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BONE MARROW TRANSPLANTS

Despite Recruitment Successes, National Program May Be Underutilized



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Abbreviations

ABMTR	Autologous Blood and Marrow Transplant Registry
CPI	Continuous Process Improvement
HHS	Department of Health and Human Services
HLA	human leukocyte antigens
HRSA	Health Resources and Services Administration
IBMTR	International Bone Marrow Transplant Registry
NMDP	National Marrow Donor Program
OIG	Office of Inspector General
OPA	Office of Patient Advocacy
PBSC	peripheral blood stem cells



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Congressional Committees

More than 30,000 people are diagnosed annually with leukemia or other blood, metabolic, or immune system disorders, many of whom may die without stem cell transplants, using stem cells from bone marrow or another source.¹ When a patient needs a transplant of donated stem cells and no genetically compatible related (family) donor is available, the National Bone Marrow Donor Registry (Registry) may help the patient search for compatible stem cells from unrelated donors. Founded in 1986, the Registry is the largest and most diverse list of potential donors in the world. This list currently includes more than 4 million donors.² The Registry is operated by the nonprofit National Marrow Donor Program (NMDP) under contract to the Department of Health and Human Services' (HHS) Health Resources and Services Administration (HRSA), with additional support from the U.S. Navy.³ NMDP coordinates stem cell transplants through its network of more than 400 participating organizations, domestic and foreign, involved in transplantation, including donor centers, which recruit and manage donors; laboratories; blood sample repositories; bone marrow collection centers; and transplant centers. NMDP has facilitated more than 14,000 transplants since 1987.

Concerns about the Registry have been raised by the HHS Office of the Inspector General (OIG) and in our own work. These include the extent to which the Registry provides equality of opportunity for patients of all racial and ethnic groups to find compatible (matched) unrelated donors, the extent to which it is utilized by those in need of stem cell transplantation, and the effectiveness of the management of the donor

¹The first source of stem cells for transplant was bone marrow, but now stem cells from the bloodstream or from umbilical cord blood can also be used. We use the term stem cell transplant to include both bone marrow transplants and transplants involving one of these newer sources of stem cells.

²We use the term donors throughout this report to refer to potential donors on the Registry, most of whom have not donated stem cells, only expressed their willingness to do so.

³The Navy was instrumental in the founding of the Registry and has maintained its interest in stem cell donation over the years. HRSA and the Navy each contributed a little less than 20 percent of the Registry's fiscal year 2002 funding (about \$21 million and \$20.5 million, respectively), with program revenue and private sources providing the rest of the total of about \$108 million.

centers. We reported in 1992 that the proportions of African American and Hispanic donors on the Registry were less than their proportions in the U.S. population.⁴ This imbalance results in a decreased likelihood of an individual from a minority group finding a match and eventually receiving a transplant because matches are more likely to be found from among donors of one's own group. In an effort to address these concerns, a 1996 OIG report recommended that HRSA and NMDP reexamine the method used to finance the donor centers that recruit volunteers to join the Registry.⁵ It recommended a performance-based method to pay donor centers for specific activities including monetary incentives tied to performance indicators and emphasizing recruitment and retention of donors, especially those from racial and ethnic minority groups.

The National Bone Marrow Registry Reauthorization Act of 1998⁶ required, among other things, that the Registry carry out a donor recruitment program giving priority to minority and underrepresented donor populations, ensure efficiency of operations, and verify compliance with standards by organizations that participate in the Registry. In addition, the act required that we conduct a study of the Registry, including an examination of the extent to which it has increased representation of racial and ethnic minority groups so that a member of such a group has a probability of finding a match comparable to that of a person who is not a member of such a group. In conducting this study, we addressed the following questions: (1) To what extent have the program's recruitment efforts increased the enrollment of donors, including those from racial and ethnic minority groups, since the 1998 act took effect, and has the chance of finding a suitable match increased? (2) To what extent is the Registry utilized to search for and obtain transplants? (3) Are the donor centers and other organizations in the NMDP network complying with its standards and procedures?

To answer these questions, we analyzed NMDP data on racial and ethnic representation on the Registry from 1998 through 2001 and, to provide a broader context for examining these changes, also analyzed data on racial

⁴U.S. General Accounting Office, *Bone Marrow Transplants: National Program Has Greatly Increased Pool of Potential Donors*, GAO/HRD-93-11 (Washington, D.C.: Nov. 4, 1992).

⁵HHS OIG, *National Marrow Donor Program: Financing Donor Centers*, OEI-01-95-00123 (Washington, D.C.: December 1996).

⁶Pub. L. No. 105-196, 112 Stat. 631 (1998).

and ethnic representation in relation to the patients who searched the Registry from 1988 through 2001. In addition, we analyzed data provided by the International Bone Marrow Transplant Registry (IBMTR)⁷ on transplants from related donors from 1997 through 2000, which enabled us to estimate the demand for unrelated donor transplants in the United States and relate this estimate to Registry utilization by patients searching for donors during this period; analyzed NMDP data on matches, canceled searches, and transplants obtained for patients needing donors during this period; reviewed NMDP's standards for participating in the Registry; and reviewed evidence of compliance with the standards and procedures by the organizations that participate. We also interviewed officials of NMDP; HRSA; the Department of the Navy; the American Red Cross; and selected donor, stem cell collection, and transplant centers. We did not independently verify the accuracy of the data provided by NMDP. We conducted our work from June 2001 through June 2002 in accordance with generally accepted government auditing standards.

Results in Brief

From 1998, when the National Bone Marrow Registry Reauthorization Act was enacted, through 2001, the number of stem cell donors on the Registry increased for all racial and ethnic groups. NMDP recruitment efforts focused on minority groups appear to have been effective in increasing the number of donors from these populations. Since 1998 the number of donors on the Registry has increased by 36 percent, and increases for minority groups ranged from 30 percent to 53 percent. The total of more than 1 million minority donors listed in 2001 contrasts with the approximately 80,000 we reported in 1992. The proportional distribution of racial and ethnic groups on the Registry was much closer to their proportional distribution in the U.S. population at the end of 2001 than it was in our 1992 review. However, when viewed as a percentage of each group's proportion of the U.S. population, African Americans and Hispanics are underrepresented by 17 and 15 percent, respectively. The underrepresentation of minorities is somewhat mitigated by the Registry's efforts to have complete genetic information needed for typing on a higher proportion of minority donors, which facilitates more rapid matching. For all racial and ethnic groups, the theoretical probability of finding a match has grown as the Registry size has increased, but equal access to a match may not be attainable. Differences among racial and ethnic groups in the rarity and variability of the genes responsible for compatibility in

⁷IBMTR is not a donor registry; it records data about transplants performed.

transplants may mean that the Registry cannot achieve equal probability for all groups. Further, devoting many resources in pursuit of a small number of rare genetic types may divert resources from other efforts, such as recruiting Caucasians and other groups with more common genetic types, which might more readily increase the number of matches.

Although the exact number of patients in need of transplants is not known, estimates suggest that about one-third of them utilize the Registry to search for donors. The number of transplants facilitated by NMDP represents about one-tenth of those we estimate to be in need of unrelated donor transplants. These figures suggest that the Registry may be underutilized for both searching and facilitating transplants. From 1997 through 2000, an estimated 44,740 U.S. patients were in need of unrelated donor transplants. During this period, physicians for approximately 15,000 U.S. patients conducted preliminary searches for donors on the Registry, and about 4,000 of these patients obtained unrelated donor transplants facilitated by NMDP. About 25 percent of formal searches were not completed because stem cells were obtained from donors or organizations without the involvement of NMDP.

