ONE CHANCE IN A MILLION: ALTRUISM AND THE BONE MARROW REGISTRY

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Abstract

Transplants of donated stem cells save the lives of many patients with blood diseases. Donation is somewhat painful, but rarely has lasting adverse effects. Patients can accept transplants only from donors with compatible immune systems. Those lacking a sibling match must seek donations from the population at large. The probability that two persons of the same race are compatible is less than 1/10,000. Health authorities maintain a registry of several million genetically-tested potential donors who have agreed to donate if asked. We study the peculiar structure of voluntary public good provision represented by the registry, and compare the marginal benefits and marginal costs of expanding the registry.

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Introduction

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 Center [9]

> "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. Finding a compatible stem cell donor is vastly more difficult than finding a match for blood donation. The blood type that has the fewest compatible donors (O negative) can accept transfusions from about seven percent of the population.[1] For stem cell donations, one's best chance of a match is a brother or sister. The probability that two siblings are acceptable matches is one-fourth. The chance of a match with a relative other than a sibling is very small. Patients who lack a genetically compatible sibling generally must seek a match from the population at large. People of the same race are more likely to be a match than those of different races, but the probability of a match between two randomly selected persons of the same race is less than one in ten thousand.

Over the past twenty years, a remarkable set of institutions has been developed for matching needy patients with compatible donors. (See McCullough et al [25] and Fisher [17] for discussions of the history of bone marrow registries in the United States.) The United States National Marrow Donor Program (NMDP) began to operate in 1986 and currently maintains a registry of more

[1] Roth, Sönmez, and Ünver, [34] report that kidney donations require the same compatibility between donor and receiver as blood donations, with the additional complication that some patients have preformed antibodies against one of the donor's proteins. Although compatible pairs for kidney donation are orders of magnitude more common than compatible pairs for stem cell donation, the costs to the donor are far greater, and people are much less likely to be willing to donate a kidney to save a stranger's life than to contribute bone marrow. Though few would sacrifice a kidney for a stranger, many are willing to do so for a loved one. Roth et al devised ingenious 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.

than six million potential donors whose type has been determined. The NMDP now includes approximately 1.5 million registrants from the German Bone Marrow Registry (DKMS) and smaller numbers from the registries of Sweden, Norway, the 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. Those who join a registry must express their willingness to make a stem cell donation if someone of their type should need a transplant. At the time of registration, a saliva sample is collected from the potential donor for DNA testing. The outcome of the test is stored along with the donor's contact information.

The existence of bone marrow registries raises interesting questions about the prevalence and nature of altruistic behavior. The matching technology of stem cell donations poses a rather unusual and interesting "free-rider problem." Given the large size of the current registry, a potential registrant can reasonably conclude that there is a good chance that someone of his type is already present in the registry. If so, his own contribution would simply replace that of another registered potential donor. In this paper, we explore the incentive problem that arises for a thoughtful potential donor who is deciding whether to join the registry.

Joining the registry is painless and takes little time. Making a donation is a more serious matter. There are two major alternative procedures by which stem cells can be contributed.[2] The more traditional method is a bone marrow transplant. Bone marrow is "harvested" from the donor's pelvis by means of insertions of a large 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.[3] Neither procedure is likely to have long term health effects

[2]A third source for 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 people in the bone marrow registry.

[3]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." According to the German bone marrow registry web site, "Pain usually occurs directly after collection and can vary greatly in duration and intensity. The feeling is

on the donor.

Everyone in society faces a risk that at some time they or a loved one will need a stem cell transplant. The bone marrow registry is a public good that increases everyone's probability of finding a suitable donor in case of need. As the number of people in the registry increases, there is a diminishing probability that an additional registrant adds to the number of distinct types represented in the registry. Eventually, the value of marginal benefits from adding a registrant will fall below the marginal cost. This paper includes a benefit-cost analysis in which we estimate the marginal value of lives saved from adding an additional registrant of specified race, and compare this benefit to the marginal cost. For each race, we also estimate the optimal number of registrants and compare these to existing numbers.

Our results suggest a strong case for increasing the number of persons of all races in the registry, with the greatest net benefit from additional African Americans. This leads us to inquire whether a sufficiently large registry can be maintained on a purely voluntary basis, and to consider alternative mechanisms for increasing the size of the registry. To approach this problem we consider the motives that lead people to join the registry and to contribute if asked.

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. The probability that two randomly selected individuals are HLA compatible is less than one in ten thousand.

A person's HLA type is determined by genes located on chromosome 6, one copy of which is inherited from each parent. The current medical standard for an HLA match focuses on the specific contents, or *alleles*, of the genes HLA-A, HLA-B, and HLA-DRB1.[4] Two siblings have matching HLA types with probability one-fourth, since they match only if they both inherit the same version

often described as if you had banged into a table leg." According to the NMDP, PBSC donors often experience bone pain and flu-like symptoms, as well as occasional insomnia, headaches, fatigue, nausea, and vomiting.

