and Jason X. Kuang [12], Dana, Daylian M. Cain, and Robin M. Dawes [11], Tomas Broberg, Tore Ellingsen, and Magnus Johannesson [9], and Edward P. Lazear, Ulrike Malmendier, and Weber [26] indicates that while people often act generously when the consequences of their actions are clearly spelled out, they are adept at finding “moral wiggle room.” These papers report evidence from laboratory experiments in which people who would behave generously with full information are willing to conceal information from themselves or from potential recipients so that they can behave selfishly without making their motives transparent. This is the case even though the potential recipient never learns who has behaved selfishly or unselfishly toward him.

Richard Titmuss [47] argued that paying people for blood “donations” might reduce the supply of blood from those who would otherwise contribute for free. Many donors are motivated either by social acclaim or by self-satisfaction. Benabou and Tirole [4] suggest that if blood donors are paid, the value of blood donation as a signal of generosity will be weakened, possibly producing the “Titmuss effect.” In a field experiment conducted in Gothenberg, Sweden, Carl Mellström and Magnus Johannesson [31] gave subjects an opportunity to donate blood. In a control treatment they offered no monetary payment. In a second treatment they offered to pay subjects about \$7 for contributing blood. In a third treatment they offered potential contributors a money payment but allowed them to specify that the payment be given to a charity. For men, they found no significant difference among the treatments. But when women were offered a payment in the second treatment, only about half as many were willing to contribute as when they were not paid. In the third treatment, with the option to give the payment to charity, the proportion of contributors was restored to that with no payment.

A desire to signal altruism may be a useful motivator for blood donations,

which occur as soon as one agrees to donate. This motivation serves the bone marrow registry less well. A bone marrow registrant could signal altruism by joining the registry, while realizing that the probability is small that he will be asked to donate. Since the registry cannot make binding contracts, one could gain acclaim by registering, while intending to refuse to donate if called upon.

Motives and ethical views that guide generous actions are likely to differ widely. There is likely to be wide variation in perceptions of the cost and danger of stem cell donations. The current registry contains less than four percent of the eligible population, while an optimal registry would contain almost ten percent. Much as crime-prevention policies must focus on the actions of those who believe they are least likely to be caught and who are least troubled by conscience, membership in the bone marrow registry is likely to come from those who most strongly believe that their gifts will be pivotal and who have the strongest altruistic feelings.

## An Enriched Model

Our model of consequentialist altruists assigned the same utility  $U_{0i}$  to joining the registry and not being asked to donate as to not joining the registry at all. If there is no social acclaim and no payment for joining the registry, people would join only if they hope to be called on to donate. Those who register would certainly intend to donate if asked. But if joining the registry is rewarded, either with money or status, some may choose to register although they hope never to be asked to donate. Since registrants are under no contractual obligation to donate if asked, some may register to gain social acclaim (or money if registrants are paid), while intending to decline if asked to donate.<sup>17</sup> Others are likely to regard it as shameful not to keep their promise and would donate even if they regretted having joined the registry.

We employ a simple additive utility model to keep track of these interacting effects. Let  $x_i$  be the net time-and-money cost of joining the registry. (If there are payments for joining the registry,  $x_i$  could be negative.) Let  $a_i(x_i)$  represent  $i$ 's utility valuation of the social acclaim for joining. The social acclaim that one receives for joining the registry may be greater if

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<sup>17</sup>According to Kollman et al [25], approximately 30 percent of white registrants, 60 percent of African-American registrants, and 50 percent of Asian-American and Hispanic registrants who are asked to donate either are not able to or do not agree to make a donation. Not all of these are direct refusals. Some are unable to donate for medical reasons and some cannot be found at the address listed with the registry.

joining the registry is more expensive and may be reduced if one is paid to join. Person  $i$  receives a net utility increment of  $a_i(x_i) - x_i$  from joining the registry, whether or not  $i$  is asked to donate.

If the net gain  $a_i(x_i) - x_i$  from registering is positive,  $i$  might join with the intention to decline if asked to donate. Refusing to donate after promising to do so may entail shame, which we quantify as  $S_i$ . Then if called on to donate,  $i$  will donate only if

$$S_i > C_i - h_i B_i - (1 - h_i) V_i. \quad (8)$$

Taking account of the option to refuse when asked to donate, a necessary and sufficient condition for  $i$  to join the registry is

$$a_i(x_i) - x_i > \pi_i \min\{S_i, C_i - h_i B_i - (1 - h_i) V_i\}. \quad (9)$$

Expression 9 tells us that  $i$  compares the net direct benefit from joining the registry with the expected cost of being asked to donate if registered. If asked to donate,  $i$  will do so only if Condition 8 is satisfied.

