SPECIAL ARTICLE

HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry

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ABSTRACT

BACKGROUND

Hematopoietic stem-cell transplantation (HSCT) is a potentially lifesaving therapy for several blood cancers and other diseases. For patients without a suitable related HLA-matched donor, unrelated-donor registries of adult volunteers and banked umbilical cord–blood units, such as the Be the Match Registry operated by the National Marrow Donor Program (NMDP), provide potential sources of donors. Our goal in the present study was to measure the likelihood of finding a suitable donor in the U.S. registry.

METHODS

Using human HLA data from the NMDP donor and cord-blood-unit registry, we built population-based genetic models for 21 U.S. racial and ethnic groups to predict the likelihood of identifying a suitable donor (either an adult donor or a cord-blood unit) for patients in each group. The models incorporated the degree of HLA matching, adult-donor availability (i.e., ability to donate), and cord-blood-unit cell dose.

RESULTS

Our models indicated that most candidates for HSCT will have a suitable (HLA-matched or minimally mismatched) adult donor. However, many patients will not have an optimal adult donor — that is, a donor who is matched at high resolution at *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*. The likelihood of finding an optimal donor varies among racial and ethnic groups, with the highest probability among whites of European descent, at 75%, and the lowest probability among blacks of South or Central American descent, at 16%. Likelihoods for other groups are intermediate. Few patients will have an optimal cord-blood unit — that is, one matched at the antigen level at *HLA-A* and *HLA-B* and matched at high resolution at *HLA-DRB1*. However, cord-blood units mismatched at one or two HLA loci are available for almost all patients younger than 20 years of age and for more than 80% of patients 20 years of age or older, regardless of racial and ethnic background.

CONCLUSIONS

Most patients likely to benefit from HSCT will have a donor. Public investment in donor recruitment and cord-blood banks has expanded access to HSCT. (Funded by the Office of Naval Research, Department of the Navy, and the Health Resources and Services Administration, Department of Health and Human Services.)

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N Engl J Med 2014;371:339-48.
DOI: 10.1056/NEJMsa1311707

Hematopoietic stem-cell transplantation (HSCT) is a potentially curative therapy for several life-threatening blood cancers and other diseases. Although an HLA-matched sibling is the preferred donor, only about 30% of patients who may benefit from HSCT have such a donor available. To address this issue, registries of adult volunteers and, more recently, umbilical cord–blood banks have been developed around the globe. In the United States, the National Marrow Donor Program (NMDP) was established in 1986 and has grown to include more than 10.5 million adult volunteers and nearly 200,000 cord-blood units. With contracts from the federal government, the NMDP currently operates the congressionally authorized C.W. Bill Young Cell Transplantation Program and the Be the Match Registry.

There have been increasing numbers of unrelated-donor HSCT procedures; the NMDP facilitated nearly 6000 transplants in 2012, as compared with 1500 a decade ago. This growth is a result of the expansion of indications for HSCT, therapeutic advances that have allowed HSCT to be used safely to treat older and sicker patients, the emergence of cord-blood-unit HSCT as an alternative option with less stringent requirements for HLA matching, and substantial increases in the numbers of adult volunteer donors.[1-5] The relative importance of each of these developments is difficult to ascertain, but having unrelated adult-donor or cord-blood-unit grafts available has led to the use of grafts from unrelated donors for more than half of allogeneic HSCT procedures in the United States.

The success of unrelated-donor HSCT is greatly influenced by the degree of HLA matching between the donor or cord-blood unit and the recipient.[6-12] An optimal adult donor for transplantation will match the recipient at the *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1* loci (i.e., an 8/8 high-resolution HLA match). Mismatching at only one of these loci (a 7/8 HLA match) reduces the 5-year overall survival rate by about 8 percentage points[7] but is considered suitable in many clinical situations in which alternative, nontransplantation therapy offers little chance of a cure. Matching requirements for cord blood are less stringent. Under current standards, antigen-level matching at *HLA-A* and *HLA-B* and high-resolution matching at *HLA-DRB1* with mismatching at one or two loci are considered acceptable, although some data suggest that 6/6 matching is optimal.[13] A limitation of cord-blood-unit transplantation is the limited numbers of hematopoietic cells in each unit, such that many units lack a sufficient dose for engraftment in recipients with higher body weight.

