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STEM CELL DONOR MATCHING FOR PATIENTS OF MIXED RACE

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Abstract

The plight of multiracial leukemia patients who are unable to find matching stem cell donors has received much media attention. These news stories, while dramatic, are short on statistical information and long on misconceptions. We apply simple probability theory, the genetics of sexual diploid reproduction, and the theory of public goods to produce estimates of the probabilities that multiracial patients will find matching donors in the existing registry. We then compute the benefits and costs of registering more potential donors of single and mixed races.

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1 Introduction

Patients with leukemia and other blood diseases stand a good chance of recovery and a return to normal life if they receive a stem cell transplant from a living donor. In the absence of a transplant, their survival prospects are grim. For a transplant to be successful, the immune systems of donor and recipient must be of matching genetic type. Finding a match is often difficult because the distribution of types in the human population is extremely diffuse. Approximately half of the population of European descent belongs to types with frequency less than one in one hundred thousand, while twenty percent belong to types with a frequency of less than one in a million. The distribution of types for persons of Asian and African descent is even more diffuse. Type distributions differ substantially between races, and two individuals are more likely to match if they are of the same race.

Many nations have established volunteer registries of potential stem cell donors. New registrants contribute a saliva sample from which their genetic type is determined and state their willingness to donate to any patient for whom they are a match.¹ The largest of these registries is the National Marrow Donor Program (NMDP) which includes more than 7 million registrants from the United States, Germany, Scandinavia, the Netherlands, and Israel. The number of persons of European ancestry in the NMDP registry is more than 10 times that of the other races. Because of this, whites are much more likely to find a match than persons of other races.

In a previous study [7] we performed an economic benefit-cost analysis of adding registrants of each race, white, African-American, Asian-American and Hispanic, to the NMDP registry. We concluded that the expected present value of adding registrants of every race to the NMDP registry exceeds the cost, with the largest net benefits arising from the addition of minority registrants. Recently, much attention has been devoted to the plight of mixed race individuals in need of a transplant and the efficacy of recruiting individuals of mixed race to the registry to facilitate these transplants. Because the number of persons of mixed race in the NMDP registry is relatively small, there are no published estimates of the probability distribution of genetic types for multiracial individuals. This has led to serious misconceptions in the popular press as well as in the medical profession.

The news media regularly present dramatic accounts of biracial and multi-racial individuals who need stem cell transplants but are unable to find a matching donor[45], [10], [49], [16], [3]. One story [3] reports that:

If Nick Glasgow were white, he would have a nearly 90 percent chance of finding a matching bone marrow donor who could cure his leukemia.

But because the 28-year-old bodybuilder is one-quarter Japanese, his doctor warned him the outlook was grim. Glasgow's background would make it almost impossible to find a match, which usually comes from a patient's own ethnic group.

¹Stem cells may be collected from donors either by means of bone marrow transplants or by means of peripheral blood stem cell (PBSC) transfer. Either procedure involves temporary discomfort for the donor, but normally donors are restored to full health within two to three weeks.

The doctor “didn’t say it was slim-to-none. He didn’t say it would be hard. He said ‘zero chance,’ ” Glasgow’s mother . . . recalled.

The same news story quotes an NMDP spokesperson saying:

“The truth is, when people of different backgrounds marry and produce offspring, it creates more types that are harder to match. The probability just gets lower when you have people of mixed ancestral DNA.”

According to a recent *Time Magazine* story [45]:

“It’s difficult to ascertain the exact chances of finding a match for a mixed race person because the different combinations have different success rates, and the U.S.-based National Marrow Donor Program (NMDP) . . . does not have statistics on the success rates of mixed race patients....Athena Mari Asklipiadis, the founder of the California-based Mixed Marrow, one of the only outreach groups devoted to recruiting mixed race donors ...maintains the rates are lower—much lower. ‘God forbid I need a match, because I’m a very rare combination,’ Asklipiadis says of her mixed Japanese, Italian, Armenian, Egyptian and Greek background.”

These reports raise interesting questions: What are the probabilities that biracial individuals will find a match in the current registry? Are biracial individuals less likely to find matches than either of their parents? Is a biracial registrant more likely to be the only match for some patient than is a person of single race? Are matching prospects worse for persons with complex multiracial ancestry than for those who are simply biracial?

This paper applies the genetics of sexual diploid reproduction to estimate the distribution of types for persons of mixed race. With these estimates in hand, we complete the first benefit-cost analysis of recruitment of mixed-race donors. Our analysis reveals several interesting facts about the stem cell registry and matching prospects for persons of mixed ancestry:

- 1) Prospects of finding a match for biracial patients are not as dire as news stories suggest. Although biracial patients with one white parent are less likely to find a match than patients with two white parents, such patients have a better chance of finding a match than does a single-race patient of the minority parent’s race.

- 2) Although a biracial individual is more likely to match a random person of the same biracial background than a random individual of any other race, the most frequent source of matching donors for biracial patients with one white parent is the white registry.

- 3) If the only beneficiaries of donations from biracial donors were patients of the same background, the benefits from adding biracial registrants to the NMDP registry would be relatively small. The probability that a new biracial registrant is the only available match for someone of the same biracial ancestry turns out to be smaller than the probability that a new white registrant will be the only available match for a white patient. But it also turns out that a new biracial registrant is more likely to be the only available match for a white patient than is an additional white registrant. Therefore

the expected social benefit from recruiting additional biracial registrants is higher than that from recruiting whites.

4) Contrary to accounts in the news media, persons of complex multiracial ancestry are no less likely to find a match than biracial individuals.

5) The expected value of adding a new registrant to the stem cell registry exceeds the cost for persons of all single-race and mixed-race backgrounds. The ratio of benefits to costs is highest for an African-American registrant, intermediate for a registrant of mixed race or other minority race and lowest for a white registrant.