### Should registrants or donors be paid?

We have argued that the current bone marrow registry falls short of optimal size for all races. When resources are undersupplied, it is natural for economists to consider using the price mechanism to remedy the shortage. Alvin Roth [43] observed that many people view the sale of human organs and tissue with repugnance and, in response, governments frequently outlaw such sales. Gary Becker and Julio Elías [3] argued that such prejudices are not well founded and that a strong humanitarian case can be made for using markets to increase the supply of organs and tissue. Roth notes that current distinctions often seem arbitrary. In the U.S. it is illegal to buy and sell human kidneys, livers, and other organs, although it is legal to pay financial expenses that the donor incurs in the process. In contrast, the sale of human eggs and sperm is permitted, as are “womb-rental payments” to surrogate mothers. Sale of blood for transfusions is illegal, but sale of blood for plasma extraction is legal and commonly practiced.

Not only are bone marrow registrants and donors currently unpaid; joining the registry entails significant costs in time and money. The internet has reduced the time cost of joining. New registrants no longer need to travel to a collection center. An eligible donor can simply go to the NMDP’s web site, complete an online form, and order a tissue-typing kit. When the kit arrives, the registrant takes a swab of his or her cheek cells, and mails the swab to

the registry for testing. Although the time costs have fallen, the money cost of registering has increased. Until recently, potential donors could join the bone marrow registry without paying a fee. This is no longer the case. Those who join the registry by the internet must pay a fee of \$52 when they order the tissue-typing kit.<sup>18</sup> It is not surprising that the NMDP must charge fees to recover its costs. The major source of government funding for the NMDP is the US Department of Health and Social Services. Funds received from this source decreased from \$25 million in 2005 and 2006 to \$23 million in 2007. Given that there are currently too few registrants of all races, these fees seem an unfortunate impediment to recruitment.<sup>19</sup>

Would greater recruitment efforts and free registration be sufficient to attract a registry of optimal size? Comparison of registration rates among prosperous industrialized countries suggests that the number of voluntary registrations may be quite sensitive to recruitment effort. The United States registry currently includes less than three percent of the white population aged 18-61 while an optimal registry would include about seven percent. Two countries, Israel with ten percent, and Germany with seven percent, register larger proportions of the eligible population. In the UK, approximately two percent, in Canada, Denmark, and Norway approximately one percent, and in France, the Netherlands, and Switzerland less than one-half of one percent of the eligible population is registered.<sup>20</sup> If a voluntary bone marrow registry in the United States could achieve the registration rates of Germany, the number of white Americans registered would be reasonably close to optimal.

Attracting an optimal number of Asian-American registrants is a more formidable task. About six and a half percent of Asian-Americans of eligible age are currently registered. An optimal registry would require registration of approximately twenty-five percent. The countries of Asia are a potential alternative source of stem cell donors for Asian-Americans. The largest bone marrow registries in Asia are in Japan, which has about three hundred thousand registrants, and Taiwan, which has about two hundred seventy thousand. This compares with four hundred thirty thousand Asian-Americans

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<sup>18</sup>The registry web site states that: "For volunteers who join in person, sometimes all or part of the tissue-typing costs may be covered by a patient family, community group, or corporation." The US Department of Defense pays all costs for military personnel who join at a designated collection center.

<sup>19</sup>If fees were eliminated, new registrants could be encouraged to make voluntary cash donations designated to recruit more registrants.

<sup>20</sup>The size of national registries is published online by Bone Marrow Donors Worldwide [8].

in the U.S. registry. Mainland China currently has only six thousand registrants and India has only one thousand. Expansion of the Asian registries and international sharing agreements would greatly improve the prospects of Asian-Americans seeking stem-cell transplants.

The current registry includes two and a half percent of African-Americans of eligible ages, while an optimal registry would contain nearly twenty-five percent. It is difficult to see how the registry can attract sufficient numbers of African-American registrants without providing much stronger incentives than are currently available. African-Americans seeking a stem cell donor have little chance of finding one in Africa. In Africa, the only country with a registry is South Africa, which has registered about sixty thousand persons, most of whom are white.