Unfortunately, optimally HLA-matched unrelated donors and cord-blood units are not available for many patients, even within large registries, because the levels of polymorphism of HLA genes are extremely high, and allelic variation is population-specific.[14,15] In this article, we answer the question, "What is the likelihood of finding a suitable matched adult donor or cord-blood unit in the NMDP registry?" The answer cannot be gleaned from retrospective search statistics, because most searches did not proceed with HLA testing to confirm all potential matches, and data on the racial and ethnic background of patients are limited in detail. Here, therefore, we present a population-based genetic model consistent with current graft-selection standards that gives likelihoods of finding 8/8 or 7/8 HLA-matched adult donors and 6/6, 5/6, or 4/6 HLA-matched cord-blood units. The development of accurate models required the determination of high-resolution HLA haplotype frequencies with adequate population coverage of 21 racial and ethnic groups.[16]

METHODS

STUDY POPULATION

We used data on HLA genotypes and cord-blood-unit cell doses from the NMDP registry, which included 10,759,087 adult donors and 186,166 cord-blood units at the end of 2012. Projected registry sizes for 2013 through 2017 were based on anticipated recruitment growth of 9% cumulatively each year. The effect of searching international registries was not evaluated (see Section A in the Supplementary Appendix, available with the full text of this article at NEJM.org). The institutional review board of the NMDP approved this study.

HLA-MATCH DEFINITIONS

Donor–recipient HLA-matching models were based on currently accepted clinical standards for adult-donor and cord-blood transplantation. For adult donors, we considered donor–recipient high-resolution matching at *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*. Matching at all these loci is desig-

nated as 8/8 HLA matching.[7] A single-allele mismatch at any of these loci is designated as 7/8 HLA matching.[7] For cord-blood units, we considered donor–recipient antigen-level matching at *HLA-A* and *HLA-B* and high-resolution matching at *HLA-DRB1*.[13] Matching at all these loci is designated as 6/6 HLA matching.[13] A 5/6 HLA match includes a mismatch at a single locus, and a 4/6 HLA match includes a mismatch at any two loci.[13] In the model, we did not consider two HLA mismatches at the same locus, because this accounts for less than 5% of cord-blood transplants, reflecting the clinical preference to avoid such mismatches.

RACIAL AND ETHNIC GROUPS

The racial and ethnic backgrounds of donors were self-reported and collected on standardized forms[17]; these data were abstracted to develop 21 groups for analysis (Table 1). The goals of this categorization were to adequately reflect the large diversity of the U.S. population in the NMDP registry and to have a sample that would be large enough to characterize the HLA genetic profiles of each group.

AVAILABILITY OF ADULT DONORS

After potentially HLA-matched donors are identified, there are several donor-specific barriers to transplantation, and it was necessary to model these barriers accurately to reflect the process of finding a donor. First, donors are contacted so that they can affirm their commitment and provide a DNA sample to confirm HLA matching to the patient, in a process referred to as confirmatory typing. Not all donors listed in the registry are available for confirmatory typing; reasons include an inability to be contacted and personal and professional conflicts. Second, some confirmatory typing results are inconsistent with the results of initial recruitment typing. Third, after a medical evaluation, some potential donors are deemed ineligible to donate. Consequently, only a subset of suitably HLA-matched donors are available. In our study, adult-donor availability was calculated separately for each racial and ethnic group as the cumulative product of the percentage of donors proceeding through each step toward donation (Table 2).[18] Match likelihoods were adjusted for availability in our model by multiplying the number of donors in each population in the registry by this cumulative availability factor.