The racial categories by which NMDP registrants are currently classified is somewhat crude and arbitrary. We explore the possibility of estimating type distributions for more finely classified populations and suggest ways in which such data might be used for targeted recruitment of potential donors. We also compare the allocation problem for stem cell transplants with that for kidney transplants and we discuss the question of whether donor payments are called for.

2 Genetic Background and Data Sources

The human leukocyte antigen (HLA) system is a complex of genes related to the immune system. The immune system uses the HLA genes to differentiate self cells and non-self cells, a task that is central to defense against disease. Cells that do not match the body's own HLA type are treated as invaders. In order for a stem cell transplant to be successful, the HLA genes of the donor and recipient must be a close match. Human HLA types are determined by the pairs of alleles found in a small number of genetic loci located on the same chromosome. The traditional medical standard for a suitable match for stem cell transplant has been that donor and recipient share the same six alleles in three specific loci, known as HLA-A, HLA-B, and HLA-DRB1.² The combination of six alleles that an individual has in these three loci is referred to as his or her *phenotype*.

The critical six alleles are inherited in the form of two strings of three, one from each parent. These three-allele strings are known as *haplotypes*. The haplotype that each parent passes to a child is randomly chosen from the parent's two haplotypes. Because the HLA alleles are located in close proximity on the same chromosome, recombination between these loci is very infrequent. Therefore, with rare exceptions, HLA haplotypes remain intact from generation to generation.

The largest available source of data on the distribution of HLA types is the NMDP registry. The NMDP records the self-reported race and the HLA type of each registrant. In a 1997 paper, M. Mori *et al* [29] used a sample of about 400,000 registrants who had been typed at three loci to estimate the distribution of HLA haplotypes in several racial subgroups of the U.S. population. More recently, Kollman *et al* [24] constructed new estimates using a sample of about two million registrants, including 1.2 million European-Americans, 250,000 Asian-Americans, 280,000 African-Americans,

²This standard is evolving. Currently, clinicians also attempt to match donors and patients at the loci HLA-C and HLA-DPB1, whenever possible.

and 320,000 Hispanics.³ Although the samples used in the Mori and Kollman studies are large, they are not nearly large enough to provide good direct estimates of the distribution of relatively rare types. Since there are more than 25 million possible HLA phenotypes, many of the rare types will not appear even in a sample of 2 million. But the mechanics of diploid genetics make it possible, under reasonable assumptions about mating patterns, to use the observed distribution of phenotypes to construct maximum-likelihood estimates of the distribution of HLA haplotypes for each race. Since the number of possible haplotypes at the three-locus level is “only” of the order of 25,000, the data available from the NMDP registry is sufficient to yield reasonably accurate estimates of haplotype distributions. The Mori and Kollman studies followed this strategy and published tables of estimated frequency distribution of haplotypes in each racial group.

3 Methods

3.1 Estimating Distributions For Mixed Race Populations

Previous studies have not attempted to estimate the distribution of HLA types for persons of mixed race. The number of mixed race persons in existing registries is too small to provide reliable direct estimates of the distribution of types for these groups. But the fundamental combinatorics of sexual diploid reproduction allow us to estimate these distributions indirectly, from the distribution of haplotypes for persons of single races.

In a recent paper [7], we used estimates of HLA haplotype distributions for whites, African-Americans, Asian-Americans, and Hispanics to estimate the distribution of phenotypes for each race. We calculated the probability that individuals of each race would find a matching HLA type in the current NMDP registry and we estimated the effects of adding new registrants of each race on matching probabilities for persons of all races. We then performed an economic benefit-cost study, estimating the expected present value and the cost of adding persons of each race to the registry. We found that the expected benefits of adding new registrants of any race to the registry exceed costs and that the largest net benefits come from adding minority registrants.

To calculate the probability that persons of a given race will find a match in the registry, given the number of registrants of each race, we proceed as follows. Let R_x be the number of persons of race x in the registry and let p_i^x be the fraction of the population of race x that is of HLA type i . 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

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

³The Kollman study was able to achieve this larger sample partly because of the increased number of persons in the registry who have been typed at all three loci and partly because it applied a more general estimation method that extracts information from data about early registrants who had been typed only at two loci.

A registry 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

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

It follows that the probability that a person of race x has no match in the registry is

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

Remarkably, the simple combinatorics of sexual diploid reproduction allow us to extend this procedure to find the distribution of HLA-types for biracial individuals. Someone with one parent of race X and one of race Y could acquire the six alleles A_1 , A_2 , B_1 , B_2 , D_1 , and D_2 in any one of 8 ways. For example, she could inherit the three alleles A_1 , B_1 , and D_1 from the parent of race X (in the form of haplotype $A_1B_1D_1$) and the remaining alleles A_2 , B_2 , and D_2 (in the form of haplotype $A_2B_2D_2$) from the parent of race Y . Alternatively, she could inherit the haplotype $A_2B_1D_1$ from the parent of race X and the haplotype $A_1B_2D_2$ from the parent of race Y . There are a total of 8 such combinations. Since we have the estimated haplotype distribution for each race, we can calculate the probability of each of these eight combinations. Adding these 8 probabilities yields the probability that someone with one parent of race X and one parent of race Y will possess the six alleles A_1 , A_2 , B_1 , B_2 , D_1 , and D_2 . With this strategy, and the computational power of MatLab, we are to calculate the probability of each of the roughly 25 million possible HLA phenotypes for persons of biracial parentage.

Estimates in our earlier paper [7] were based on the estimates of haplotype distributions by Mori *et al* [29]. The current paper uses the more recent Kollman [24] estimates of haplotype distribution. Not only are we able to extend our results to mixed-race populations, but we are also able to verify that the results found in [7] are broadly confirmed with independent data from a larger sample of haplotype distributions.