[4]Some medical centers seek "higher-resolution" matches, based on additional genes of the HLA family. The genetic data available to us is only at the resolution level of the three genes mentioned. Most available data on the effectiveness of transplants is based on the experience of matches at the three-gene level. If more rigorous matching standards lead to improved outcomes, then the benefits from increasing the size of the registry will be greater than those that we have calculated. Until medical evidence of the effectiveness of higher resolution matches becomes available, our estimates serve as a useful lower bound on the value of an increased registry.

of chromosome 6 from each parent. A specified combination of three alleles 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*. At the level of resolution used for donor matching, there are several thousand possible haplotypes and about twenty million possible phenotypes.

We obtained data on the population distribution of HLA types from a study by Motomi Mori *et al* [28], 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 genetic theory, geneticists are able to exploit this data much more powerfully. Mori *et al* assume that within racial groups, mating is random with respect to HLA type. With this assumption, they use the observed distribution of phenotypes to construct a maximum likelihood distribution of haplotypes for each of the five racial groups. By this process, they assign non-zero estimated frequencies to about eleven thousand haplotypes. With an estimate of haplotype frequencies and the assumption of random mating within races, one is able to estimate the frequency distributions of a large number of genetic types that are not directly observed in the sample. Our study uses the haplotype distribution published by Mori *et al* to reconstruct an estimate of the distribution of phenotypes in each group.[5] 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

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

Table 1: Probability of HLA Match by Race

	White	Afr Am	Asian Am	Hisp	Nat Am
White	1/11,000				
Afr Am	1/113,000	1/98,000			
Asian Am	1/223,000	1/1,310,000	1/29,000		
Hisp	1/44,000	1/259,000	1/254,000	1/34,000	
Nat 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 [28] of haplotype distribution.

more heterogeneous. The probability that two randomly selected African Americans have matching types is less than 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 that they can find a donor if one is needed.

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 the probability distributions of HLA types by race that we constructed from the Mori data on the distribution of haplotypes. Since there are about ten million types with 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 registrants have moved without leaving forwarding addresses, some have health conditions that prevent them from donating, and some are no longer willing to contribute. The registry sizes that we use to estimate probabilities of finding a match are "effective" registry sizes—estimated numbers of persons in the registry who are available, willing,

and able to donate if called. Kollman *et al* [23] supply statistics, by race, on the fraction of persons from the registry who were fully available when asked. For each race, Table 2 reports the number of persons in the registry, the effective number in the registry, and the probability that a randomly selected member of this race lacks an HLA-match in the registry.

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
Afr Am	485,791	.34	165,169	.38
Asian Am	432,293	.44	190,209	.21
Hisp	594,801	.47	279,556	.16
Nat Am	70,781	.48	33,975	.11

Notes: Registration statistics are obtained from NMDP Registry and Transplant Statistics [31]. 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 also specify whether they were white, African American, Asian American, or Native American. Thus recent statistics on new registrations count Hispanic registrants twice. We have opted to retain the Hispanic classification and thus our figures include a correction for double counting in the other categories.

The probability that a person of a specified race will find a match in the registry is calculated 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 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 $(1 - p_i^x)^{R_x}$. A registry with enrollment vector R contains no persons of type i if there are no type i's among registrants of any race. Let $p_i^0(R)$ be the probability that a type i has no match in the registry when R is the vector of registrants by race. Then

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

Let $P_x^0(R)$ be the probability that a randomly selected person of race x has

no match in a registry whose membership is described by the vector R. This probability is

$$P_x^0(R) = \sum_i p_i^x p_i^0(R). \tag{2}$$

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. As we demonstrate in Appendix A,

$$G_{xy}(R) = \sum_i p_i^y p_i^x P_i^0(R). \tag{3}$$

It is interesting to see that $G_{xy}(R)$ is symmetric in x and y. Thus, we know that 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 increase in the probability of finding a registered match for persons of each race that result from adding one person of specified race to the registry.

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

Gain to this Race	**Race of Added registrant**				
	White	Afr Am.	Asian Am	Hisp	Nat Am.
White	0.143	0.136	0.094	0.146	0.132
Afr Am	0.136	6.043	0.154	0.547	0.287
Asian Am	0.094	0.154	3.727	0.212	0.201
Hispanic	0.146	0.546	0.212	1.124	0.305
Nat Am	0.132	0.287	0.207	0.305	1.012

Notes: Entries are calculated with MatLab using Equations 2 and 3 above, with estimated frequency distribution of phenotypes based on Mori's haplotype distribution [28]. 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 would accept transplants if they could find a match. We then calculate the expected increased probabilities of finding a transplant that would result from adding one more donor of each race. Finally, we multiply the increased probabilities of finding a transplant

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 reports our estimates of the numbers who would have obtained transplants had a match been available, but were unable to find a match. The third column is the estimated number of persons who sought a transplant and would have received one if a match were available.