AVAILABILITY OF CORD-BLOOD UNITS

Cord-blood units are made from umbilical and placental blood collected soon after birth; this blood is processed and frozen in liquid nitrogen. Cord-blood units used for HSCT contain 50×10^7 to 400×10^7 total nucleated cells; in selecting a unit, it is necessary to consider the total-nucleated-cell dose for the potential recipient, in addition to the HLA match. A dose of at least 2.5×10^7 total nucleated cells per kilogram of recipient body weight is considered adequate for cord-blood transplantation, whereas approximately 10 times that dose is harvested for adult hematopoietic cell grafts.[3,4,13]

Therefore, when modeling cord-blood availability, we considered the distributions of patient body weight obtained from NMDP search records and cord-blood-unit cell counts in the inventory. Patient body weights were stratified into deciles for groups made up of patients younger than 20 years of age and patients 20 years of age or older, and the proportions of cord-blood units in the inventory that met the minimum acceptable cell dose for each patient body-weight stratum were estimated (Fig. S1 in the Supplementary Appendix).[19]

STATISTICAL ANALYSIS

HLA haplotype frequencies for the 21 racial and ethnic groups were calculated from all DNA-typed registry donors with the use of the expectation-maximization algorithm.[15,16,20] For each group, four-locus high-resolution haplotype frequencies (*HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*) were used for adult donors, and three-locus haplotype frequencies (*HLA-A* and *HLA-B* at the antigen level and *HLA-DRB1* at high resolution) were used for cord-blood units. The haplotype frequencies and effective adult-donor and cord-blood-unit registry sizes for each group were put into a matching model that assumes genotypes are in Hardy–Weinberg equilibrium.[21,22] We used the model to calculate the population-specific HLA-match likelihoods at varying match stringencies for the given registry size and the specified search strategy. Match likelihoods were modeled for two matching strategies, each of which incorporated adult-donor availability and cord-blood-unit cell dose. The first strategy involved modeling the likelihood that an 8/8 or 7/8 HLA-matched adult donor was available, followed by modeling the likelihood of a suitable cord-blood unit. The

Table 1. Likelihood of Identifying HLA-Matched Adult Donors and Cord-Blood Units.

U.S. Racial and Ethnic Group	Likelihood of Identifying an Adult Donor*		Likelihood of Identifying a Cord-Blood Unit for Patients ≥20 Yr of Age†			Likelihood of Identifying a Cord-Blood Unit for Patients <20 Yr of Age†		
	8/8 HLA Match	≥7/8 HLA Match	6/6 HLA Match	≥5/6 HLA Match	≥4/6 HLA Match	6/6 HLA Match	≥5/6 HLA Match	≥4/6 HLA Match
	percent							
White European	75	97	17	66	96	38	87	99
Middle Eastern or North African	46	90	6	46	91	18	75	98
African American	19	76	2	24	81	6	58	95
African	18	71	1	23	81	5	56	95
Black South or Central American	16	66	2	27	82	7	58	96
Black Caribbean	19	74	1	24	81	6	58	95
Chinese	41	88	6	44	91	19	77	98
Korean	40	87	5	39	89	17	73	98
South Asian	33	84	4	41	90	14	73	98
Japanese	37	87	4	37	88	16	72	97
Filipino	40	83	5	42	89	19	76	98
Southeast Asian	27	76	3	37	89	12	70	98
Vietnamese	42	84	6	44	89	20	76	98
Hawaiian or Pacific Islander	27	72	3	32	84	10	64	96
Mexican	37	87	6	45	91	19	75	98
Hispanic South or Central American	34	80	5	43	90	17	73	98
Hispanic Caribbean	40	83	5	40	89	17	71	98
Native North American	52	91	10	54	93	25	80	99
Native South or Central American	49	87	11	53	93	26	79	98
Native Caribbean	32	77	4	35	86	14	66	97
Native Alaskan	36	83	7	47	91	18	75	98

* Data are the probabilities of identifying an adult donor who is available.
† Data are the probabilities of identifying a unit with an adequate cell dose.

second strategy eliminated consideration of the 7/8 match; thus, if an 8/8 HLA-matched adult donor could not be identified, consideration of a cord-blood unit immediately followed. Models were cross-validated with the use of two separate analyses (see Section B in the Supplementary Appendix).