3.2 Effective Registry Size and Composition

The NMDP reports the numbers of potential donors who designate themselves as white, African-American, Asian-American, and Hispanic. They also report 250,000 registrants of “multiple race”, but do not report the numbers of specific multi-race combinations. To provide such estimates, we make the simplifying assumptions that the multi-race registrants are all biracial and that the proportions of each biracial combination in the registry are the same as those found in the U.S. Census.⁴

Not every registrant is able or willing to donate when called upon to do so. The NMDP has provided statistics on the availability rate for donors of each race. We

⁴The 2000 U.S. Census, asked respondents to specify their race and, if they were multi-racial, to specify the races to which they belonged. About 0.28 percent of the population was identified as mixed-race African-American and white and 0.31 percent as mixed-race Asian and white, about 0.8 percent were identified as white and “some other race”. [30]

Table 1: Number of Registrants and Available Registrants by Race and Biracial Group

Race or Biracial Group	Number of NMDP Registrants	Probability Registrant is Available	Number of Effective Registrants
White	6,090,000	0.57	3,471,300
African-American	600,000	0.27	162,000
Asian-American	561,000	0.35	196,350
Hispanic	800,000	0.34	272,000
African-American, White	43,700	0.42	18,400
Asian-American, White	50,900	0.46	23,400
Hispanic, White	92,500	0.46	42,100
African-Amer., Asian-Amer.	8,000	0.31	2,500
African-American, Hispanic	44,600	0.30	13,600
Asian-American, Hispanic	10,400	0.34	3,600

Notes: Registry numbers were obtained from the NMDP [33]. Numbers for mixed races are imputed as described in the text. The first four entries of the second column are from the NMDP (personal communication, Martin Maiers). Entries for mixed races are arithmetic means of the rates for constituent single races.

used these estimates of availability to estimate the size of the “effective” registry for each race: the expected number of persons of each race who are registered and will be available if called upon to donate. Table 1 reports the resulting registry composition.

3.3 Match Probabilities and Expected Lives Saved

We use Equations 2 and 3, along with our estimates of the effective size and composition of the NMDP registry, to estimate the probability that a randomly selected person of specified racial background will find a match in the NMDP registry. The resulting probabilities are reported in Table 2 of the Results section.

To estimate the expected number of lives saved by additional registrants, we first estimate the probability that a new registrant of given race will provide a match for someone who did not previously have a match in the registry. Let us define $G_{xy}(R)$ as the increase in the probability that a person of race y will have a match in the registry that results from adding a registrant of race x , when the vector of registrants by race is R . Let $p_i^0(R)$ be the probability that there is no potential donor of type i in the registry. 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

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

Adding one more HLA type to the registry will result in an additional stem cell transplant only if a patient of that HLA type is in need of a transplant. To calculate the probability that adding a person of race x to the registry will result in an additional transplant to a person of race y during a given year, we must multiply $G_{xy}(R)$ by the number of persons of race y who will seek transplants during that year. We display the resulting estimates in Table 5 of our Results section.

4 Results

4.1 Probability of Finding a Match

Table 2 reports our estimates of the probability that patients of specified racial backgrounds will find a matching HLA type in the current NMDP registry.

Table 2: Probability of a Match by Race or Biracial Group

Race or Biracial Group	Probability of A Match in NMDP Registry
White	0.93
African-American	0.58
Asian-American	0.77
Hispanic	0.82
African-American, White	0.71
Asian-American, White	0.80
Hispanic, White	0.87
African-American, Asian-American	0.50
African-American, Hispanic	0.65
Asian-American, Hispanic	0.72

Notes: Table entries are the probabilities that a person of specified racial background has a 6/6 HLA-A,B,DRB1 match in a registry of the composition given in Table 1.

We see that the probability of finding a match for biracial patients with one white parent and one minority parent is higher than that of finding a match for persons with two parents from the same minority group. Children of one Asian-American and one African-American parent and children of one Hispanic and one Asian-American parent have slightly lower probabilities than those of either parent, while children of one Hispanic and one African-American parent have probabilities higher than those of the African-American parent but lower than those of the Hispanic parent.

4.2 Source of Matches for Biracial Patients

Although the distributions of HLA haplotypes differ across races, there is substantial overlap. Mixed-race patients will often find matching donors who are classified as

belonging to a single race. Table 3 reports the probabilities that single-race minority patients and biracial patients with one white parent will find a match among registrants of their own racial background as well as the probability that they will find a match among white registrants. Because the number of white registrants is large relative to the number of minority and biracial registrants, we see that biracial patients with one white parent are more likely to find a match with a white registrant than with someone of their own biracial background.

Table 3: Probability of Match in Registry by Race of Donor and Recipient

Race of Recipient	Probability of Match from Own Minority	Probability of Match from White Registry	Probability of Having Some Match
African-American	.39	.30	.58
African-American, White	.34	.59	.71
Asian-American	.62	.43	.77
Asian-American, White	.42	.70	.80
Hispanic	.60	.70	.82
Hispanic, White	.58	.82	.87

Notes: Table entries are probabilities that a person of specified race or mixed race has a 6/6 HLA-A,B,DRB1 match from a registry of the composition given in Table 1.

4.3 Matches Generated by Mixed-Race Registrants

Although a new biracial registrant is more likely to add a new phenotype to the registry than a person of single race, this does not necessarily imply that an additional minority registrant is more likely to result in a life-saving match. Since the number of biracial individuals in the population is small, the number of biracial patients seeking transplants is also small, as is seen in Table 4.

If the only beneficiaries from biracial registrants were biracial patients of their own type, the expected benefits from adding biracial registrants would be small relative to that from adding registrants to the larger single-race groups. However, it turns out that biracial registrants are also relatively likely to provide unique matches for needy patients in the larger single-race classifications. Table 5 displays the probability that an additional registrant of each race or biracial background will turn out to be the only available match for some individual of each specified racial category. (The numbers reported are the estimated probabilities times 10^5 .)