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

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

Notes: The NMDP report *Number of Allogenic Transplants Performed* [32], 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 registrants by race reported in the *2004 Biennial Report of the NMDP* [30] 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 transplants by $1 - p_r^0$ where p_r^0 is the estimated probability that a person of race r finds no match in the registry, as 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 recipients 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.

Not every additional transplant will "save 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 ([30], 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 estimates for each condition of long term survival probabilities of those who receive transplants and those who receive the next best available treatment. From this study, 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
Afr American	0.166	0.035
Asian American	0.072	0.015
Hispanic	0.077	0.016
Native American	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 [27], and further developed for analysis of public projects by T.C. Bergstrom [5] and Pierre Dehez and Jacques Drèze [14]. The underlying theory and its empirical implications are lucidly explained in a survey by Kip Viscusi and Joseph Aldy [39]. 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 adding 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 (Jones-Lee, Hammerton, and Philips [22] and Johannesson, Johansson, and Lofgren [21]), 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 [39] review a large number of these studies. Estimated valuations vary widely across studies and methodologies, but according to Viscusi and Aldi, 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" [38], which recommends a VSL that is 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 [30] (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

Present value	**Race of the Additional Registrant**				
to this group	White	Afr Am	Asian Am	Hispanic	Nat Am
White	$1012	$961	$664	$1,028	$928
Afr Am	$71	$3155	$81	$285	$150
Asian Am	$27	$44	$1,063	$60	$59
Hispanic	$91	$341	$132	$701	$190
Nat Am	$5	$10	$8	$11	$37
Total Value	$1,206	$4,512	$1,947	$2,085	$1,364

The entries in the first row of this table show that the white population

benefits substantially from additional registrants of the 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 website reports the cost of tissue typing an additional registrant is $52 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, that is a registrant who is able and willing to make a donation if called upon. Since not all registrants are available when called upon, the registry must on average add more than one registrant to gain an effective resident. Therefore, our cost estimates must include the cost of registering more than one person per additional effective registrant. Kollman *et al* report that, based on NMDP experience, the fractions of 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.[6]

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 are about $166,000.[7] Multiplying this cost by the probability that an additional registration results in an additional transplant, 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 our estimates of benefits and costs from adding an effective registrant to the bone marrow registry. We see that the benefit-cost ratio is well above unity for registrants of all races, and is highest for African Americans. The 2004 Biennial Report of the NMDP [30] (page 2.27) 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." The

[6]These fractions are slightly larger than the fractions of the the current registry who are available for donation because a significant number of earlier registrants are unavailable because their HLA type was misclassified. Current DNA testing methods have apparently eliminated this problem for new registrants.

[7]This estimate is based on a survey of costs in 2001 by Redeaelli et al [33] and converted to 2007 dollars.

report shows that the number of new registrants of Caucasian ancestry 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 is consistent with our estimates of benefit cost ratios. Unless total funding for the program is increased,[8] however, this entails a reduction in efforts to recruit members of other racial groups. Our results suggest that there is a strong case for increasing the total budget of the NMDP to allow increased registration of all races.

Table 7: Benefit-cost comparison for an additional registrant

	Race of the additional registrant				
	White	Afr Am.	Asian Am	Hispanic	Nat Am
Benefit	$1206	$4,512	$1,947	$2,078	$1364
Total Cost	$297	$800	$446	$455	$455
B/C Ratio	4.1	5.6	4.4	4.6	3.8

Our calculations of benefits and costs have treated the population served by the NMDP as a closed system. Thus we have not accounted for the possibility that patients in the countries served by the NMDP may get transplants from registries in other countries. If the world clearing house for registrants operated entirely smoothly, the total number of registrants available would be almost twice as large as the number in the NMDP. It would also be the case that the number of persons seeking transplants would be on the order of twice the number seeking transplants from the NMDP. We do not have data on the racial composition of registries outside the NMDP, nor do we have data on the number of persons receiving or seeking transplants from non-NMDP countries. To get a rough idea of the effect of including the entire world registry, we calculated expected present value of an additional registration, based on the assumptions that the racial composition of total world registry is the same as that of the U.S. population in the NMDP, that the ratio of number of transplant recipients to the size of the registry is the same as for the NMDP, and that sharing across registries is frictionless. With these assumptions, the ratio of the present value of benefits to costs for a new registrant is 3.3 for whites, 3.8 for Asian Americans, 4.1 for Hispanics, and 5.4 for African Americans.