Paying new registrants may attract some who join for the money and expect to refuse if asked to donate. A more effective system of rewards would make payments only to those who actually make a donation. As is seen from Equation 9, payments to donors increase not only the incentive to register, but also the incentive for registrants to donate if asked. Thus payments to donors could be expected to increase the fraction of effective registrants as well as the number of registrants.

It has been argued that people wish to signal their altruism to others (or perhaps to themselves), that paying contributors of organs or tissue reduces the effect of a contribution as a signal, and hence that payments to contributors may reduce contributions from those who were willing to do it for free. The blood donation experiments of Mellström and Johannesson [31] suggest that payments sometimes deter donations, but they also suggest a simple way to overcome this effect. When Mellström and Johannesson offered subjects the opportunity to donate their payments to charity, the deterrent effect of payments disappeared. This suggests that if stem cell donors are paid, they should be allowed an opportunity to publicly waive any payment for themselves, with the understanding that the registry would use the money saved to recruit more donors.

Paying donors raises another interesting question. Our benefit-cost analysis did not count the pain and inconvenience of donors as costs. This seems appropriate for unpaid volunteers. The fact that donors choose to donate without pay indicates that the pleasure they feel from contributing outweighs the costs. For the marginal donor, these unmeasured benefits and costs are equal. If donors must be paid to achieve an adequate registry, then the costs to marginal donors must exceed the benefits by the amount of payments. Thus marginal costs of adding registrants would have to include expected payments made to these registrants if they are asked to donate. An op-

timal U.S. registry requires much larger proportions of the population for minority groups than for whites. If donor payments are used to achieve a nearly optimal registry, payment rates would have to be higher for African-Americans than for whites. Higher payments to African-American donors imply a higher marginal cost of adding African-American donors than of adding white donors. A more refined calculation of optimal registry sizes would need to take this into account.

## Conclusion

Our benefit-cost analysis indicates that for every racial group, marginal benefits from an additional registrant exceed marginal costs, and that the benefit-cost ratio is highest for African-Americans. The NMDP currently focuses on recruitment of minority donors and has allowed the annual number of new white registrants to decline. Although a focus on African-American and minority registration appears to be justified by the relative benefit-cost ratios, our calculations indicate that the current registry has fewer people of all races than is optimal.

We estimated optimal registry sizes for each race. An optimal registry would have almost ten times as many African-Americans, between four and five times as many Asian-Americans and Hispanics, and three times as many whites as the current registry. Even with an optimal registry, African-Americans would be less likely to find a match than persons of other races. This is a consequence of the relatively small size and great genetic diversity of the African-American population.

The bone marrow registry confronts us with an interesting variant of the standard free-rider problem. Donations by people of different HLA types are not substitutes. Each potential donor will, with some probability, be the only person who can save the life of one particular stranger. As the size of the registry increases, it becomes less likely that a new registrant will be the only potential donor of her type. In an optimal registry, these probabilities would be less than half as large as in the current registry.

The bone marrow registry has attracted almost three percent of the eligible US population. Despite the impressive generosity displayed by these volunteers, it would be difficult to achieve an optimal registry in the U.S. solely by increased recruitment effort. This difficulty is compounded by the fact that as the registry approaches optimal size, the free rider problem becomes more severe, since new registrants are less likely to be unique in the registry.

Some of the current shortfall can be made up by increases in the size of foreign registries, particularly in wealthy countries where stem cell transplants are commonly practiced. For African-Americans however, it seems highly unlikely that an optimal registry can be achieved by voluntary means or by expansion of international registries. We have argued that if money payments are used to increase the size of the registry, it would be more effective to pay only those who are called upon and consent to contribute rather than to pay all new registrants.