If we look down the column for white recipients, we see something remarkable. The largest entries in this column are in the rows corresponding to biracial individuals. If we were to select a single registrant to add to the current registry with the objective of improving the chances that a white person would find a match, the best option would be to add someone who had one white parent and one parent of African ancestry and the second-best would be to add someone with one white parent and one of Asian

Table 4: Annual Number of Patients Seeking Transplants by Race

Race	Number
White	3,401
African-American	392
Asian-American	205
Hispanic	425
African-American, White	10
Asian-American, White	16
Hispanic, White	22
African-American, Asian-American	3
African-American, Hispanic	10
Asian-American, Hispanic	3

Notes: The number of NMDP-facilitated transplants by single race was obtained from [37]. The number of transplants for mixed races is imputed from the 2000 US Census on mixed race populations and estimates by Qian [34] of the ratio in which persons with one white and one minority parent self-identify by single race. We assume that biracial persons with two minority parents are equally likely to identify with each race.

ancestry. There is a plausible explanation. The number of whites in the registry is very large and so the types that are not currently represented are very rare in the white population. Many of these rare types will come from individuals who are classified as white, but carry haplotypes passed down from one or more nonwhite ancestors. For such persons, the biracial population is the most promising potential source of a match.

The first column of Table 6 records the diagonal elements of Table 5 corresponding to each race or mixed race. These entries represent the probability that adding a registrant of specified single race or biracial ancestry will result in a match for a patient with *the same* ancestry who has no other match. The second records the probability that an additional registrant will produce a match for a patient *of any race* who would otherwise have no match.

We see that the beneficiaries of additional biracial registrants are more likely to be patients from one of the larger single race populations than those of the same biracial background. We also see that a biracial registrant is more likely to be the only available match for some patient than is a white, Asian, or Hispanic registrant, but less likely to be so than an African-American registrant.

4.4 Matching for Multiracial Patients

It might seem that finding a match for someone with a complex multiracial heritage would be more difficult than for someone who is simply biracial. But this is not the case. Matching HLA phenotypes is not like matching paint. Because genetic crossover of HLA alleles is very rare, the HLA type of any individual is almost certainly determined by two haplotypes, one of which is inherited from a paternal and one from a maternal grandparent. Someone whose four grandparents are of four distinct races will have

Table 5: Annual Probability that a Registrant will be the Only Match for a Patient Needing a Transplant by Race of Registrant and of Recipient (times 10^5)

Race of Registrant	Race of Recipient									
	W	Af	As	H	Af-W	As-W	H-W	Af-As	Af-Hi	As-H
W	3.78	0.42	0.19	0.54	0.02	0.02	0.03	0.00	0.01	0.00
Af	3.63	23.42	0.27	2.47	0.22	0.03	0.08	0.05	0.25	0.01
As	3.09	0.51	7.97	0.93	0.02	0.23	0.04	0.03	0.02	0.05
H	4.28	2.28	0.45	5.04	0.06	0.04	0.12	0.02	0.13	0.02
Af-W	5.48	8.25	0.34	2.46	0.31	0.04	0.11	0.05	0.21	0.01
As-W	5.00	0.67	2.85	1.08	0.03	0.49	0.05	0.04	0.03	0.06
H-W	4.48	1.38	0.35	2.21	0.05	0.04	0.10	0.01	0.05	0.01
Af-As	4.89	7.12	2.41	2.81	0.20	0.24	0.09	0.46	0.22	0.10
Af-H	4.84	9.56	0.45	5.47	0.22	0.04	0.12	0.06	0.45	0.02
As-H	4.80	1.48	3.48	2.78	0.04	0.34	0.09	0.09	0.07	0.16

Notes: Equation 4 was used to calculate the effect of adding a registrant of the row race on the probability that a patient of the column race will find a match. The result was multiplied by the number of patients of the column race seeking transplants in 2008, as given in Table 4.

inherited one haplotype from each of two races. If one or more of the grandparents is multi-racial, it will still be the case that the grandparent has two haplotypes, each of which is ultimately inherited from a person of a single race and will pass at most one of these haplotypes on to any particular descendant.

It follows that once we know the distribution of HLA types for biracial combinations, we can calculate the probability distribution of HLA types for any multiracial combination. For example, consider a patient who has one pair of grandparents of races W and X and another pair of races Y and Z . His HLA type will be determined by two haplotypes, one inherited from a paternal grandparent and one from a maternal grandparent. This implies that the probability distribution of his phenotype will be the same as that of a biracial individual from one of the following pairs of races: W, Y ; W, Z ; X, Y ; and X, Z , with each of these pairs as likely as the others. His HLA type distribution is therefore a mixture distribution of the type distributions of the biracial populations of races W, Y ; W, Z ; X, Y ; and X, Z , with an equal weight on each distribution.

The probability that the registry has a match for a patient with one pair of grandparents of races W and X and one pair of races Y and Z is easily calculated. This patient has is equally likely to have inherited one haplotype from each of two persons of races W, Y ; W, Z ; X, Y ; and X, Z . Therefore the probability that the patient has a match is the mean of the probabilities that patients of these four biracial pairings have a match.