The organizations that are involved in transplantation and participate in the NMDP network generally adhere to NMDP's standards and procedures. NMDP monitors the compliance and performance of these organizations with its standards by using several systems of feedback and incentives, including site visits. Centers that deviate from NMDP's standards may be placed on probation or suspended or their participation in the network may be terminated. In 2001, NMDP required 24 centers to take corrective actions because they did not meet its standards. Further, NMDP reimburses donor centers for services based on their performance by offering financial incentives to centers that consistently meet donor recruitment goals and financially penalizing centers that do not.

In its written comments on a draft of this report, HRSA stated that the report provides an accurate and helpful overview of the status of the National Bone Marrow Donor Registry. HRSA agreed that other efforts are needed in addition to minority recruitment efforts in order to improve minority access to unrelated donor transplants, but pointed out that the Registry has complete genetic information needed for matching on higher proportions of minority donors than it has for Caucasian donors. We have clarified this information in the report. HRSA agreed that many patients who could benefit from transplants do not utilize the Registry but suggested a slightly modified method of determining the number of patients in need of transplants. We accepted this suggestion, but note that

both approaches produce virtually identical estimates of overall underutilization. (See app. I.) HRSA also noted that many factors affect the time required to complete a search of the Registry and that NMDP has completed medically urgent searches in less than a month. We have included this clarification in the report. In addition, HRSA provided technical comments, which we have incorporated as appropriate.

Background

Most of the diseases treated by stem cell transplantation involve abnormalities of the blood, metabolic, or immune systems. These diseases include several forms of cancer as well as certain nonmalignant diseases.⁸ They strike all races, although one racial group or another may have a higher incidence rate for a particular disease.⁹ Not all patients with diseases that may be cured by stem cell transplants necessarily pursue them. Depending on a number of donor and patient characteristics, from about 10 to 50 percent of patients are alive 5 years after transplants. The patients who do not survive may succumb either to their diseases or to the consequences of transplantation. Because of these low survival rates, some patients and physicians may be reluctant to select this stressful treatment under most or all circumstances. For most of the diseases involved, other therapies are available that may be less invasive, carry lower risk, or be the medically preferred initial treatment. Nevertheless, some of these diseases are best treated by stem cell transplantation, either initially or after other treatments have failed.

Prior to stem cell transplantation, the patient's bone marrow and, consequently, immune system are destroyed with radiation or chemotherapy. The patient's bloodstream is then infused with healthy stem cells from a donor. Healthy stem cells can be therapeutic because they can develop into all the components of blood, including those needed to replace the patient's immune system. In an "autologous" transplant,

⁸Almost 90 percent of the transplants coordinated by NMDP are for types of cancer, including, in descending order of frequency, chronic myelogenous leukemia, acute myelogenous leukemia, acute lymphocytic leukemia, myelodysplastic disorders, and non-Hodgkin's lymphoma. The nonmalignant diseases most commonly treated by stem cells obtained through NMDP are aplastic anemia and several varieties of inherited disorders of the metabolic, immune, and blood systems.

⁹For example, the age-adjusted incidence rate per 100,000 patients with acute myelogenous leukemia over the period from 1995 through 1999 is higher for Caucasians (3.7) than for African Americans (2.9). In contrast, for patients with myeloma, the rate is higher for African Americans (11.5) than for Caucasians (5.2).

these cells come from the patient's own marrow. In a "syngeneic" transplant, the cells come from an identical twin. For many diseases, the most common type of transplant is an "allogeneic" transplant, which consists of stem cells from a genetically compatible donor.

Bone Marrow and Other Sources of Stem Cells for Transplantation

Although bone marrow was initially the only source of stem cells for transplantation, in recent years two other sources of stem cells, umbilical cord blood and peripheral blood stem cells (PBSC), have also been used. In 2001, 1,215 of the transplants facilitated by NMDP (70 percent) involved marrow, 42 (2 percent) involved cord blood, and 491 (28 percent) involved PBSC. Umbilical cord blood is collected from the placenta and umbilical cord of a newborn and then preserved in a cord blood bank until needed by a matched patient. The number of stem cells typically obtained from cord blood is relatively small but is often adequate for pediatric patients. For transplantation from cord blood, the blood is volunteered when the blood is banked, not when it is used. The Registry began an umbilical cord blood stem cell program in 1998. Stem cells from peripheral blood may be obtained in numbers sufficient for transplantation when the donor is treated with a drug that causes the cells to leave the marrow and enter the bloodstream where they can be extracted using a process where the stems cells are removed and the remaining components of the blood are returned to the donor. A donor, matched to a patient, may be asked to donate either bone marrow or PBSC, depending on the preference of the patient's physician. The Registry has offered PBSC to patients since 1999.

Matching Donor and Patient

In addition to its dependence on such common determinants of treatment success as patient age and disease severity, the outcome of a transplant depends on the degree of match between donor and patient with respect to particular blood cell proteins—the human leukocyte antigens (HLA)—that are part of a person's genetic makeup.¹⁰ Each person has three primary pairs (one set of three from each parent) of these antigens that play a major role in the compatibility of a transplant. A matched donor is defined as one for whom each of these six antigens has the same kind of HLA. If a matched donor cannot be found, then a donor with certain types of mismatch may be used, depending on the transplant center's

¹⁰An antigen is a protein found on the outside of most cells in the body that induces the formation of antibodies. There are a number of antigens in the human body, and HLA are a set of these.

preferences, although usually with poorer results. In general, the more closely related two people are, the more likely it is that their HLA will match. At one extreme, identical twins always match, and, in fact, match on all antigens, not just the six ordinarily focused upon. At the other extreme, members of separate racial groups are relatively unlikely to match one another. Full siblings can provide a six out of six match, resulting in what is called an “HLA-identical sibling transplant,” but only about 30 to 40 percent of patients can be expected to have a matched sibling donor. As a result, unrelated donors with matched HLA are sought from the registries in which their HLA type has been recorded.

The definition of a match has been refined over time as scientific understanding of HLA increases. HLA are being typed more precisely, so more types of HLA can now be distinguished. Thus, some of today’s matches may be judged as mismatches in the future because better matches are possible. This increasing refinement does not mean, however, that finding a suitable match for transplantation is inevitably becoming more difficult. Some kinds of mismatch may be less dangerous than others. As a result, as research continues, there may be fewer matches by today’s standards, but relatively harmless mismatches will be recognized as such and used. Further, there is evidence that cord blood may not require as exact an HLA match as is usually sought.

The NMDP Network

In support of the Registry, NMDP manages a worldwide network consisting of more than 400 donor centers, recruitment groups,¹¹ contract laboratories where tissue is typed, apheresis centers,¹² cord blood banks, collection centers where marrow is harvested, blood sample repositories, and transplant centers. More than half of these organizations are donor (91) or transplant centers (149). The relationship of these network components to NMDP varies. Some, such as the recruitment groups, were designed to be parts of the network and work with NMDP, whereas others, such as the transplant centers, exist separately from the network and function independently of NMDP except where specified by contract.

¹¹Recruitment groups actively seek donors, sometimes ones of a particular ethnic or racial heritage.

¹²Apheresis is a technique for separating blood into its components, using a machine that draws blood from a vein in a donor’s arm; filters out the desired product, such as PBSC; and returns the remaining blood to the donor.