## Appendix A:

### Net social benefit is a strictly concave function

Let  $R = (R_1 \dots R_k)$  be the vector of numbers of effective registrants of each of  $k$  races. Let  $S_x$  be the number of persons of race  $x$  who seek bone marrow transplants and let  $p_i^x$  be the probability that a person of race  $x$  is of HLA type  $i$ . The expected number of persons of HLA type  $i$  who seek bone marrow transplants is

$$N_i = \sum_{x=1}^k S_x p_i^x. \quad (10)$$

The probability that a person of HLA type  $i$  has a match in the registry is  $1 - p_i^0(R)$ , where  $p_i^0(R)$  is the probability given in Equation 2 that a registrant of type  $i$  is the only registrant of this type. The expected total number of bone marrow transplants administered is

$$T(R) = \sum_i N_i (1 - p_i^0(R)). \quad (11)$$

We will show that  $T(\cdot)$  is a concave function. We first show that the functions  $p_i^0(\cdot)$  are concave. The second order partial derivative of  $p_i^0(\cdot)$  with respect to  $R_x$  and  $R_y$  is

$$\frac{\partial p_i^0(R)}{\partial R_x \partial R_y} = \ln(1 - p_i^x) \ln(1 - p_i^y) p_i^0(R). \quad (12)$$

Therefore the Hessian matrix of the function  $p_i^0(R)$  can be written as

$$H_i(R) = p_i^0(R) x^T x \quad (13)$$

where  $x_i$  is the  $k$ -vector  $(\ln(1 - p_i^1), \dots, \ln(1 - p_i^k))$ . Since  $x \neq 0$ , it must be that the matrix  $x^T x$  is positive definite, and since  $p_i^0(R) > 0$ , it follows that  $H_i(R)$  is positive definite. The function  $p_i^0(\cdot)$  is therefore a convex function and hence  $1 - p_i^0(\cdot)$  is a concave function. Then  $T(R) = \sum_i N_i (1 - p_i^0(R))$  is a positively weighted linear combination of concave functions and hence must be concave.

Let  $s$  be the probability that a bone marrow transplant will save the life of a patient,  $V$  the value of a statistical life and  $m$  the hospital costs of performing a transplant. Assume that  $sV > m$ . Let  $c_x$  be the cost of registering and typing enough registrants of race  $x$  to add one effective registrant, and let  $c(R) = \sum_x c_x R_x$ . The net social benefit of the bone marrow registry is then  $NSB(R) = (sV - m)T(R) - c(R)$ . Since  $T(R)$  is concave and  $c(R)$  is linear in  $R$ ,  $NSB(R)$  must be a concave function of the vector  $R$ .



## Probability of being pivotal if asked to donate

Let  $R_x$  and  $S_x$  be the number of registrants and the number of transplant seekers of race  $x$  and let  $R$  and  $S$  be the corresponding vectors of registrants and transplant seekers. Let  $h_x(R, S)$  be the conditional probability that a registrant of race  $x$  is the only person of his type in the registry, given that he is asked to make a donation.

Define  $\pi_x(R, S)$  as the annual probability that a registrant of race  $x$  will be chosen to make a donation and  $\varphi_x^0(R, S)$  to be the probability that a registrant of race  $x$  is chosen to donate and is the only registrant of his HLA type in the registry. Then by Bayes' law,

$$h_x(R, S) = \frac{\varphi_x^0(R, S)}{\pi_x(R, S)}. \quad (14)$$

We estimate  $\varphi_x^0(R, S)$  and  $\pi_x(R, S)$  as follows. Let

$$n_i(S) = 1 - \prod_x (1 - p_i^x)^{S_x} \quad (15)$$

be the probability that there is at least one patient of type  $i$  seeking a donation. The probability that a donor of type  $i$  is pivotal in saving a life is

$$p_i^0(R) n_i(S) \quad (16)$$

where  $p_i^0(R)$  is the probability given in Equation 2 that a registrant of type  $i$  is the only registrant of this type. The probability that a registrant of race  $x$  is pivotal in saving a life is now

$$\varphi_x^0(R, S) = \sum_i p_i^x p_i^0(R) n_i(S). \quad (17)$$

Let

$$m_i(S) = \sum_x p_i^x S_x, \quad (18)$$

which is the expected number of type  $i$  persons seeking a transplant. The fraction of type  $i$  registrants that are of race  $x$  is

$$r_i^x(R) = \frac{p_i^x R_x}{\sum_y p_i^y R_y}. \quad (19)$$

The expected number of registrants of race  $x$  who are asked to donate is then

$$\sum_i m_i(S) r_i^x(R). \quad (20)$$

The probability that a registrant of race  $x$  is asked to donate is therefore

$$\pi_x(R, S) = \frac{\sum_i m_i(S) r_i^x(R)}{R_x}. \quad (21)$$

We can now use equations 14, 17, and 21 to calculate  $h_x(R, S)$ .