The news stories about Nick Glasgow do not make it clear whether the Stanford doctors concluded on *a priori* grounds that because of his racial background he had no chance of finding a match, or whether they made this proclamation after an initial search found no match for him in the NMDP registry. Certainly it would be incorrect

Table 6: Annual Probability that a Registrant Will Be The Only Match for Some Patient by Race of Registrant

Race of Registrant	Probability of Unique Match For Own Race	Probability of Unique Match For Any Race
White	3.8×10^{-5}	5.0×10^{-5}
African-American	23.4×10^{-5}	30.4×10^{-5}
Asian-American	8.0×10^{-5}	12.9×10^{-5}
Hispanic	5.0×10^{-5}	12.4×10^{-5}
African-American, White	0.3×10^{-5}	17.3×10^{-5}
Asian-American, White	0.5×10^{-5}	10.3×10^{-5}
Hispanic, White	0.1×10^{-5}	8.7×10^{-5}
African-American, Asian-American	0.5×10^{-5}	18.5×10^{-5}
African-American, Hispanic	0.4×10^{-5}	21.2×10^{-5}
Asian-American, Hispanic	0.2×10^{-5}	13.3×10^{-5}

Notes: The first column repeats the diagonal entries from Table 5 while the second column is the row sum from that table.

to conclude that his racial background, by itself, was grounds to believe that he had a negligible chance of finding a match. Recall that Glasgow had one Japanese grandparent and three white grandparents. In the absence of additional information, we would conclude that with probability $1/2$ he had two haplotypes inherited from white ancestors and with probability $1/2$, he had one haplotype inherited from a white ancestor and one from a Japanese ancestor. It follows that the probability that he would find a match in the registry is the mean of the probabilities of finding a match for a white patient and that for a biracial, Japanese-white patient. If we approximate the latter probability by the probability that a biracial Asian-white patient will have a match, the probability that Glasgow would have a match in the registry is $\frac{1}{2} \times .93 + \frac{1}{2} \times .80 = .865$ —a far cry from “zero chance.”

Even if the doctors’ statement was made after they found no match in an initial registry search, their remark seems misinformed. Finding no match in the registry would be a distressing outcome, regardless of one’s race. But if the registry had no match for him, the fact that Glasgow was one quarter Japanese offered a ray of hope rather than cause for despair. If all four of his grandparents had been white and he had no match, it would mean that his type was so rare as not to be matched in a registry of 7 million donors. If so, the chances for turning up a donor by means of additional recruitment efforts would be negligible. But given that he has a Japanese grandparent and is unable to find a match in the registry, it is likely that his HLA type is determined by one haplotype inherited from a Japanese ancestor and one from a white ancestor. Without direct knowledge of his HLA type, Bayes’ Law informs us that the conditional probability that Glasgow had one Japanese-inherited haplotype,

given that he had no match in the registry, is .741.⁵ Thus with probability of about 3/4, Glasgow’s HLA type was of biracial Japanese-white origin. The pool of biracial Japanese-white individuals in the NMDP registry is very small, probably fewer than 2,000 effective registrants.⁶ Therefore, although he had no match in the existing pool, it is possible that he had one haplotype that is relatively common among Japanese⁷ and one that is relatively common among whites. If so, there was a possibility that further search, either by recruitment of additional Japanese-white volunteers or by search of Asian registries might turn up a match.⁸

In the weeks after he was told that he had no chance of finding a match, a vigorous campaign was conducted to recruit persons of mixed race as potential donors for Glasgow. As it turned out, not one, but two HLA-matched donors were found.⁹ He received a transplant from one of these donors. Sadly, Nick Glasgow’s leukemia returned after the transplant, and he died a few weeks later. An online account of these events can be found at [14].

4.5 Comparing Economic Benefits and Costs

It is possible to place rough money values on adding potential donors to the NMDP registry. Since no one knows in advance who will be in need of a transplant and few know whether their HLA type is common or rare, the stem cell registry is properly viewed as a public good that contributes a small amount to the survival probability of each person in the community. Economists have developed a tool, known as the “value of a statistical life” for calculating benefits of public projects that enhance public safety. The value of a statistical life (VSL) is an estimate of the rate at which individuals are willing to exchange money for small increments of survival probability. Several studies have estimated willingness to pay for small changes in survival probability by various methods. These studies include surveys (Michael Jones-Lee, M. Hammerton and P. R. Philips [20] and Magnus Johannesson, Per-Olav Johanson, and Karl-Gustav Löfgren [19]), studies of market wage premiums for dangerous work, consumer decisions about

⁵Let A be the event “has no match in the registry” and B be the event “has one haplotype inherited from Japanese ancestors”. Let $P(A)$ be the probability of A , $P(B)$ the probability of B , and $P(A|B)$ and $P(B|A)$ the conditional probabilities of A given B and B given A . Then $P(B|A) = \frac{P(A|B)P(B)}{P(A)}$. But $P(A) = \frac{1}{2}.07 + \frac{1}{2}.20 = .135$, $P(B) = \frac{1}{2}$ and $P(A|B) = .20$. It follows that $P(B|A) = .10/.135 = .741$.

⁶We estimate that there is an effective registry of 23,400 Asian-American donors (Table 1. About 7 percent of Asian-Americans are of Japanese descent (Table 8). If 7 percent of Asian-American registrants have one Japanese and one white parent, then there were only about 1638 biracial Japanese-white donors available in the NMDP registry.

⁷The 6 most common Japanese haplotypes in the Japanese population have frequency 8.2%, 4.6%, 4.6%, 3.7%, 3.7%, and 3.7% and the 10 most common haplotypes comprise 25% of the Japanese distribution.[17]

⁸Clinicians treating his case would be able to make sharper estimates, since their tests would reveal his actual phenotype and they could determine directly whether this phenotype included an allele combination that is common in the Japanese population.

⁹Both of these donors were 10/10 matches, matching Glasgow’s alleles not only at the A , B , and $DRB1$ loci, but also at the loci HLA-C and HLA-DPB1, see[14]. News accounts are not clear on whether the matches that were found after he was told that he had zero chance of a match were new registrants recruited in the “Save Nick Glasgow” campaign or existing registrants found after more careful search.

purchasing consumer safety devices, health care decisions, and decision rules used by government agencies. The VSL can be described as the total amount that members of a community would be willing to pay per expected life saved if the increments in survival probability for each individual are small. Detailed discussions of the theoretical underpinnings of the VSL in project evaluation can be found in [6], [13], [52], and [8].

According to a survey by Viscusi and Aldy [52], estimates of the value of a statistical life are concentrated in the range \$4 million to \$9 million 2004 dollars. We assume a VSL 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” [51], which recommends a VSL equivalent to 6.75 million 2004 dollars.