The NMDP network includes donor centers and other organizations in foreign countries.¹³ The foreign donor centers merge their files with the Registry, contributing more than one million donors. These centers are required to comply with NMDP policies, program standards, and other criteria, although fees for recruiting donors and other financial incentives and payments that go to U.S. centers are not paid to foreign centers.¹⁴ NMDP has also signed cooperative agreements with national registries in 13 foreign countries.¹⁵ Although certain data on donors recruited into these registries are not entered into the Registry's computer system, these foreign registries will search their donor files on behalf of a U.S. patient searching the Registry. In addition, 6 foreign apheresis centers, 18 foreign bone marrow collection centers, and 36 foreign transplant centers are affiliated with the Registry. NMDP's affiliations with foreign donor and transplant centers result in its facilitation of both foreign-to-U.S. and U.S.-to-foreign donations.

The existence of these international affiliations with the Registry does not prevent U.S. transplant centers from obtaining stem cells through foreign registries directly, that is, without going through Registry channels. Even domestically, the Registry is not a monopoly; other U.S. registries also maintain lists of donors, conduct searches for stem cells, or perform both of these functions.¹⁶ These other registries, however, are relatively small; often specialize in donors from particular racial or ethnic groups; and are private, with no national requirements.

¹³There are seven such donor centers. Three of these are in Germany, and the others are located in the Netherlands, Israel, Sweden, and Norway.

¹⁴HRSA consults with the Department of State on proposed membership of foreign organizations.

¹⁵These countries are Australia, Austria, Canada, the Czech Republic, England, France, Ireland, Italy, Japan, Singapore, Spain, Switzerland, and Taiwan.

¹⁶For example, the American Bone Marrow Donor Registry of Mandeville, Louisiana, is composed of a Patient Advocacy Office that coordinates and processes search requests and a Donor Services Division that educates, recruits, and maintains the records of donors. Moreover, it has regional components, also called registries. Other U.S. registries include the Caitlin Raymond International Registry of Worcester, Massachusetts, and the Gift of Life Foundation of Boynton Beach, Florida. In addition, there are a number of U.S. cord blood banks including ones in New York, New Jersey, Missouri, and Massachusetts (part of the Caitlin Raymond International Registry).

Operation of the NMDP Registry

The Registry serves two groups of people, donors and patients. The Registry's donor centers and recruitment groups recruit donors, who are then managed by the donor centers. The Registry pays these centers and groups for signing up donors. In view of the past underrepresentation of minorities in the Registry, NMDP has initiated several recruitment efforts to increase its racial and ethnic diversity. For example, it provides free or low-cost minority-specific educational materials to donor centers and recruitment groups. Probably the most important aspects of managing donors are to maintain their commitment to donation so that they are locatable and willing to donate when their stem cells are requested, to keep records of how to contact them, and to drop from the list any individuals who are too old¹⁷ or no longer able or willing to donate.

A patient's first contact with the Registry occurs when his or her physician or a transplant center conducts a free, preliminary search of the Registry for stem cell donors and cord blood units. The preliminary search, which takes about 24 hours, produces a list of donors and cord blood units that are potentially suitable for that patient. However, many patients for whom such searches are conducted are not necessarily good candidates for stem cell transplants. For example, some searches may be conducted for patients who are too sick for transplantation or who are good candidates for less invasive therapies.

If the physician and patient decide to continue a search for an unrelated donor (or unrelated cord blood) on the Registry, then more information about the matching stem cells is required and a formal search is begun. Only a physician affiliated with a transplant center in the NMDP network may conduct a formal search of the Registry. The Registry bills the transplant center a one-time activation fee of \$600. It also bills the center for the cost of the four or five testing components of the search process, each of which costs more than \$100. Since several donors may have to be tested before one is selected for the patient, these component charges may be made repeatedly, resulting in a search costing thousands of dollars to the transplant center, and more to the patient when the center adds its markups. Relatively few insurance plans pay for searches; however, plans often pay for the actual transplantation including the procurement of stem cells. The details of the formal search and the subsequent steps in the process possibly leading to transplantation depend on the additional information needed; the results of laboratory tests; and the kind of stem

¹⁷Donors are considered too old to donate at age 61.

cells sought, whether stored blood from an umbilical cord or blood or marrow from a living donor.

If a suitable donor or suitable cord blood unit is found, and if other requirements in the process toward transplantation are fulfilled,¹⁸ then either (1) the marrow is harvested from the donor at a collection center, (2) PBSC are collected from the donor at an apheresis center, or (3) the cord blood is shipped from a cord blood bank. The stem cells are transported to the transplant center, often by courier. The final step is the infusing of the patient's bloodstream with the selected marrow, PBSC, or cord blood. The entire process—from the initiation of the formal search to the transplant (infusion)—typically requires many months and sometimes more than 1 year. However, some patients cannot wait this long for transplants because their medical conditions are deteriorating.

During the search process, NMDP offers patient advocacy services through two channels. Its Office of Patient Advocacy (OPA) provides several services, including education, support, case management intervention, financial assistance, and special advocacy projects. For example, OPA publishes the *Transplant Center Access Directory*, a patient guide listing all transplant centers in the NMDP network. The directory describes each center's HLA matching criteria and lists the diseases each typically treats with unrelated donor marrow transplants. The directory also provides information on comparable search charges and risk-adjusted patient survival data. In addition to the services provided through OPA, NMDP requires that each transplant center have a patient advocate on staff. The patient advocate must be familiar with the center's transplant program and with issues of unrelated donor stem cell transplantation and must not be a member of the transplant team.

OIG Review

A 1996 OIG review raised concerns about donor center costs and performance. Before the review, NMDP used two methods to finance donor centers. NMDP paid for services at some donor centers through cost-based contracts for direct expenses, such as labor and fringe benefits and donor expenses. Other donor centers received payments from NMDP for specified activities, such as donor recruitment and donor search activities. The OIG recommended that HRSA and NMDP develop a

¹⁸These include confirmation of donor availability and willingness, satisfactory results of laboratory tests done on the donor, and the patient's desire to continue the search.

payment approach for all donor centers that more directly linked funding to performance and emphasize recruitment and retention of donors, particularly donors from racial and ethnic minority groups. Further, the OIG recommended that HRSA and NMDP develop procedures to monitor the performance of donor centers and other organizations in the NMDP network.

NMDP Has Succeeded in Increasing Recruitment of Donors, Including Minorities, but May Not Be Able to Equalize Access to Matches

The program's recruitment efforts have apparently increased the number of donors on the Registry since 1998 for all racial and ethnic groups, and the theoretical probability of finding a match has increased steadily over the life of the Registry. By 2001, the number of donors from each minority group on the Registry had grown by at least 30 percent and was either greater than or no more than 2 percentage points below its representation in the general population. However, when viewed as a percentage of each group's population, African Americans and Hispanics are still substantially underrepresented. For all racial and ethnic groups, the theoretical probability of finding a match has grown as the Registry size has increased, but equal access to a match may not be attainable. Differences among racial and ethnic groups in the rarity and variability of the genes responsible for compatibility in transplants may mean that the Registry cannot achieve equal probability for all groups. Further, the goal of equal access to a match conflicts to some extent with attempts to maximize the overall numbers of matches and transplants for the Registry.

Number of Donors on Registry Has Increased for All Groups

The size of the Registry has increased since 1998 by 36 percent, and no minority group increased by less than 30 percent. NMDP's efforts to recruit minorities may have substantially increased the number of donors from these populations. Percentage increases for minorities ranged from 30 percent for Native Americans to 53 percent for Hispanics. Caucasian donors increased 28 percent. (See table 1.) The multiple race category had the largest increase, 123 percent, but this may result in part from an increase in the use of that category by those to whom it applies, rather than solely from an increase in the availability of donors of that group.