[8]The major source of government funding for the NMDP is the US Department of Health and Social Services. Funding from this source was $25 million in 2005 and 2006 and fell to $23 million in 2007.

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. Therefore a larger registry is called for on efficiency grounds. As the registry gets larger, a new addition becomes less likely to add a new HLA type to the registry and so the expected benefit from an additional registrant diminishes. If there were no cross-race matches, finding the optimal registry size would be relatively simple. For each race, we would simply find the registry size at which the marginal benefit from adding an additional person of that race is equal to the marginal cost. Our task is complicated by the fact that registrants sometimes match patients of other races. Therefore to calculate the optimal number of persons of each race, we need to account for the number of persons of each other race who are registered. We used MatLab's numerical optimization procedures to find an optimal registry, such that the marginal benefit to persons of all races from adding an additional registrant of any race is equal to the marginal cost. Table 8 reports the results of this calculation. Here we present the actual and optimal registry sizes for whites, African Americans, Asian Americans and Hispanics.[9] 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 times as large for African Americans.[10]

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
Afr 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.[11] Current registration rates, however, do not

[9]We omit estimates for Native Americans. The distribution of HLA types of Native Americans in the registry is very similar to that of whites. As a result, the calculation of the optimal number of Native American registrants is volatile with respect to the relative cost of adding a Native American or a white to the registry.

[10]We also calculated the optimal size for the entire world registry, based on the assumption that the distribution by race in the world registry and among those seeking transplants would be in the same as fir the NMDP. This crude estimate indicates that the optimal size for the world registry is about 32 million, as compared to the current 11 million.

[11]The number of new registrants was 630,000 in 1996 and was approximately 500,000 in

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, 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
Afr Am	30,000	189,000	6.3
As 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 [30], Table 2.19. Annual registrants for optimal steady state is calculated as four percent of the optimal registry size reported in Table 8.

In Table 10, we see that between two and three percent of the eligible population of whites, African Americans, and Hispanics are enrolled in the bone marrow registry, while six-and-a-half percent of Asian Americans are enrolled. In an optimal registry, this percentage would be about seven percent for whites and close to twenty-five percent for African Americans and Asian Americans.

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	P(No Match) in actual registry	P(No Match) in optimal registry
White	2.7	7.1	.08	.03
Afr Am	2.4	23.8	.38	.12
As Am	6.5	26.5	.21	.09
Hisp	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.

Table 10 also shows the probability that a patient seeking a transplant will fail to find a match given the current registry size and the optimal registry size. It is interesting to note that although an optimal registry includes larger fractions of the African American and Asian American populations than of

2004. In 2004, approximately 85,000 registrants turned 61 and were removed from the registry.

whites, whites would remain more likely than other races to find a match. In an optimal registry, the probability that an African American patient would fail to find an HLA match falls from the current thirty-eight percent to twelve percent, while for white patients this probability would fall from seven percent to three percent. This discrepancy arises largely because there are "economies of scale" in the technology of matching. The African American and Asian American populations are both smaller and more genetically diverse than the white population. Our calculations indicate that even if all eligible African Americans were added to the registry, the probability of finding a match in the registry would be lower for an African American patient than for a white.

What Motivates Potential Donors?

Those who join the bone marrow registry are explicitly 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 problem for bone marrow donors is not the same as that for donating money to the poor. Private donations to the poor could be encompassed in the standard Nash-equilibrium model of private provision of public goods (see Bergstrom, Blume, and Varian [6]), where the well-being of the poor people is treated as a public good. In that model, a donation from one person is a perfect substitute for an equal donation from another. The biology of immune systems ensures that this is not the case with the bone marrow registry. Contributions by two people of different HLA types can not be substituted for each other. If someone is the only representative of his HLA type in the registry, then his contribution would be essential should a needy patient of this type appear. But if there are others of this HLA type in the registry, then even if he were called upon to donate, his participation would not be essential to anyone's survival probability, since another equally suitable donor would be available.

The probability that a registrant will ever be asked to donate is small; the lifetime probability for a white who joins the registry at age 35 is about one percent and for other races it is even lower. If a registrant is the only person of his HLA type in the registry, we say that he is *pivotal*. If there is more than one registrant whose HLA type matches a patient seeking a transplant, only one of them needs to make a donation. We assume that in this case, selection is at random and we calculate the conditional probability that someone who is asked to donate is pivotal. This probability depends on the registrant's own race and on the size and racial composition of the registry. In Appendix A, we present

a detailed probability model that estimates the probability π that a registrant will ever be asked to donate and the conditional probability h that a registrant who is asked to donate is pivotal.