Table 6 reports the probability that an additional registrant of specified ancestry will be the only available match for some patient in need of a transplant. Not every additional transplant saves a life. Possibly the patient would have survived without a transplant and possibly the patient will die despite receiving a transplant. In [7] we estimated the probability that providing a transplant will actually save a patient’s life to be approximately 0.21. To determine the probability that adding an additional registrant will save a life during a single year, we must therefore multiply the probability found in Table 6 by 0.21.

Persons who join the bone marrow registry can remain in the registry until they reach age 61. The mean age of new registrants as reported by the NMDP is 35 years. We assume that a new registrant will, on average, remain in the registry for 25 years. Although medical technology is bound to change over the next 25 years and the number of persons annually seeking transplants may change dramatically,¹⁰ we assume that the annual number of persons of each race seeking transplants will remain constant for the next 25 years and that the probability that a transplant saves the patient’s life will remain constant as well. Following standard practice in economic benefit cost analysis, we discount future benefit flows by two percent per year. With these assumptions, we can calculate the expected present value of an additional effective registrant of each race. This quantity is found in the second column of Table 7.

The NMDP web site reports that 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. Since not all registrants are available when called upon, the registry must on average add more than one registrant to gain an effective registrant. The fractions of registrants who can be located, pass the physical examination, and who consent to make a donation are .57 for white registrants, .27 for African Americans, .35 for Asian Americans, and .34 for Hispanics.

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

¹⁰The annual number of stem cell transplants from NMDP-registered donors has increased steadily over the decade from 1998 to 2008 at an average annual rate of 8.5 percent.

Table 7: Present Value, Cost, and Benefit-Cost Ratios of a New Effective Registrant: by Race or Biracial Ancestry of Registrant

Race of Registrant	Present Value	Cost	Benefit-Cost Ratio
White	\$1,300	\$297	4.4
African-American	\$8,100	\$800	10.1
Asian-American	\$3,400	\$446	7.6
Hispanic	\$3,300	\$455	7.3
African-American, White	\$4,600	\$549	8.4
Asian-American, White	\$2,700	\$371	7.3
Hispanic, White	\$2,300	\$376	6.2
African-American, Asian-American	\$4,900	\$623	7.9
African-American, Hispanic	\$5,700	\$627	9.1
Asian-American, Hispanic	\$3,600	\$450	8.0

Notes: The annual value of adding an effective registrant was calculated by multiplying the final column of Table 6 by 0.21 statistical lives saved per transplant and multiplying again by \$6,500,000 per statistical life. Entries in the table are present values of 25 years of this annual value discounted at 2%, rounded to the nearest \$100. Costs were calculated as discussed above. The benefit-cost ratio is the ratio of column 2 to column 3.

\$166,000.¹¹ 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.

The third and fourth columns of Table 7 show our estimates of total costs attributable to adding an effective registrant of each racial group and the ratio of the present value of benefits to that of costs. These estimates indicate that benefits from adding new registrants of any race exceed costs. The difference between benefits and costs is greatest for African-Americans, slightly smaller for biracial individuals and smallest for whites.

5 Racial Categories and HLA Matching

The four major racial categories into which NMDP registrants are partitioned are coarse and quite arbitrary. Since the recorded race of a registrant is self-declared, it indicates a social construction that does not necessarily correspond to genetic inheritance. Statistics show, however, that the distribution of HLA types differs markedly across these self-identified categories. For example, the probability that a randomly selected white American will match another randomly selected white is 34 times that of matching a random Asian-American, 16 times that of matching a random African-American, and

¹¹This estimate is based on a survey of costs in 2001 by Redealli et al [35] and converted to 2007 dollars.

6 times that of matching a random Hispanic.

Our statistical computations are based on the Kollman *et al* [24] estimates of the distribution of haplotypes within each race. Kollman's estimates, like those in the earlier study by Mori *et al* [29], are based on two critical assumptions about marriage patterns. The first assumption is that each racial group is *endogamous*, that is marriage occurs almost entirely within races. The second is that conditional on marrying within their group, the probability that two people marry is independent of their HLA types.

Since the social construct of race is more likely to influence marriage patterns than genetic classification, the use of self-declared race to determine categories seems appropriate for the model that is being estimated. Jacobs and Labov [18] collected data on all married heads of households and their spouses from a 1 percent sample of the 1990 U.S. Census. They determined the self-declared race or national origin of each member of each couple, and found that almost 98 percent of marriages of whites and 96 percent of marriages of African-Americans were endogamous. The Jacobs-Labov study shows that approximately 85 percent of Asian-Americans are married to other Asian-Americans and 77 percent of Hispanics are married to other Hispanics.^{12 13}

The genetic composition of the current population depends, of course, on the marriage patterns of their parents' generation, not on current marriage patterns. There is good reason to believe that the current population of Asian-Americans and of Hispanics are children of more endogamous populations than is indicated by current marriages. About 2/3 of the existing population of Asian-Americans were born in Asia and their ancestors for many generations would have had little exposure to non-Asians. About 1/3 of the existing population of Hispanics are immigrants from regions where the population is almost entirely Hispanic.

While the assumption that Asian-Americans marry endogamously is not wildly inaccurate, the assumption that marriage among Asian-Americans is random with respect to HLA type is clearly violated. The marriage patterns of the parents of the current generation of Asian-Americans were far from random. Two-thirds of the current population of Asian-Americans are immigrants, coming from several distinct Asian populations that have been geographically separated for many generations. Even after reaching the United States, Asian-Americans have been far more likely to marry within their own nationality than outside of it. Jacobs and Labov [18] find that about 80% of Asian-American marriages are between two people of the same national origin. Table 8 reports the distribution of national origins of the Asian-American population in the year 2000.