Table 1: Percentage Increase in Registry Donors, by Racial and Ethnic Group, 1998 to 2000, and Current Proportion of Groups on the Registry and in the Population

Race/ethnicity	Number on Registry, September 30, 1998	Number on Registry, December 31, 2001	Percentage change	Percentage of donors on the Registry with known race ^a	Percentage of U.S. population ^b
African American	264,868	363,246	37	10	12
Asian/Pacific Islander	194,118	287,129	48	8	4
Caucasian	1,926,675	2,460,725	28	7	69
Hispanic	252,569	386,059	53	11	13
Multiple race	34,443	76,937	123	2	2
Native American	45,478	59,112	30	2	1
Other	13,089	14,142	8	0 ^c	0 ^c
Declined to specify	4,629	6,498	40	N/A	N/A
Unknown ^d	623,659	902,802	45	N/A	N/A
Total	3,359,528	4,556,650	36	100	100

Note: N/A = not applicable.

^aAs of December 31, 2001.

^bBased on 2000 U.S. Census.

^cRounds to zero.

^dSome foreign registries that are part of the NMDP network do not collect information on race or ethnicity.

Sources: NMDP and U.S. Bureau of the Census.

The total of more than 1,000,000 minority donors listed in 2001 contrasts with the approximately 80,000 we reported in 1992. As can be seen in table 1, by 2001, the proportions of both African Americans and Hispanics on the Registry were within 2 percentage points of their proportions in the 2000 U.S. population. The proportions of other minorities on the Registry were either approximately equal to or exceeded their proportions in the population. While the differences between Registry and population levels of representation for African Americans and Hispanics reflect improved representation of these groups, the 2-percentage point differences still indicate a substantial underrepresentation in comparison with their proportions in the U.S. population. Specifically, in 1992, the proportions of African Americans and Hispanics, both at 4 percent of the Registry, were 8 and 5 percentage points lower, respectively, than their proportions in the U.S. population (which were 12 and 9 percent, respectively). This translated to a 67 percent underrepresentation for African Americans and a 56 percent underrepresentation for Hispanics. The current 2-percentage point differences on the Registry for these groups translate to a 17 percent

underrepresentation for African Americans and a 15 percent underrepresentation for Hispanics.¹⁹

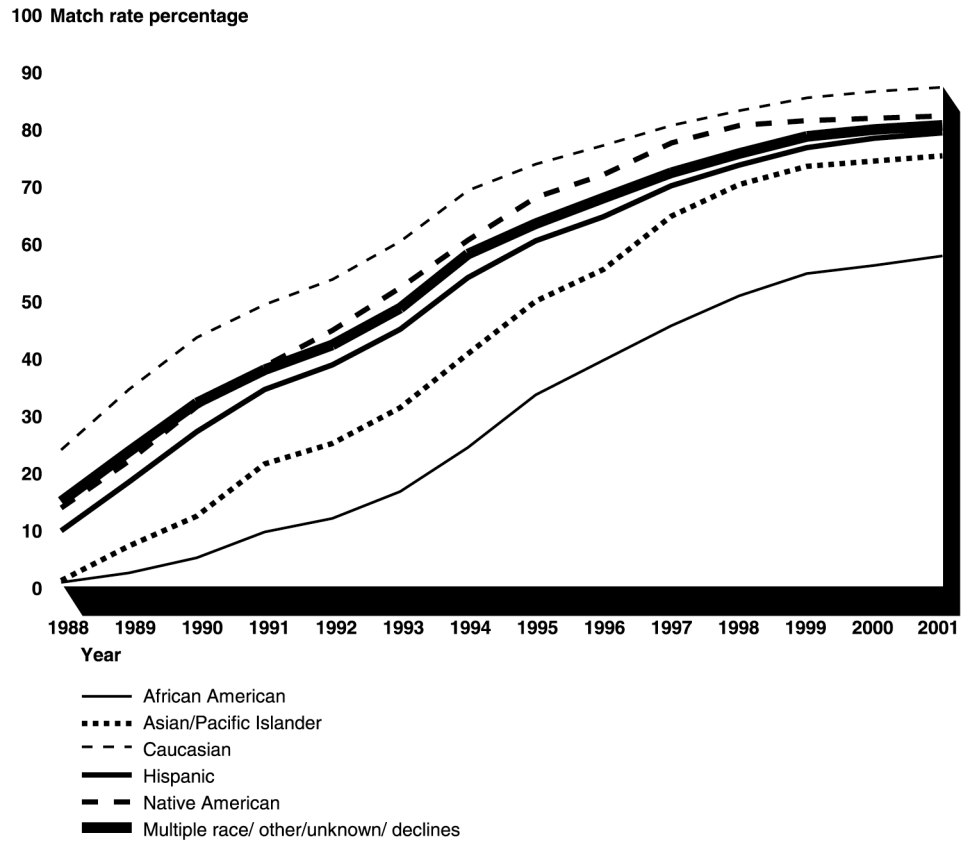
Theoretical Probability of Finding a Match Has Increased over Life of Registry

For all racial and ethnic groups the theoretical probability of a patient's finding at least one matched donor has increased every year since 1988 but has leveled off somewhat since 1998.²⁰ The increase in theoretical probability represents significant progress in raising the likelihood of a match. It reflects inclusion in the Registry of the most common genetic types over the period when the Registry was small and new, and recruitment efforts were beginning. The leveling off likely reflects the fact that for all groups, after years of recruitment activity, improvement now occurs mainly when rare types are added. (See fig. 1.)

¹⁹For example, the African American difference of 2 percentage points is 17 percent of that group's 12 percent share of the population.

²⁰This probability was computed in 2001 by considering all patients who had searched the Registry by that time and, using NMDP's matching criteria, asking what proportion of these would have found a match during each year of the Registry's existence, given the donors on the Registry during that year. This theoretical probability has advantages over the observed proportion of matches as a measure of access by patients. One is that a large and representative number of searching patients are repeatedly applied to the Registry over its history so that any fluctuations cannot be a result of fluctuations in the numbers or kinds of patients searching from year to year. Another advantage is that today's definition of a match has been applied throughout the years covered so that any fluctuations cannot be a result of changes in that definition over the years.

Figure 1: Theoretical Probability of Patient's Finding at Least One Matched Donor, by Racial and Ethnic Group, 1988 to 2001



Source: NMDP.

Nevertheless, the theoretical probability of finding a match varies by race, ranging in 2001 from under 60 percent for African Americans to over 80 percent for Caucasians. This probability has always been higher for Caucasian patients than for patients in any minority group, in part, perhaps, because of Caucasians' greater numbers and level of representation on the Registry. The theoretical probability of finding a matched donor has been lowest for African American patients. This is because, in addition to their smaller numbers and lower level of representation on the Registry, their rarer and more varied HLA combinations make matching harder.

Equal Access for All Groups May Be Unattainable

Because of genetic differences among racial and ethnic groups, there is reason to believe that patients from some minority groups, notably African Americans, may never have the same probability of finding matches, and therefore of access to transplants, as Caucasian patients, regardless of the efforts made to recruit them. Any patient is more likely to find a match in his or her own racial and ethnic group than in another group, so patient matching rates depend, to some extent, on the number of people in the patient's group on the Registry. All minorities are at a disadvantage for this reason. Further, some minority groups, such as African Americans, are known to have more rare and more varied HLA combinations than do Caucasians. The likelihood of finding a match from among a group of racially or ethnically defined donors declines with the rarity and number of possible genetic types found among the members of that group.