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

	Current Registry		Optimal Registry	
	P(Asked|Reg)	P(Pivotal|Asked)	P(Asked|Reg)	P(Pivotal|Asked)
Race	π	h	π	h
White	.013	.08	.004	.03
Afr Am	.005	.78	.001	.19
As Am	.006	.30	.002	.11
Hisp	.008	.22	.003	.08

Table 11 reports the probabilities π and h by race. We see that the conditional probability is about eight percent that a white registrant will be pivotal if asked to donate. The corresponding probability for an Asian American is thirty percent and for an African American is almost eighty percent. As the table shows, 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 much larger for the other races than for whites.

Those who join the registry currently have no way of knowing the probability h. Perhaps many donors would not be interested in this number if they were told. We believe, however, that the number of people willing to join the registry would be an increasing function of the perceived likelihood that if asked to donate, they would play a pivotal role in saving a life. It is therefore instructive to consider the decision problem faced by a potential donor who is aware of the probability that he will be asked to donate if he joins the registry, and of the conditional probability that he will be pivotal if asked to donate.

Meditations of a Consequentialist Altruist

Let us consider the choice problem faced by a rational donor with specified beliefs about the probability distributions of relevant outcomes and whose choices are consistent with a von Neumann Morgenstern utility function. For a first pass at this problem, we consider a "consequentialist altruist," who values actions only by their results.[12]

Three distinct possible states of the world are of concern to a consequentialist altruist who considers joining the registry. One possibility is that she is never

[12]The *Stanford Encyclopedia of Philosopy* [41] defines consequentialism is "the view that normative properties depend only on consequences."

asked to donate. A second is that she is asked to donate and is the only person of her type in the registry. The final possibility is that she is asked to donate, although the registry contains at least one other person of her type. Let π_i be the probability that person 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.[13]

Assume that there is no cost, positive or negative, for joining the registry. 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 $V_i < C_i$ be the utility that i attaches to saving someone else the trouble of donating. Then i assigns utility $U_{0i} + V_i - C_i < U_{0i}$ to making a donation that is not pivotal.

The NMDP asks registrants to promise that they are "willing to donate to any person in need," but there is no contractual obligation to do so. A consequentialist altruist who is not rewarded for joining the registry would join only if she intended to donate if asked. The expected utility of i for joining the registry is then:

$$(1 - \pi_i)U_{0i} + \pi_i \left(h_i(U_{0i} + B_i - C_i) + (1 - h_i)(U_{0i} + V_i - C_i)\right). \tag{4}$$

Therefore i will prefer to join the registry if and only if the utility in Expression 4 exceeds U_{0i}. This is the case if and only if

$$h_i(B_i - C_i) + (1 - h_i)(V_i - C_i) > 0. \tag{5}$$

It seems reasonable to assume that a consequentialist's value V_i of saving another donor the trouble of donating is small. Let us simplify by setting $V_i = 0$. Then Condition 5 becomes

$$\frac{B_i}{C_i} > \frac{1}{h_i}. \tag{6}$$

As shown in Table 11, we estimate the probability h of being pivotal at about 0.08 for white Americans. If this were the probability perceived by all potential donors, then Condition 6 tells us that those who join the registry

[13]It is the policy of the NMDP not to reveal to potential donors whether they are the only person of their HLA types in the registry. Although we have been able to estimate the probability h for persons of each race, no such estimates are publicly available, and perceptions about this probability are likely to vary widely.

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, 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 adept at 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 several models and laboratory experiments that explore alternative motives for altruistic behavior. Andreoni [2] proposed that people feel a "warm glow" from giving that depends on the size of their own gift, independent of the ultimate stock of public goods. Duncan [15] introduces the notion of "impact philanthropy," where people take pleasure in the difference made by their own actions. Benabou and Tirole [3] suggest 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." These authors show that to determine motives from actions requires a somewhat

subtle signal extraction model in which good actions may or may not impress others. As Ellingsen and Johannesson [16] 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 Dana, Weber, and Kuang [13], Dana, Cain, and Dawes, [12], Broberg, Ellingsen, and Johannesson [8], and Lazear, Malmendier, and Weber[24] shows 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 separate experiments in which people who would play 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 will never know who has behaved selfishly or unselfishly toward him.

Richard Titmuss [37] argued that paying people for blood "donations" might reduce the supply of blood from those who had previously contributed for free. Many donors are motivated either by social acclaim or by self-satisfaction from performing a good deed. Benabou and Tirole [3] 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." Mellström and Johanneson [26] investigated the effect of payments on donations by means of a field experiment, conducted in Gothenberg, Sweden. In one treatment they gave subjects an opportunity to donate blood without compensation. In a second treatment they offered subjects a small payment (about $7) to make a donation, and in a third treatment they offered those who donated a choice between a payment and the opportunity to give the payment to charity. For men, they found no significant difference among the treatments, but they found that in the second treatment only about half as many women were willing to contribute as in the first and the third. Thus, they suggest that money payments seem to reduce rather than increase donations from Swedish women.