RESULTS

ADULT-DONOR MATCH LIKELIHOOD

Table 1 shows the rates of finding suitably HLA-matched grafts in the NMDP adult-donor registry, with donor availability taken into consideration. Most patients will have a 7/8 or 8/8 HLA-matched unrelated adult donor available in the registry. The likelihood of finding an available 8/8 HLA-matched donor is 75% for white patients of European descent (hereafter referred to as white Europeans) but only 46% for white patients of Middle Eastern or North African descent. The likelihood of finding an 8/8 HLA-matched adult donor for other groups is lower and varies with racial and ethnic background. For black Americans of all ethnic backgrounds, the probabilities are 16 to 19%; for Hispanics, Asians, Pacific Islanders, and Native Americans, they range between 27% and 52%.

Adult-donor availability also differs according to racial and ethnic background (Table 2), and

Table 2. Adult-Donor Availability in 2010, According to Broad Racial and Ethnic Category.

Racial and Ethnic Category*	Confirmatory Typing Available†	Typing Not Discrepant‡	Workup Available§	Available Overall
	percentage of donors			
White	62	98	83	51
Black	36	95	69	23
Asian or Pacific Islander	42	97	73	29
Hispanic	44	96	68	29
Native American	45	98	63	28

* The white category includes the white European and Middle Eastern or North African groups; the black category includes the African American, African, and black South or Central American groups; the Asian and Pacific Islander category includes the Chinese, Korean, South Asian, Japanese, Filipino, Southeast Asian, and Vietnamese groups; the Hispanic category includes the Mexican, Hispanic South or Central American, and Hispanic Caribbean groups; and the Native American category includes the Native North American, Native South or Central American, Native Caribbean, and Native Alaskan groups.
† Shown are data for donors who can be contacted and who have a DNA sample collected for confirmatory HLA typing.
‡ Shown are data for donors whose confirmatory HLA typing was consistent with HLA typing performed at recruitment.
§ Shown are data for donors who were cleared as healthy by means of a medical examination and who agreed at this stage to proceed toward donation.

models including this variable have substantially lower match likelihoods than models in which it is assumed that all potential donors in the registry are available (Table S1 in the Supplementary Appendix). Although the likelihood of HLA matching is greatest with a donor from the patient's racial and ethnic group, donors from other racial and ethnic groups may increase this likelihood. Patients belonging to groups with high levels of genetic admixture, such as Hispanic groups, are more likely than other patients to have donors identified from outside their group (Table S2 in the Supplementary Appendix). In contrast, patients from groups with relatively low admixture levels, such as Asian groups, are less likely to have donors identified from outside their group.

CORD-BLOOD MATCH LIKELIHOOD

Cord-blood units are the most immediately available graft in cases involving an urgent indication for transplantation. Cord-blood-only match likelihoods, especially relevant in this scenario, are provided in Table 1. Most patients will have a 4/6 or better HLA-matched cord-blood unit with an adequate cell dose identified (Table 1), although the likelihood of finding a 6/6 HLA-matched unit is much lower than the likelihood of finding an 8/8 HLA-matched adult donor, because the registry contains fewer cord-blood units than adult donors. The likelihood of identifying 6/6 and 5/6 or higher HLA-matched cord-blood units with an adequate cell dose is highest for white Europeans: 38% and 87%, respectively, for patients younger than 20 years of age, and 17% and 66%, respectively, for patients 20 years of age or older (Table 1). The corresponding probabilities for African Americans are 6% and 58% for patients younger than 20 years of age and 2% and 24% for patients 20 years of age or older. The probabilities for patients of other races and ethnic groups are intermediate between the probabilities for white Europeans and African Americans.

The cell dose provided by the cord-blood units substantially limits the effective size of the cord-blood inventory, as is evidenced by the differences in rates of finding suitable units according to patient age (Table 1) and by the rates calculated without consideration of cell dose (Table S1 in the Supplementary Appendix). The probability of identifying a 6/6 or 5/6 HLA-matched cord-blood unit is higher for patients younger than 20 years of age than for older patients because most units have sufficient cells to provide an adequate cell dose for patients who weigh less than 50 kg. In fact, almost all patients in all racial and ethnic groups in this age category will have a 4/6 or better HLA-matched cord-blood unit with an adequate cell dose. Among patients 20 years of age or older, almost all white Europeans but only 81% of African Americans will have a 4/6 or higher HLA-matched unit with an adequate cell dose.