In addition to these factors related to finding a match, there are other factors that may contribute to differences in access to a transplant. Some of these depend on the characteristics of those who volunteer for the Registry. For example, donors from different groups may differ in their tendency to be available (locatable, willing, and physically able) when called upon to actually donate. Other possible factors involve the attitudes, health, medical care, resources, and preferences of the patients. Patients of different groups may differ in their tendency to engage the health care system at all, to seek help early enough in their illnesses, or to search the Registry as opposed to pursuing other options. It may be possible to effect changes in these factors, thereby moving closer to the goal of equal opportunity for all racial and ethnic groups.

However, not only is the goal of equal access to transplants for all groups difficult to attain, but it also may conflict with the statutory goal of maximizing the number of patients who find a match and thereby maximizing the number of transplants facilitated. Recruiting donors with the rare HLA combinations that may be needed for minorities is difficult. Large numbers of donors must be recruited and retained in the Registry in order to identify and add each rare genetic type to the donor pool, so the cost of recruiting such donors—the incremental cost of adding these rare genetic types to the donor pool—is large. Thus, devoting many resources in pursuit of a small number of rare genetic types may divert resources from other efforts, such as recruiting Caucasians and other groups with more common genetic types, which might more readily increase the number of matches.

Because of the difficulty encountered in finding matches for minority patients, NMDP engages in a number of initiatives to increase the

Registry's diversity. It conducts outreach, recruitment, and educational efforts directed towards minorities. In addition, NMDP has initiated a program to pay the full costs of HLA tissue typing for minority donors.

Although the difficulty in finding matches for minority patients may be unavoidable, it may be mitigated somewhat by the efforts of the Registry to increase the number of donors on whom it has complete HLA typing. The vast majority of actual donations are obtained from by donors whose HLA is fully typed.²¹ When only these donors are considered, each minority constitutes a larger portion of the Registry than its representation in the population. Therefore, because access to a match depends upon, for the most part, the fully typed donors on the Registry, access for minorities may be somewhat better than might be assumed by looking at the Registry as a whole.

National Registry May Be Underutilized

Although the exact number of patients in need of transplants from unrelated donors is not known, the number of patients utilizing the Registry to search for matches is about one-third of the estimated number of patients in need of unrelated donor transplants. About one-tenth of the number of patients estimated to be in need of unrelated donor transplants obtain transplants facilitated by NMDP. These figures suggest that the Registry may be underutilized for both searching and facilitating transplants.²² Physicians for approximately 15,000 U.S. patients requested preliminary searches of the Registry from 1997 through 2000. This number represents 34 percent of the 44,740 U.S. patients estimated to be in need of stem cell transplants from unrelated donors in that 4-year period. About 4,000, or 27 percent, of the patients whose physicians searched the Registry eventually received transplants facilitated by NMDP. However, a significant proportion of searches were not completed because stem cells were obtained from donors or organizations without the involvement of NMDP.

²¹A fully typed donor is one for whom all crucial antigens are determined at the time the donor volunteers.

²²See app. I for an explanation of how we estimated the number of patients in need.

Estimates Suggest about One-Third of Patients in Need Search the Registry and about One-Tenth Receive Transplants

From 1997 through 2000, physicians carried out preliminary searches for 34 percent of the number of U.S. patients estimated to be in need of transplantation from unrelated donors at any time during that period. The number of transplants facilitated by NMDP for all U.S. patients was 9 percent of the number estimated to be in need. The precise number of patients in need of unrelated donor transplants is not known. However, there is a greater than 10 to 1 ratio between the number of such patients estimated to be in need and the number of transplants facilitated by NMDP. This suggests that the Registry may be underutilized, as many more U.S. patients may need unrelated donor transplants than obtain them through the Registry.²³ The ratio of the number of preliminary searches to the number of patients in need varied by race and ethnicity. Among specific racial and ethnic groups, the percentage of preliminary searches was highest for Caucasian patients (35 percent), and was lowest for Hispanic patients (24 percent) and Native American patients (24 percent). (See table 2.) We do not know why these apparent disparities in search rates exist.

²³NMDP has used a similar method of estimation and draws a similar conclusion about possible underutilization.

Table 2: U.S. Patients' Utilization of the Registry, by Race and Ethnicity, 1997 to 2000

Race/ethnicity	Estimated number of patients without matched sibling donor^a (patients in need)	Actual number of preliminary searches	Ratio of number of preliminary searches to number of patients in need	Actual number (percentage) of preliminary searches resulting in formal searches	Actual number (percentage) of preliminary searches resulting in NMDP-facilitated transplants	Ratio of number of NMDP-facilitated transplants to number of patients in need
African American	5,397	1,694	0.31	958 (57)	256 (15)	0.05
Asian/Pacific Islander	1,666	439	0.26	270 (62)	96 (22)	0.06
Caucasian	30,929	10,844	0.35	7,079 (65)	3,321 (31)	0.11
Hispanic	5,613	1,366	0.24	840 (61)	317 (23)	0.06
Native American	329	80	0.24	56 (70)	20 (25)	0.06
Other	806	365	0.45	213 (58)	39 (11)	0.05
Total	44,740	15,231^b	0.34	9,623^c (63)	4,056^d (27)	0.09

^aFor Caucasians, the number of HLA-identical sibling transplants multiplied by the number of patients expected to be without matched sibling donors for each such transplant was derived from data obtained from the Statistical Center of the IBMTR and Autologous Blood and Marrow Transplant Registry (ABMTR). (The analysis has not been reviewed or approved by the Advisory Committees of the IBMTR and ABMTR.) See appendix I for a description of this method of estimation. For each of the other groups, the number was derived by assuming that the group's need is the same as it is for Caucasians and in proportion to the group's representation in the U.S. population.

^bIncludes 443 preliminary searches, not included elsewhere in the column, from patients of unknown race/ethnicity.

^cIncludes 207 formal searches, not included elsewhere in the column, from patients of unknown race/ethnicity.

^dIncludes 7 transplants, not included elsewhere in the column, from patients of unknown race/ethnicity.

Source: GAO analysis of data from the Statistical Center of the IBMTR and ABMTR and NMDP.

About one-fifth of the number of patients estimated to be in need formally searched the Registry (9,623 out of 44,740). Less than one-tenth of those estimated to be in need ultimately received NMDP-facilitated transplants. The numbers and percentages of preliminary searches that progressed to formal searches from 1997 through 2000 are presented by racial and ethnic group in table 2. The overall rate of progression from preliminary to formal search is 63 percent. Further, 4,056 of the 15,231 U.S. patients (27 percent) for whom preliminary searches were conducted from 1997 through 2000 eventually received NMDP-facilitated transplants. This number corresponds to 9 percent of the number of patients estimated to be in need of unrelated transplants during that period.

Reasons for Cancellation Vary and Include Obtaining Stem Cells from a Provider Other than NMDP

Reasons for cancellation of preliminary searches or formal searches vary. Although clinical reasons, such as a change in medical condition, are the most commonly cited explanations for cancellation of both preliminary and formal searches,²⁴ another relatively frequent reason is that stem cells are obtained from a provider other than NMDP, such as a related donor or another registry. (See tables 3 and 4.) We do not know the proportion of these cases that used a related donor, and some cases may not have been able to find a potential match at NMDP. However, it is likely that in at least some of these cases, NMDP might have facilitated a transplant if the patient’s transplant center had not selected another registry to provide the stem cells, thus representing another kind of possible underutilization of NMDP. Lack of donor availability—not finding any potential matches—and financial reasons are not commonly cited as reasons for cancellation of either kind of search, although it is possible that patients with limited financial resources or insurance may not be encouraged to make preliminary searches.