A desire to signal altruism appears to be a useful motivator for blood donations, which occur immediately and certainly after one has agreed to donate. This motivation does not necessarily serve the bone marrow registry so well. The problem is that a bone marrow registrant can signal altruism by joining the registry, while realizing that the probability is small that he will have to follow through with an actual donation. Since the registry cannot make binding contracts, registrants who are motivated by a desire for acclaim may refuse to donate if they are "unlucky" enough to be called upon.

It is important to remember that the motives and ethical views that guide generous actions differ widely in the population. There is also likely to be wide variation in people's perceptions of the probability distribution of consequences of joining the registry. Even if people are, on average, correct about the probabilities, the average perception is not what is relevant here. The current registry contains less than four percent of the eligible population, and an optimal registry would contain less than 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

We do not aspire to capture the full variety of plausible motivations for donors in one simple model, but we do think it important to account for altruistic behavior motivated by the desire for social acclaim. We also want to extend our earlier model to account for possible time and/or money costs of joining the registry and to explore likely effects of paying those who join the registry or those who make donations.

Our earlier 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. But if there is social acclaim for registering or social stigma to not doing so, then the utility of joining and not being called upon would exceed that of not joining. 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 even though they hope never to be asked to donate. Moreover, registrants are under no contractual obligation to donate when called on, though they are asked at the time of registration to affirm that they intend to do so. Some persons might register to gain payments or social acclaim, with the intention to decline if asked to donate. A significant fraction of those called upon to donate fail to do so. According to Kollman et al [23], 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. Others are likely to regard it as shameful not to keep their promise and would donate even if they regret having joined

the registry.

We will work with a simple additive utility model that provides a useful way of keeping track of these interacting effects. Let x_i be the net cost in terms of time and money 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 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.

Suppose that person i intends to donate if asked. The probability that i will be asked is π_i. The gain (or loss) in expected utility from having to make a donation is $h_i B_i + (1 - h_i)V_i - C_i$, where h_i is i's perceived probability of being pivotal if asked. Weighing the direct benefit and/or cost of registering and that of donating if asked, i will prefer to join the registry if and only if

$$a_i(x_i) - x_i + \pi_i \left(h_i B_i + (1 - h_i)V_i - C_i\right) > 0. \tag{7}$$

To complete this model, we need to account for the possibility that someone may join the registry for social acclaim or financial reward, but would decline to donate if called upon. If $h_i B_i + (1 - h_i)V_i > C_i$ then i is glad to be called upon and will donate willingly. But if $C_i > h_i B_i + (1 - h_i)V_i$, then if asked to donate, i will do so only if the shame, S_i, from not donating is greater than the expected disutility of donating. That is

$$S_i > C_i - h_i B_i - (1 - h_i)V_i \tag{8}$$

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

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

Expression 9 tells us that 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.

Fees and Payments for Registrants and Donors

Until recently, potential donors could join the national bone marrow registry without paying a fee. This is no longer the case. The bone marrow registry lacks sufficient funding to pay the costs of adding new registrants and has begun to charge a fee of $52 to volunteers who wish to join the registry online. With the use of the internet, the time cost of joining the registry has been much reduced.

Previously, to join the registry one would have to travel to a collection center. With internet registration, an eligible donor simply completes an online form, pays a fee, orders a "tissue-typing kit," takes a swab of cheek cells, and mails the swab to the registry for testing. Apparently some donors can avoid the fee by registering in person. According to the registry web site: "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 the registry at a designated collection center.

Our study suggests that the number of persons of all races in the current registry is less than optimal. It seems unfortunate that the NMDP must charge a significant fee to new registrants. The likely effect of fees is to deter new registrants. It is possible in principle that there is a "reverse Titmuss effect" making people more likely to register if they have to pay to do so, but this seems highly unlikely. There is, however, one likely beneficial side-effect of fees. Fees should tend to deter registration by those who join for social acclaim but have no intention of donating if asked. Thus a registration fee is likely to reduce the number of registrants, but it might increase the proportion of registrants who are ready to donate if called upon.

Although the bone marrow registry continues to grow, our analysis suggests (see Table 9) that for all races, current rates of registration will not be sufficient, even in the long run, to sustain a registry of optimal size. This suggests that it may not be possible to achieve an optimal registry solely with unpaid volunteers.