Studies indicate that the distribution of HLA types differs significantly among Asian populations [11]. Therefore the fact that Asian marriages tend to be within sub-populations implies that mating is not random with respect to HLA type. Even if our estimates are reasonably accurate measures of the average distribution of HLA types, much useful information is lost by treating Asian-Americans as aggregate groups. The

¹²Jacobs and Labov report rates of out-marriage for each of several Asian nationalities. We weighted these rates by the number of marriages of each type to find an average rate of out-marriage. Of those who marry outside of their nationality group, about 40 percent of men and 25 percent of women marry other Asians.

¹³According to Jacobs and Labov, among Hispanics, the marriages of 82 percent of Mexican-Americans, 76 percent of Cuban-Americans and 66 percent of Puerto Ricans were endogamous.

Table 8: National Origin of Asian-American Population

National Origin	Fraction
China & Taiwan	0.24
Indian subcontinent	0.17
Philippines	0.17
Vietnam	0.10
Korea	0.10
Pacific Islander	0.08
Japan	0.07
Other	0.06

Notes: Fractions are calculated from the 2000 U.S. Census publication [4], Table 4.

probability distribution of HLA-types for an individual who is known to be of Japanese ancestry will certainly be different from the average distribution of Asians.

Although current rates of intermarriage between African-Americans and whites are low, African-Americans carry a significant amount of genetic material obtained from white ancestors. As Kittles *et al* [22] observe, “The vast majority of contemporary African Americans are descendants of enslaved Africans kidnapped and transported to America during the transatlantic slave trade from 1619 to 1850.” During the period of slavery, there was substantial mixing of the white and African-American gene pool. Kittles *et al* reports that it is estimated that in 1860, “there were 4.5 million people of African descent in the U.S., of which 600,000 were of mixed ancestry or “mulattos”.

Geneticists have developed methods for using genetic markers to estimate *admixture* proportions, that is the proportions of genetic material in a single population that is inherited from members of two or more distinct ancestral populations.¹⁴ Several studies have estimated admixture proportions from samples of African-Americans. These studies indicate that the percentage of European admixture in the African-American population differs substantially by region, ranging from 3.5 percent in the Gullah sea island community of South Carolina, 10 percent in the rural South, about 20 percent in the industrial North, and 22-35 percent on the West Coast, see [22](Figure 2) and [31]. The admixture of African-American genetic material in the U.S. white population appears to be much smaller.¹⁵ The geographic differences in the genetic makeup of the African-American population suggests that the accuracy of estimations of HLA-distributions for African Americans could be improved by disaggregating according to region of birth.

The Hispanic population of the United States includes significant subpopulations that differ in ethnic makeup and have had little contact with each other for many generations. About 66 percent of the Hispanic population of the United States is of

¹⁴See [48] for a brief discussion of these methods and further references.

¹⁵We have not found results based on large and diverse samples of U.S. whites. Based on a sample of 187 individuals of European-American ancestry living in State College, Pa, Shriver *et al* [48] estimates a mean admixture rate of less than one percent.

Mexican extraction, 13 percent come from Central and South America, 9 percent are Puerto Rican, and 4 percent are of Cuban extraction. Genetic admixture studies of Hispanics in the U.S. reveal that Mexican-Americans on average have 30-40 percent Native American ancestry, while immigrants from the Spanish Caribbean have African genetic contributions that range from 20-40 percent and contributions of about 18 percent from the native American Arawaks and Caribs; see [22] and [23].

Estimation of HLA-distributions for more finely distinguished population groups would be feasible with existing data and would be valuable in directing recruitment by the world's stem cell registries. Better estimates would be possible if registries were to collect more detailed information about the ancestral background of registrants. While the NMDP collects some such data, it is not routine for registries outside the United States to do so.

There are many available estimates of the distribution of HLA-haplotype distributions based on relatively small samples from localized regions. Populations studied include Korea [21], China[47] and [46], Taiwan [44], India [1], France [32], Sardinia [25], Wales [12], and several other quite narrowly defined regions of Europe[9] and throughout the world [11]. Since these estimates are usually based on samples of only a few hundred individuals, they can provide reliable information only about the distributions of the most common haplotypes. But the distribution of the most common haplotypes in subpopulations is exactly the information that is likely to be useful in targeting potential donors for a patient who finds no match in the registry. In this case, it may be that the patient carries two haplotypes, each of which is relatively common in some subpopulation that rarely intermarries with the other. If this is the case, recruitment efforts targeted persons who share these two ancestries may offer a reasonable chance of success.

6 Discussion

6.1 Kidney Transplants

Kidney transplantation, the most common form of organ transfer, also involves an interesting matching problem, which is described by Roth, Sönmez, and Ünver [38] [39]. The medical technology of kidney transplantation is very different from that of stem cell donation and consequently, the matching problem and the incentives of donors are also very different.

Kidneys, unlike stem cells, can be transplanted either from living donors or from cadavers, but transfers from living donors have a substantially higher probability of success.¹⁶ Matching the donor's ABO blood type with that of the recipient is crucial for the success of kidney transplantation,¹⁷ but matching of HLA types is believed to

¹⁶In 2009, in the U.S., 6,387 kidneys were transplanted from living donors and about 7248 from cadavers. US Department of Health and Human Services Organ Procurement and Transplantation Network at <http://optn.transplant.hrsa.gov/latestData/rptData.asp> (accessed Sept 30, 2010) Five year survival rates are approximately 80% for recipients of kidneys from living donors and 70% for those who received kidneys from cadavers.[15]

¹⁷In addition to being of matching blood type, the recipient must not have developed antibodies to the

be much less important [42]. A perfectly HLA-matched donor offers slightly better prospects than a mismatched donor, but kidneys transferred from a living donor are more likely to be successful than those from a cadaver, regardless of HLA type. The distribution of blood types is far less diffuse than that of HLA types. (Almost everyone can accept transfusions from at least 7 percent of the population.) While there is some variation of blood types across races, this variation is small, and does not significantly reduce the prospects of mixed-race or minority race patients finding a match.