Patients are more likely to have a 5/6 or 6/6

HLA-matched cord-blood unit outside their own racial and ethnic group than they are to have 8/8 HLA-matched adult donors outside their own racial and ethnic group (Table S3 in the Supplementary Appendix).

SEARCH STRATEGIES AND MATCH LIKELIHOODS

The type of donor or graft identified for a patient depends, in part, on the search strategy adopted by the transplantation center, as well as on the recipient's age and racial and ethnic background. When a strategy is used in which the search is for an 8/8 HLA-matched adult donor or a 7/8 HLA-matched adult donor, followed by a search for a cord-blood unit if no adult donor is found, 75% of white Europeans will have an 8/8 HLA-matched donor, and another 22% will have a 7/8 HLA-matched donor. Among white Europeans, another 1.2% of patients younger than 20 years of age and 0.5% of patients 20 years of age or older will have a 5/6 or 6/6 HLA-matched cord-blood unit of adequate size, and another 1.5% of patients in the younger age group and 1.8% of those in the older age group will have a 4/6 HLA-matched cord-blood unit of adequate size (Fig. 1). With this search strategy, nearly all white Europeans will have a suitable graft identified, with grafts from adult donors identified for 97% of such patients. Among African Americans, if the same search strategy is used, 19% will have an 8/8 HLA-matched donor identified, and another 57% will have a 7/8 HLA-matched donor; an additional 10% of patients younger than 20 years of age and 3% of patients 20 years of age or older will have a 5/6 or 6/6 HLA-matched cord-blood unit, and an additional 13% of patients in the younger age group and 14% of those in the older age group will have a 4/6 HLA-matched cord-blood unit (Fig. 1). Therefore, if this search strategy is used, 95% of African Americans should have a suitable graft, but less than 20% will have an optimal match. The distribution of graft types for other racial and ethnic groups is shown in Figure 1.

With the use of an alternative search strategy, in which cord-blood units are given priority over 7/8 HLA-matched adult donors (i.e., a search is made for a suitable cord-blood unit in the absence of an 8/8 HLA-matched adult donor), most grafts identified will be cord-blood units, for every ethnic group except white Europeans (Fig. S2 and S3 in the Supplementary Appendix). More units will be 5/6 HLA-matched than 4/6 HLA-matched for patients younger than 20 years of age, and more units will be 4/6 HLA-matched than 5/6 HLA-matched for patients 20 years of age or older.

DONOR-REGISTRY GROWTH

The probabilities of finding a match in the NMDP have increased substantially since the registry was established (Fig. 2, and Fig. S4 in the Supplementary Appendix). The NMDP added slightly more than 1 million adult donors to the registry in 2012 and plans recruitment growth of 9% cumulatively each year through 2017.

DISCUSSION

Using the NMDP donor registry of volunteer adults and banked cord-blood units, we built population-based genetic models that predict the likelihood of identifying a suitable adult donor or cord-blood unit for U.S. patients in 21 groups based on racial and ethnic background. In addition to HLA matching, adult-donor availability and cord-blood-unit cell dose affect the likelihood of identifying a suitable graft. For both graft sources, the racial and ethnic group of the patient strongly influences the likelihood of having a suitable graft identified. The results suggest that almost all patients likely to benefit from HSCT will have a donor, even after donor availability, cell dose, and racial and ethnic group were taken into account. However, many will not have an optimal graft — that is, a graft from an 8/8 HLA-matched adult donor or a 6/6 HLA-matched cord-blood unit.

We anticipate that an additional 5.5 million donors will be added by 2017 and project that this will increase the probability of identifying an 8/8 HLA-matched donor by 4 to 7 percentage points (Fig. 2). During the same period, the NMDP anticipates that 70,000 additional cord-blood units will be listed. This will increase the likelihood of finding a 5/6 HLA-matched cord-blood unit by 3 to 5 percentage points, depending on age and on racial and ethnic group (Fig. S4 in the Supplementary Appendix).