One strategy for attracting more registrants would be to pay people to join the registry. Aside from possible Titmuss effects, this method of attracting donors has a significant disadvantage. Paying new registrants may attract people who plan to collect the reward, while intending to refuse to donate if asked. Alternatively, payments might be made only to those who actually make a donation. Paying donors would increase the utility of joining the registry only for those who intend to donate if asked. Thus, paying donors should increase the proportion of registrants who agree to donate, and also attract more registrants. Since less than one percent of all registrants are ever called upon to donate, the same total expenditure would support much larger payments to donors than to registrants.

Payments to bone marrow donors do not represent a diversion of resources from other purposes, but are simply transfer payments. Standard benefit-cost methodology[14] does not treat transfer payments as costs, though it does count administrative costs and dead-weight loss due to incentive effects. Transfer

[14]See, for example, Boadway and Wildasin [7], pp 40-41.

payments are evaluated mainly on grounds of equity. It is arguable that there is a strong equity case for payments to bone marrow donors, who bear pain, risk, and inconvenience for the benefit of strangers. The case for regarding payments to donors simply as transfer payments can be disputed, however. If paying donors deprives them of the good feeling of having sacrificed for others, then the net gain to donors from being paid will be less than the loss to the taxpayers who contributed the payments. Measuring this difference requires a deeper understanding of the motives of donors than we now have. Future experimental studies and field interviews may shed useful light on this question.

Conclusion

Our benefit-cost analysis suggests that for all of the large racial groups, benefits from an additional registrant are more than four times as large as costs, and 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 benefit-cost ratios, the current registry has fewer people of all races than is optimal.

We estimated optimal registry sizes for each race. Currently, the registry contains between two and three percent of eligible whites, African Americans, and Hispanics, and six-and-one-half percent of eligible Asian Americans. Optimal levels are almost ten times as large as the existing registry for African Americans, three times as large for whites, and between four and five tims as large for Asian Americans and Hispanics. 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.

A lack of sufficient funds has forced the NMDP to charge potential donors for joining the registry. Charging fees for those who wish to join the bone marrow registry seems an unfortunate impediment to participation given that the current registry appears to be much smaller than optimal. Because the registry is relatively new, it is still growing, but the current rate of new registrations is not large enough to sustain an optimal registry size in the long run. This suggests a strong economic case for providing sufficient funding to the NMDP to allow it to waive fees for all new registrants. New registrants could be given the option to make voluntary cash donations to cover the costs of their registration.

The bone marrow registry confronts us with an interesting variant of the standard free-rider problem. Donations by two 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 they are with the current registry.

The bone marrow registry has been able to attract almost three percent of the eligible US population. This is impressive evidence of generous behavior. But an optimal registry would need almost ten times as many African Americans and between two and five times as many persons of other races as the current registry. If those who have already joined are the "most generous" individuals in society, it may be difficult to find enough volunteers to double their number. This difficulty is compounded by the fact that if the registry approaches optimal size, the free rider problem will become more severe, since new registrants will be less likely to be unique in the registry.

If increased recruitment efforts do not achieve sufficient increases in voluntary enrollments, one might consider offering financial rewards to attract donors. This could be done either by paying a small sum to each new registrant, or by paying a larger sum to those who actually make a donation. Payments to new registrants may attract some who join for the reward, but refuse to donate when asked. Registrants who refuse to donate are likely to cause damaging delays for a patient in urgent need of a transplant. A policy of rewarding only those who make a donation would avoid this ill effect, and instead would be likely to increase the proportion of registrants who intend to donate.

Appendix A:

The effect of an additional registrant on the probability of a match

Recall that an effective registrant is defined as one who will be willing and able to donate if asked to do so. Where R is the vector of numbers of effective registrants of each race, define $G_{xy}(R)$ to be the effect that adding a randomly selected person of race x to the registry has on the probability that a randomly selected person of race y will find a match. Let p_i^x be the probability that a person of race x is of type i, and let $P_i^0(R_x, x)$ be the probability that a person of type i has no match of race x in a registry that contains R_x persons of race x. Then

$$P_i^0(R_x, x) = (1 - p_i^x)^{R_x}. \tag{10}$$

The probability that a person of type i has no match in the registry from any race is the product across races of the probabilities that there is no match in each race. This probability is given by the product

$$P_i^0(R) = \prod_z P_i^0(R_z, z). \tag{11}$$

Adding one person of race x to the registry changes the probability that a person of type i will *not* find a match by the amount

$$\Delta_i^x(R) = \left(\prod_{z \neq x} P_i^0(R_z, z) \right) \left(P_i^0(R_x + 1, x) - P_i^0(R_x, x) \right). \tag{12}$$

Now

$$P_i^0(R_x + 1, x) = (1 - p_i^x)^{R_x + 1} = (1 - p_i^x) P_i^0(R_x, x). \tag{13}$$