Table 3: Reasons for Preliminary Search Cancellation, January 2000 through September 2001

Reason for cancellation	Number of preliminary search cancellations	Percentage of preliminary search cancellations
No donor available	105	7
Another provider	317	20
Patient stable	383	25
Financial reasons	114	7
Personal reasons ^a	187	12
Deterioration/death	160	10
Other	284	18
Total	1,550	100

Note: These data are based on a survey, conducted by OPA, of individuals making preliminary searches.

^aPersonal reasons for preliminary search cancellations include decisions made by physicians and patients.

Source: NMDP.

²⁴Cancellation of a preliminary search means that 45 days have occurred since the search without a formal search having been initiated. Cancellation of a formal search means that the transplant center has submitted a particular form indicating a desire to terminate the search and included a reason for doing so.

Table 4: Reasons for Formal Search Cancellation, 1997 to 2000

Reason for cancellation	Number of formal search cancellations	Percentage of formal search cancellations
No donor available	131	3
Another provider	1,200	25
Financial reasons	22	0
Personal reasons ^a	733	15
Deterioration/death	2,096	44
Alternative therapy	357	7
Other	262	5
Total	4,801	100

^aPersonal reasons for formal search cancellations include decisions made by physicians, patients and patients' families.

Source: NMDP.

Several factors may influence a decision to obtain stem cells from a provider outside the NMDP network, including the source of stem cells preferred by the physician, the costs involved, and the timeliness of the response. Outside providers may need to be used when the physician sees cord blood as a viable alternative source to bone marrow or PBSC because some cord blood banks do not list their cord blood units with NMDP.²⁵

Search and procurement costs can also be a factor. Administrators of transplant centers that have done non-NMDP-affiliated transplants told us that other registries charge less for searches than NMDP does. For example, we were told that only a few other registries worldwide charge a search activation fee in addition to their charges for the specific medical procedures needed to confirm that a particular donor is healthy and matched to the patient. In addition, the cost of stem cell procurement at NMDP tends to be higher. One transplant center director told us that the center pays about \$13,000 for stem cells obtained directly from overseas registries and about \$21,000 for NMDP stem cells. However, even when NMDP is not paid for a formal search or for stem cells, it may still have been utilized. An official at NMDP informed us that it is possible for a transplant center to determine the NMDP-affiliated registry at which a foreign (but not domestic) potential match is registered on the basis of a

²⁵Although several blood banks list their cord blood units with NMDP, others, including the largest, the New York Blood Center, do not, and thus NMDP cannot facilitate transplants from those banks.

preliminary search and to contact the foreign registry directly to obtain the stem cells. Moreover, that official stated that some transplant centers may do this regularly. Thus, although NMDP may not be recorded as having facilitated the transplants that result, its role in helping to locate donors in such cases means that its utilization is somewhat greater than the record suggests.

Timeliness can be another factor. A few center administrators mentioned that NMDP takes longer to provide stem cells than do other registries. For example, one administrator told us that the time it takes to obtain a donor sample for testing at the transplant center—an important component of the overall search process—can be a week longer for NMDP than for a foreign registry, depending on whether NMDP judges the search to be urgent. Waiting this additional week can be frustrating for those at the transplant center who are anxious to determine whether they have a confirmed match or will have to continue searching. Another director told us that stem cells from non-NMDP providers are more likely to be received by the date the transplant center requests them than are stem cells from NMDP. NMDP has attempted to shorten its time from formal search initiation to transplant and reports that its median time has decreased from 4.8 months from 1992 through 1993 to 3.7 months in 2000. The optimal time frames for patients vary. Some may not be urgent, but NMDP has shown that it is possible to complete urgent searches in less than a month and reports that it expects to begin offering urgent searches as an option to transplant centers.

Organizations in the NMDP Network Generally Comply with Its Standards and Procedures

Organizations that participate in the NMDP network generally comply with the standards and procedures it has established. In order to encourage adherence, NMDP uses various mechanisms to monitor compliance and performance. These include site visits, the Continuous Process Improvement (CPI) program, and incident reports, as well as a financial incentive system designed to improve the performance of donor centers. The results of the selected site visits, analysis of CPI measures, and incident report summaries we reviewed show that the organizations in the NMDP network generally adhere to NMDP's standards and procedures. In general, NMDP ensures compliance by taking action against noncompliant organizations. (See app. II for examples of how NMDP uses these systems to achieve compliance with respect to selected activities.) In 2001, NMDP required 24 donor and transplant centers to take corrective actions because they did not meet its standards. The incentive system encourages compliance by linking donor center reimbursement to performance.

NMDP Monitors Network Compliance and Performance

NMDP uses several mechanisms to encourage the compliance and performance of the participating organizations in its network. NMDP staff members conduct site visits to donor centers to monitor the centers' compliance with NMDP's standards and procedures and to provide feedback about the results. It also employs the CPI program to assess and provide feedback at donor, transplant, and bone marrow collection centers. Further, NMDP monitors incident reports from donor, transplant, and collection centers and may take corrective action including, in serious cases, suspension or termination.

According to NMDP officials, NMDP staff members conduct site visits at donor centers approximately every 2 years to assess donor center compliance with program standards and procedures. NMDP staff members review the organization of the program (such as its support and staffing structure), recruitment activities (such as performance against goals and donor drive compliance), donor management activities (such as management of patient-related donor search requests, confidentiality procedures, and records management), and billing and reimbursement to determine adherence to NMDP's standards and procedures. They also compare performance against goals for various recruitment activities. Upon completion of these visits, NMDP staff members discuss the results with the center staff and provide a summary report. Centers that are noncompliant are advised of the problems and are required to submit corrective action plans to NMDP that address the problems. Our review of donor center site visit reports indicates that the reports identified problems and the corrective actions required of the centers to meet NMDP criteria.

Since 1998, NMDP has conducted additional site visits at transplant centers to verify the accuracy of the data that the transplant centers submit electronically to NMDP. NMDP staff members compare the data from the centers' records with the data from NMDP's computer system. During these visits, NMDP staff members may also review other activities, such as the signing of patient consent forms. The site visits are scheduled for each transplant center every 4 years. NMDP plans to issue its first annual report on the results of the first cycle of site visits in September 2002.

NMDP monitors the operations and performance of its centers through the CPI program. The program includes nine goals to increase the efficiency of key activities in the search and donation process and measures performance against these goals. For example, at donor centers, NMDP measures the timeliness of registering new donors, resolving search-

related requests, and processing requests for HLA blood typing. At transplant centers, NMDP measures the time it takes to resolve and report confirmatory testing results. NMDP also monitors post-transplant data submission through CPI. These outcome data are used in research studies to analyze outcomes for donors and patients. NMDP also monitors the accuracy and timeliness with which donor and transplant centers submit donor and patient blood samples to NMDP's research repository. NMDP provides regular feedback to donor and transplant centers concerning their performance on CPI measures. For example, each center receives a monthly report summarizing the results of its activities, along with those of all other centers, in the previous month. The reports allow centers to analyze how consistently they perform and to compare their results to those of other centers in the network. NMDP also conducts a year-end analysis to provide feedback to centers.