Donating a kidney is much more costly to the donor than donating stem cells. Stem cell donors experience a few days of minor discomfort and the majority feel completely recovered within two or three weeks of donation. The human body eventually adjusts to loss of a single kidney. Long term survival rates of kidney donors are not significantly different from those of a demographically matched control and the postoperative mortality rate for kidney donors is small, though not negligible—about 3 deaths per 10,000 donors [43]. But recovery is much slower than for stem cell donors. A recent study [53] reports that kidney donors took a median of 23.5 days off of work and the median time before donors self-reported quality of life returned to 90 percent of predonation levels was 110 days. Because donating a kidney is costly and because an HLA match is not required, the great majority of kidney donations are from a relative, spouse, or friend of the recipient.¹⁸ Unlike those who need a stem cell donation, those who need a kidney donation can not search a list of willing potential donors who are waiting for a match. Instead of a registry of willing donors, there is a queue of more than 80,000 patients on U.S. waiting lists for donated kidneys. Frequently, a spouse or relative of a kidney patient is willing to donate, but is not of matching blood type. Although it is illegal to purchase a kidney, federal law permits barter of kidneys in the form of “paired donations” where one patient’s mismatched donor gives a kidney to another patient, whose donor in turn would give his organ to the first patient and more elaborate multilateral swaps. Roth *et al* [38] [39] have devised efficient trading mechanisms to organize complex trades of kidneys among patients and their willing donors.

6.2 Should donors be paid?

The U.S. National Organ Transplant Law explicitly prohibits sale of bone marrow, as well as hearts, lungs, kidneys, livers, eyes, bones, and skin. The sale of human eggs and sperm is permitted, as are “womb-rental payments” by surrogate mothers. Sale of blood for transfusions is illegal, but sale of blood for plasma extraction is legal and commonly practiced. In the fall of 2009, the Institute of Justice filed a lawsuit against the U.S. Department of Justice, arguing that prohibition of the sale of bone marrow is unconstitutional, since bone marrow, like sperm, eggs, and blood plasma and, unlike kidneys or eyes, is a “renewable resource” which the donor’s body replaces in a relatively brief span of time [41].

potential donor. Such antibodies occasionally develop after pregnancy or a blood transfusion. Recently developed techniques have made it possible for some patients with no matching donors to receive transplants from a living ABO-incompatible donor.[2]

¹⁸In 2009, there were about 6,000 kidney transplants from living donors. Siblings of the recipient comprised 25% of donors, other relatives 40%, spouses, 12.5% and other unrelated individuals, 23.5%. [36]

Gary Becker and Julio Elías [5] present a strong case for the use of markets to increase the supply of organs and tissue. Alvin Roth [40] observed that many people view the sale of human organs with repugnance and, in response, governments frequently outlaw such sales. Roth points out that current rules about which body products are marketable seem quite arbitrary.

There is a longstanding controversy about whether paying blood donors would increase the supply of blood. Some donors who are motivated by social acclaim or self-satisfaction might choose not to contribute if their actions are seen as performing services for pay [50]. Field experiments in Sweden [28] and in Italy [26] suggest that offering a small amount of cash in return for contributions may reduce participation, particularly by women. But there is also evidence that material inducements when properly framed act to increase donations. Macis, Lacetera and Slonim [27] examined the results of more than 14,000 American Red Cross blood drives in which various inducements and prizes were offered to blood donors. They conclude that “offering donors economic incentives significantly increases turnout and blood units collected, and more so the greater the incentives monetary value.”

Stem cell donors undergo considerably more inconvenience and discomfort than blood donors, but receive no monetary payment.¹⁹ The beneficiary will almost certainly be a complete stranger to the donor. Yet more than 7 million NMDP registrants have offered to donate stem cells if asked. This is powerful evidence that many people feel a strong obligation to behave altruistically. Our study suggests that numbers of persons all races in the current bone marrow registry fall short of optimality and that the shortage of minority and mixed race registrants is particularly acute. The NMDP has, quite properly, focused its efforts on recruiting persons of minority races for which the return on investment is highest. Recruitment of white donors has been less aggressive. Until very recently, white registrants were asked to pay a fee of \$52 on registration. Currently, in the U.S., approximately 2 percent of the population of appropriate age have joined a stem cell registry. This fraction is 7 percent in Germany and 10 percent in Israel, though neither country pays donors. According to calculations made in [7], an optimal registry for the U.S. would include about 5 percent of the eligible white population, but would need much larger fractions of the eligible population of minority and mixed races. While it may be possible to recruit an optimal number of volunteer white stem cell registrants without paying donors, this possibility seems unlikely for mixed and minority-race donors.

7 Conclusion

As far as we know, this is the first study to estimate probabilities that persons of mixed race will find a match in the existing stem cell registry. While multiracial patients have a smaller chance of finding a match than white patients, in general their prospects are not much worse than for patients of a single race. Patients with one minority parent and one white parent have a better chance of finding a match than patients whose parents both belong to the same minority. Moreover, contrary to the impression given

¹⁹In fact, some NMDP donors are asked to pay approximately \$50 for their donation to be accepted.

by popular news accounts, the genetics of HLA types imply that the chances of finding a match for persons of complex multiracial ancestry are no worse than for biracial individuals.

We combine economic analysis with simple genetic principles to perform an economic benefit-cost analysis of recruitment of potential donors of mixed race as well as single races. We find that expected benefits of new recruits from all groups exceed costs. African-Americans have the highest benefit-cost ratio, with benefits being 10 times costs. Mixed-race African-American and Hispanic individuals and African-American and white individuals are next in line with benefit-cost ratios of 9.1 and 8.4, respectively. The benefit-cost ratios for all minority and mixed-race combinations exceed those for whites.

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