## Appendix B

We estimate the expected gain in survival probability from receiving a stem cell transplant rather than the next best treatment. Transplants are used to treat many conditions and data varies across diseases in availability, quality, and generality. Using available studies, we estimate the expected number of lives saved by an additional transplant for each of the most common conditions. We then calculate an average net gain in long term survival probability, weighted by the frequency of ailments. This figure, which is 0.21, is our estimate of the expected number of lives saved by an additional transplant facilitated by the bone marrow registry.

More than twenty thousand patients with various conditions have been treated by bone marrow transplantation using NMDP donors between 1987 and 2004. The numbers by disease as reported by the NMDP [35], are listed in Table 12.

Table 12: Net Survival Gains From Transplants, by Disease

Disease	Number of Transplants	Fraction of Transplants	Net Survival Gain
Acute myelogenous leukemia	4,800	0.24	0.16
Chronic myelogenous leukemia	4,686	0.23	0.15
Acute lymphoblastic leukemia	3,815	0.19	0.42
Myelodysplastic syndromes	2,110	0.10	0.25
Non-Hodgkin's lymphomas	1,344	0.07	0.00
Severe aplastic anemia	733	0.04	0.20
Other	2,886	0.14	0.21

### Disease-by-disease review

**Acute Myelogenous Leukemia:** An examination of long-term survival for patients with acute myelogenous leukemia (AML) observed 5-year survival rates of 45% for bone marrow transplantation and 29% for an alternative chemotherapeutic approach [5]. We therefore use a value of 0.16 as the change in survival probability attributable to bone marrow transplantation for patients with AML. This value is consistent with those found in other studies (e.g. Zittound et al [54]).

**Chronic Myelogenous Leukemia:** The bone marrow registry notes that use of bone marrow transplantation to treat chronic myelogenous leukemia

(CML) decreased after the 2001 introduction of the drug imatinib mesylate. (NMDP Biennial Report 2003-2004 [35]) A more recent review article [44] concludes that while imatinib mesylate improves outcomes, it is not curative for CML and there remains a role for bone marrow transplantation. We therefore include CML in our calculation. A textbook discussion of treatment for CML [20] refers to four studies comparing bone marrow transplantation with chemotherapy. We use the arithmetic mean survival advantage of these studies, 0.15, as the change in survival probability attributable to bone marrow transplantation for patients with CML.

**Acute Lymphoblastic Leukemia:** A recent study found 68% 15-year survival for patients with acute lymphoblastic leukemia (ALL) who received a bone marrow transplant from an unrelated donor [10]. Two studies that assess the effectiveness of chemotherapy in treating ALL found long term survival rates of 20% and 32% [45] [53]. We take the arithmetic mean of these two studies to compute a change in survival probability attributable to bone marrow transplantation of 0.42.

**Myelodysplastic Syndromes:** There is no curative chemotherapy available for myelodysplastic syndromes and ten year survival is on the order of 2% [21]. Among patients treated with bone marrow transplants facilitated by the national registry, 10 year survival is approximately 27% (NMDP Biennial report [35]). We attribute a change in survival probability of 0.25 to bone marrow transplantation for myelodysplastic syndrome. This value is consistent with at least one study directly assessing the impact of bone marrow transplantation in patients with myelodysplastic syndrome [1].

**Non-Hodgkin's Lymphomas:** According to a recent review article [40] on the subject, "the role of [bone marrow] transplantation in the management of lymphomas remains uncertain." A recent textbook describes the use of bone marrow transplantation in Non-Hodgkin's Lymphoma as "controversial" and concludes that "only a fraction of the most advanced patients... may be salvaged by the use of [bone marrow transplantation]" [22]. Because years of research have failed to elucidate the benefit of bone marrow transplantation for patients with Non-Hodgkins Lymphoma, we assume here that there is currently no associated gain in survival.

**Aplastic Anemia:** A recent textbook presents a summary of 13 studies comparing bone marrow transplantation to immunosuppressive therapy, a primary alternative, for the treatment of aplastic anemia [51]. Because the studies vary in the age of participants, we separately computed average survival advantage (weighted by study size) attributable to bone marrow trans-

plantation for adults and children. We then weight the results by the number of adults and children who have been transplanted from donors through the registry to compute an overall average change in survival probability of 0.20.

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