Through its CPI program, NMDP monitors whether organizations in its network meet goals for timeliness and may recommend corrective actions for centers that do not meet these goals.²⁶ A year-end analysis of the CPI program shows that during 2001 almost half (44 of 91) of donor centers met all nine CPI goals for the search process. In addition, 20 more donor centers met eight of nine goals, and 9 others met seven of nine goals. According to NMDP, the remaining 18 donor centers (20 percent) that met six or fewer goals were the focus of technical assistance to improve their performance. Our analysis shows that 5 of the 91 donor centers (5 percent) were placed on review or probation for failing to meet CPI goals in 2001.

Our analysis also shows that NMDP placed 18 of the 129 transplant centers (14 percent) on probation. Eight of these were placed on probation for failure to meet CPI goals for the search process, seven for failure to meet CPI measures concerned with timely submission of recipient follow-up information, and three for problems related to the accuracy and timeliness of submissions of donor and patient research blood samples.

NMDP supplements these activities with incident reports, which are written accounts of deviations from policies and standards that are categorized by the nature of a deviation and include, but are not limited to,

²⁶Under CPI, NMDP allows up to three notices of noncompliance with a particular standard and sets interim goals to be met within a specified review period after each notice. After a third notice, centers are placed on probation. Failure to meet the requirements of the probationary period may result in termination.

categories such as confidentiality concerns, customer service, and product transport. NMDP uses incident reports to track deviations from its standards by recording the specifics of incidents. NMDP staff members follow up and investigate incidents. In addition, an NMDP committee reviews a summary report of incidents twice a year to identify developing trends that may affect an individual center or the entire network. Since NMDP reviews center participation annually, the committee may follow up on deviations from NMDP's standards or take action such as probation, suspension, or termination during the reapplication process. We reviewed a summary of incidents categorized by type of problem and the corrective actions taken to resolve them. For example, one incident involved an operating room staff member administering less appropriate blood, rather than the donor's own blood, which was available for that purpose, during a marrow harvest. NMDP monitored an investigation at the hospital to ensure that the problem would be addressed.

Donor Center Reimbursement Is Linked to Performance

To improve the operation of its donor centers, NMDP ties their reimbursement to their performance. In 1997, NMDP instituted a new reimbursement system that links payment to performance on CPI goals for all donor centers.²⁷ NMDP pays donor centers a fee for each activity to recruit donors for the Registry, such as signing up donors, typing their tissues, maintaining their files, and other activities related to confirming that the donors identified as potential matches for a searching patient actually match and are medically cleared for donation. NMDP pays each donor center a recruitment fee of \$28 and \$10 for every minority and Caucasian donor, respectively, recruited up to the number specified in its recruitment goal. NMDP establishes annual recruitment goals for each donor center based on the demographics of the local population. When donors are recruited, the donor centers that do not register a specific percentage of the new donors within a certain period incur financial penalties. For example, the CPI goal for registering new donors is to register at least 85 percent of them within 35 days of the date on which they volunteer. NMDP would reduce the total recruitment fee it pays to donor centers that register less than 85 percent of new donors within this time frame. NMDP data show that in May 2001, 98 percent of all donor

²⁷The HHS OIG recommended that HRSA standardize contracts between NMDP and donor centers for donor services to improve the cost efficiency of the centers and to link payment to performance. HRSA included this requirement in its 1997 contract with NMDP to operate the Registry.

centers met this goal. In addition, NMDP pays incentives to donor centers for retaining donors at various points in the donation process.

Concluding Observations

In spite of progress in recruiting minority donors, racial and ethnic disparities in the Registry remain, due in part to differences in the genetic variability within groups. Thus, differences among racial and ethnic groups in the probability of obtaining transplants will likely continue. Many in need of transplants may not search the Registry; those that do often do not obtain them, and for those that obtain them, the transplants may not be facilitated by NMDP. Although NMDP enhances the quality of its network by actively monitoring the compliance and performance of the component organizations, it has not attained the level of utilization that might be expected.

Agency Comments

In its written comments on a draft of this report, HRSA stated that the report provides an accurate and helpful overview of the status of the National Bone Marrow Donor Registry. HRSA agreed that recruitment of donors cannot be the sole strategy for improving access to unrelated donor transplants for minority patients or those with unusual antigens, and cited the need for other efforts to supplement recruitment activities. However, HRSA noted that the Registry consists of two distinct groups of donors, those who are fully HLA typed and those who are less than fully typed. Since the vast majority of actual donors are selected from the fully typed portion, minority racial and ethnic groups therefore make up a larger proportion of the Registry than their representation in the U.S. population. We have noted in the report that, because of this, access for minorities may be somewhat better than might be assumed by looking at the Registry as a whole.

With regard to underutilization of the Registry, HRSA agreed that many patients who could benefit from unrelated donor transplants never consult the Registry or do so too late in the course of their illnesses. HRSA suggested a slightly modified method for estimating the number of patients in need. We modified table 2 in accordance with its suggestions, but note that both approaches produce virtually identical estimates of overall utilization. (See app. I.)

Finally, HRSA noted that many factors affect the time required to complete a search of the Registry. While searches frequently take many months and the median search time has decreased, NMDP has completed medically urgent searches in less than a month, on a pilot basis, and reports that it

expects to begin offering urgent searches as an option to transplant centers. We have revised the report to include this clarification. HRSA also provided technical comments, which we incorporated as appropriate. HRSA's comments are reprinted in appendix III.

We are sending this report to the Administrator of HRSA, the NMDP Chief Executive Officer, and other interested persons. We will also make copies available to others upon request. In addition, the report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staff members have any questions about this report, please call me at (202) 512-7119. Key contributors to this assignment are listed in appendix IV.



Janet Heinrich
Director, Health Care—Public Health Issues

List of Committees

The Honorable Robert C. Byrd
Chairman
The Honorable Ted Stevens
Ranking Minority Member
Committee on Appropriations
United States Senate

The Honorable Edward M. Kennedy
Chairman
The Honorable Judd Gregg
Ranking Minority Member
Committee on Health, Education,
Labor, and Pensions
United States Senate

The Honorable C.W. Bill Young
Chairman
The Honorable David Obey
Ranking Minority Member
Committee on Appropriations
House of Representatives

The Honorable W.J. "Billy" Tauzin
Chairman
The Honorable John D. Dingell
Ranking Minority Member
Committee on Energy and Commerce
House of Representatives

Appendix I: Methods of Assessing Registry Utilization

Registry utilization is the extent to which patients in need of unrelated stem cell transplants search the Registry or obtain NMDP-facilitated transplants. In determining utilization, it is necessary to use indirect methods to calculate the number of patients in need because it is impossible to determine this number directly. For example, although we may be able to obtain data on the number of patients who have been diagnosed with certain blood and immune system diseases, we are unable to determine the number for whom stem cell transplants are the best treatment.

One measure of the utilization of the Registry is the extent to which the number of patients obtaining transplants facilitated by the Registry is as high as it could be. The maximum possible utilization of the Registry would be indicated if the number of U.S. patients conducting preliminary searches was approximately equal to the estimated number of patients needing unrelated donor transplants. A second measure of utilization is the extent to which patients search the Registry.

The method we used to assess the two aspects of utilization—searching the Registry and obtaining an NMDP-facilitated transplant—is also used by NMDP. It involves estimating the number of patients in need of unrelated donor transplants by using data on the number of HLA-identical sibling transplants obtained from IBMTR.¹ This method and two alternative methods that are also used by NMDP to assess utilization by U.S. patients, one based on the number of preliminary searches conducted and the other based on the incidence of disease, are described here.