The processes used by transplantation programs to identify suitable adult donors and cord-blood units for transplantation are complex and influenced by many factors in addition to HLA matching. The NMDP recently published recom-

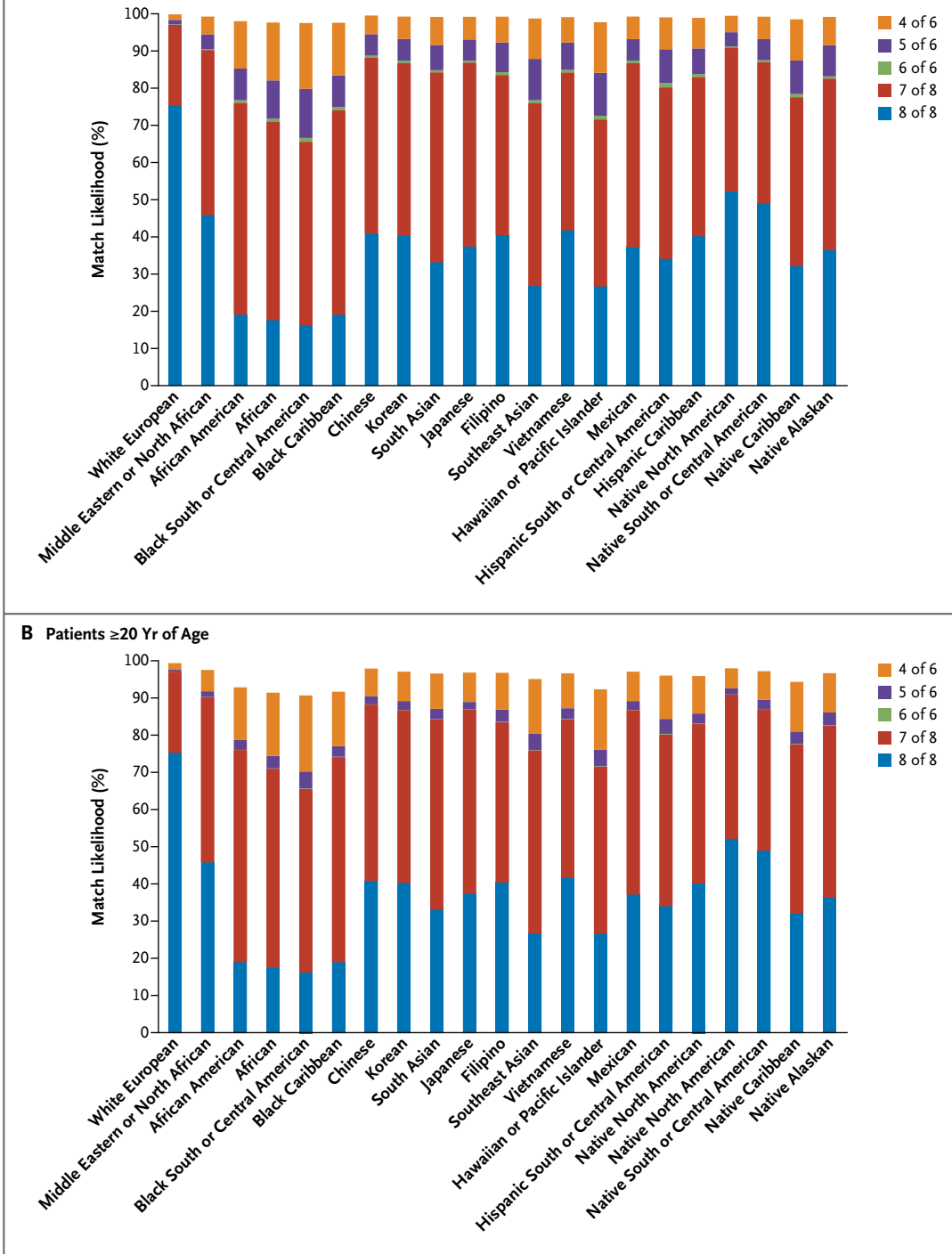

Figure 1. Match Likelihoods According to Racial and Ethnic Group and Age.