Therefore

$$P_i^0(R_x + 1, x) - P_i^0(R_x, x) = (1 - p_i^x - 1) P_i^0(R_x, x) = -p_i^x P_i^0(R_x, x), \tag{14}$$

and it follows that

$$\Delta_i^x(R) = -\left(\prod_{z \neq x} P_i^0(R_z, z) \right) \left(p_i^x P_i^x(R_x, x) \right). \tag{15}$$

Then the change in the probability that a person of race y *does* find a match if one registrant of race x is added will be

$$G_{xy}(R) = -\sum_i p_i^y \Delta_i^x(R) = \left(\prod_{z \neq x} P_i^0(R_z, z) \right) \sum_i p_i^y p_i^x P_i^x(R_x, x), \tag{16}$$

which simplifies to

$$G_{xy}(R) = \sum_i p_i^y p_i^x P_i^0(R). \tag{17}$$

This proves the desired result.[15]

Probability of being pivotal if asked to donate

Let R_x and N_x be the number of registrants and the number of needy patients of race x and let R and N be the corresponding vectors of registrants and needy patients by race. Let $H^x(R, N)$ 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 $P_d^x(R, N)$ as the annual probability that a registrant of race x will be chosen to make a donation and $P_o^x(R, N)$ 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,

$$H^x(R, N) = \frac{P_o^x(R, N)}{P_d^x(R, N)} \tag{18}$$

To estimate $P_o^x(R, N)$, we proceed as follows. The probability that there are no other registrants of type i is $p_i^0(R)$, which is defined in Equation 1. Let $n_i(N)$ be the probability that there is at least one patient of type i seeking a donation. Then

$$n_i(N) = 1 - \prod_x (1 - p_i^x)^{N_x} \tag{19}$$

The conditional probability that a donor is pivotal in saving a life, given that he is of type i is

$$p_i^o(R, N) = p_i^0(R) n_i(N). \tag{20}$$

The probability that a registrant of race x is pivotal in saving a life is

$$P_o^x(R, N) = \sum_i p_i^x p_i^o(R, N). \tag{21}$$

A potential donor has no initial knowledge of his HLA type, beyond what is implied by knowledge of his race. Therefore the prior probability of being asked to donate is the same for all members of a given race. If we know the annual number of persons of each race who are asked to donate and the size of the registry, we can estimate P_d^x as the ratio of the former to the latter.

[15] An alternative proof can be constructed as follows. The probability that someone of race y is of type i, previously had no match, but finds a match with the addition of one more person is $p_i^x p_i^y p_i^0(R)$. Therefore the probability that a randomly selected member of race y who previously had no match finds a match with a new registrant of race x is $\sum_i p_i^x p_i^y p_i^0(R)$.

Alternatively, we can use our knowledge of the distribution of HLA types and the number of transplant-seeking patients of each race to estimate the number of persons of each race who are asked to donate. We do this as follows: Let

$$m_i(N) = \sum_x p_i^x N_x \tag{22}$$

be the expected number of type i persons in need of a transplant. The fraction of type i registrants that are of race x is estimated by

$$r_i^x(R) = \frac{p_i^x R_x}{\sum_{y \in S} p_i^y R_y}. \tag{23}$$

Then the expected number of registrants of race x who are asked to donate is

$$E_R^x(R, N) = \sum_i m_i(N) r_i^x(R). \tag{24}$$

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

$$P_d^x(R, N) = \frac{E_R^x(R, N)}{R_x}. \tag{25}$$

We can now use equations 25, 21, and 18 to calculate $H^x(R, N)$.

Appendix B

Here we estimate the expected change in survival probability from receiving a stem cell transplant rather than the next best medical treatment. Transplants are used to treat many conditions and data on relative effectiveness varies across diseases in availability, quality, and generality. We use available medical data to estimate the expected number of lives saved by an additional transplant for each of the most common conditions. We then calculate an average, weighted by the frequency of each ailment. The weighted average net gain in long term survival probability across the diseases in Table 12 is 0.21. We use this figure to estimate the expected number of lives saved by an additional match from the bone marrow registry.

Survival Gains by Condition

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 [30], are listed in Table 12.

Table 12: Net Survival Gains From Transplants, by Disease

Disease	Number of Transplants	Percent 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 [4]. 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 [43]).

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 [30]) A more recent review article [35] 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 by Garcia-Manero [18] 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 [11] . Two studies that assess the effectiveness of chemotherapy in treating ALL found long term survival rates of 20% and 32% [36] [42]. 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% [19]. Among patients treated with bone marrow transplants facilitated by the national registry, 10 year survival is approximately 27% (NMDP Biennial report [30]). 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 [29] 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 transplantion 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]" [20]. 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 [40]. Because the studies vary in the age of participants, we separately computed average survival advantage (weighted by study size) attributable to bone marrow transplantation 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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