The likelihood of finding a match with the use of a search strategy in which an 8/8 HLA-matched donor is sought first, then a 7/8 HLA-matched donor, and thereafter a cord-blood unit with an adequate cell dose is shown.

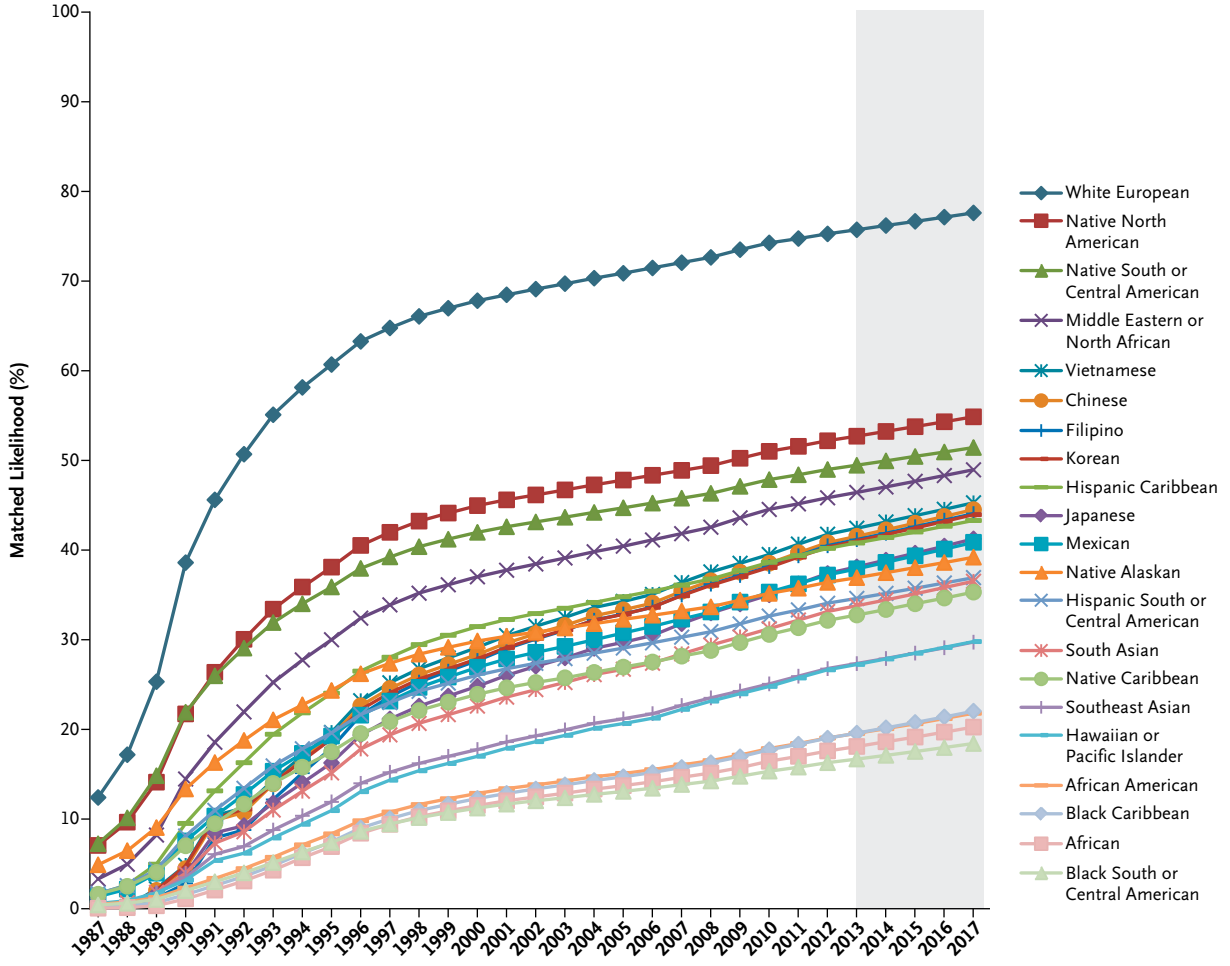

Figure 2. Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017.

Projected match likelihoods for 2013 through 2017 (shaded area) were calculated on the basis of anticipated recruitment growth of 9% cumulatively each year.

mendations for the selection of donors and cord-blood units.[23] The goal should be to identify the best available donor with minimal delay, and multiple donors, cord-blood units, or both should be pursued simultaneously. Our data provide evidence that if a fully matched donor is not identified early, delaying transplantation in the hope that such a donor will appear is unlikely to be beneficial and may indeed be detrimental, because match likelihoods increase by only 1 percentage point per year, and survival decreases as diseases progress.[7,12] A prospective study by Pidala et al.,[24] examining NMDP searches in which a match was not found initially, showed that less than 5% of searches identified a suitably matched donor successfully after 2 months. For patients without a suitably matched graft, treatments other than transplantation therapy should be considered and should not be unduly delayed.

Recruiting additional adult donors will help provide suitably matched donors for larger numbers of patients; however, the principle of diminishing returns applies. New recruits are progressively less likely to add new HLA types to the registry, and undirected recruitment is no longer the key driver of expanding access to transplantation. Consequently, recruitment strategies that target uncommon HLA types are desirable —

that is, targeting donors from racial and ethnic groups with low probabilities of having a matched donor identified in the current registry.[25] Adult-donor availability is also a limiting factor and, unfortunately, is a larger problem in the racial and ethnic groups in which finding a matched donor is already difficult. An improvement in donor availability of 5 percentage points would have the same effect on the probability of identifying an 8/8 or 7/8 HLA-matched donor as 2 years of adult-donor recruitment at current NMDP levels (Fig. S5 in the Supplementary Appendix). The NMDP has undertaken measures to improve donor availability through ongoing contact and education and through removal of barriers to donation after enrollment in the registry.

The use of cord-blood units for transplantation is a relatively recent development, and selection practices continue to evolve.[26] Currently, antigen-level matching at *HLA-A* and *HLA-B* and high-resolution matching at *HLA-DRB1*, with selection of units with 4/6 to 6/6 HLA matching and a minimum cell dose of 2.5×10^7 per kilogram of body weight, is standard practice. Future clinical practice may be affected by recent reports suggesting that matching at the *HLA-C* locus and high-resolution matching at all HLA loci lowers transplant-related mortality.[27,28] More stringent cord-blood matching standards would result in lower match likelihoods. However, several reports confirm the success of coinfusion of two cord-blood units (with each unit containing a minimum cell dose of 1.5×10^7 per kilogram and 6/6, 5/6, or 4/6 HLA matching).[29,30] On the basis of the current models of the availability of single cord-blood units, we anticipate that almost all patients will have one or two suitable 5/6 or 4/6 HLA-matched units. Because of the less stringent matching requirements, the growth of the cord-blood-unit inventory holds more promise than adult-donor recruitment in efforts to narrow the disparity in access between white European patients and patients in minority groups.

Investments by Congress to develop the unrelated-donor programs in the United States have aided in increasing access to HSCT. Although current inventories provide access to a suitable graft for most patients, many of these patients will not receive an optimal graft. Transplantation with 7/8 HLA-matched adult-donor grafts and less-well-matched cord-blood units is associated with higher rates of complications and mortality. Continued research is necessary to develop transplantation strategies that will improve outcomes for recipients of HLA-mismatched grafts.

Any views, opinions, findings, conclusions, or recommendations expressed in this article are those of the authors and do not reflect the views or the official policy or position of the U.S. Department of Health and Human Services or the Office of Naval Research.

Supported by a grant from the Department of the Navy, Office of Naval Research (N00014-11-1-0339), and under a contract with the C.W. Bill Young Cell Transplantation Program, Department of Health and Human Services Health Resources and Services Administration (HHSH234200637015C).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank William Klitz from University of California–Berkeley for his work in helping to identify operationally useful racial and ethnic categories; Rich Single, Damien Sheehan-Connor, David Howard, Abeer Madbouly, and Michelle Setterholm, and the members of the NMDP Histocompatibility Advisory Group, for their review of this work; and attendees of the 2007 Population Genetics Summit in Chicago — in particular, the late James Crow from the University of Wisconsin–Madison — for their input.

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