Method Based on Number of HLA-Identical Sibling Transplants

For the years from 1997 through 2000, we estimated the number of Caucasian patients in need of unrelated donor transplants based on the average annual number of Caucasian HLA-identical sibling transplants performed during those years. To obtain this estimate, we multiplied the number of HLA-identical sibling transplants, for Caucasians, by the number of patients of that group that genetic theory predicts—on the basis of the average number of children born to the women of that group—are

¹This registry, located in Milwaukee, registers bone marrow transplants, not donors like the other registries discussed in this report. The data used in our estimations were obtained from the Statistical Center of IBMTR and Autologous Blood and Marrow Transplant Registry (ABMTR). The analysis has not been reviewed or approved by the Advisory Committees of the IBMTR and ABMTR.

in need of unrelated donor transplants for every Caucasian HLA-identical sibling transplant in the United States.

The average number of children born to Caucasian women over a lifetime during the years from 1989 through 1995 was 1.7925.² Subtracting the individual who is in need of a transplant gives $n = 0.7925$ as the number of siblings available to be transplant donors. The likelihood of a match between two siblings is 25 percent because each child inherits one-half of each parent's HLA genes, resulting in a one out of four chance of having the same HLA genes as a sibling has. Therefore, the probability that no sibling HLA identically matches the one in need is $P = (0.75)^n$. For a Caucasian patient, $P = (0.75)^{0.7925} = 0.796134$.

The number of patients in need of unrelated stem cell transplants is equal to the number of sibling donor transplants multiplied by $P/(1 - P)$. Therefore, for every HLA-identical sibling transplant recorded for a Caucasian patient, there will be $0.796134/(1 - 0.796134) = 3.90518$ patients in need of unrelated donor transplants. Because there were 7,920 sibling transplants performed for Caucasian patients from 1997 through 2000, we estimate that $3.90518(7,920) = 30,929$ Caucasian patients were in need of stem cell transplants during that period. The estimates for other racial and ethnic groups are presented in table 2. Because minorities generally have less access to health care³ and may therefore have less access to sibling transplants specifically, these estimates were obtained by assuming that

²We determined this average by taking the median Caucasian fertility rate for the years from 1989 through 1995. Fertility rates for non-Hispanic Caucasians were not available for earlier years. We did not include rates for years after 1995 because we do not think many of the transplants occurring during the years 1997 through 2000 were done for patients born after 1995. Because fertility rates tended to be higher before about 1973, when some of the patients seeking transplants during the period of our analysis, 1997 through 2000, were born, the use of the 1989 through 1995 rates results in an underestimation of the average number of siblings and a consequent overestimation of the number of patients in need of unrelated donor transplants. The effect of this consideration of the 1989 through 1995 rates is counterbalanced to an unknown extent because (1) the fertility rates count half siblings and dead siblings as well as living full siblings and (2) the fertility rates count all of a woman's live births, including those that occur after the patient needs a transplant. The effect of these two counterbalancing considerations is to overestimate of the number of siblings available to donate and underestimate the number of patients in need. The net effect of the choice of 1989 through 1995 rates and the considerations concerning the fertility rates on the estimation of the number of patients in need is not known.

³See, for example, R.M. Mayberry, F. Mili, and E. Ofili, "Racial and Ethnic Differences in Access to Medical Care," *Medical Care Research and Review*, vol. 57, Supplement 1 (2000), pp. 108-145.

each minority group's need for unrelated donor transplants is proportional to the Caucasian group's need. The estimates were obtained by multiplying the number of persons in the minority group by the proportion of Caucasians in need of unrelated donor transplants. This approach implicitly assumes that differences across groups in fertility rates are of negligible importance in computing the numbers of patients in need of unrelated donor transplants.

An alternative approach assumes that minorities and Caucasians have equal access to HLA-identical sibling transplants. Based on this assumption, this approach derives the needs of minorities for unrelated donor transplants directly from their observed numbers of HLA-identical sibling transplants. In doing so, it allows for the possibility that each group has its own disease incidence rates and that the differences among groups in their relative levels of sibling donations reflect these rates, not differences in access. (See table 5.) This approach, while utilizing somewhat different assumptions from the method above, produces a virtually identical estimate of the underutilization of the Registry (10 percent versus 9 percent).

Table 5: Alternate Approach to the Analysis of U.S. Patients' Utilization of the Registry, by Race and Ethnicity, 1997 to 2000

Race/ethnicity	Estimated number of patients without matched sibling donor ^{a,b} (patients in need)	Actual number of preliminary searches	Ratio of preliminary searches to number of patients in need	Actual number (percentage) of preliminary searches resulting in formal searches	Actual number (percentage) of preliminary searches resulting in NMDP-facilitated transplants	Ratio of number of NMDP-facilitated transplants to number of patients in need
African American	1,880	1,694	0.90	958 (57)	256 (15)	0.14
Asian/Pacific Islander	1,355	439	0.32	270 (62)	96 (22)	0.07
Caucasian	35,964	10,844	0.30	7,079 (65)	3,321 (31)	0.09
Hispanic	1,593	1,366	0.86	840 (61)	317 (23)	0.20
Native American	97	80	0.82	56 (70)	20 (25)	0.21
Other	290	365	1.26	213 (58)	39 (11)	0.13
Total	41,179	15,231^c	0.37	9,623 (63)	4,056 (27)	0.10

Note: This table presents an alternate approach to that given in table 2.

^aNumber of HLA-identical sibling transplants multiplied by the number of patients expected to be without matched sibling donors for each such transplant was derived from data obtained from the Statistical Center of the IBMTR and Autologous Blood and Marrow Transplant Registry (ABMTR). (The analysis has not been reviewed or approved by the Advisory Committees of the IBMTR and ABMTR.)

^bNumbers based on the HLA-identical sibling transplants of the designated race/ethnicity plus a portion of those of unknown race/ethnicity. These unknowns submitted record forms that did not ask about race/ethnicity. The unknowns can be assumed to be similar in racial/ethnic distribution to the other patients, and so we distributed them among the racial/ethnic groups according to that distribution. It can therefore be assumed that there is no racial bias in this estimation method.

^cIncludes 443 preliminary searches, not included elsewhere in the column, from patients of unknown race/ethnicity.

Source: GAO analysis of data from the Statistical Center of the IBMTR and ABMTR and NMDP.

Method Based on Number of Preliminary Searches

The second method used by NMDP to assess Registry utilization is based simply on the annual number of patients conducting preliminary searches. In order to use this method, one must assume that this number directly represents those in need of unrelated donor transplants. One cannot assess the extent to which those in need search the Registry on the basis of this number since the number itself is the number of patients searching. However, one can assess the extent to which those in need obtain NMDP-facilitated transplants by considering the annual percentage of patient searches that result in NMDP-facilitated transplants. This method yields an estimate of the patients searching who obtain NMDP-facilitated transplants of 27 percent. (See table 5.)

Although this approach has been used by NMDP as a way of assessing utilization, officials at NMDP observe that the validity of this approach to utilization assessment is limited by the freedom with which patients can choose whether to search. These officials point out that preliminary searches are performed for some patients who are not good candidates for transplant and that other patients who should submit preliminary searches probably do not. Because of the lack of correspondence between the number of patients in need and the number performing preliminary searches, this estimate is not likely to be as accurate as the other two.

Method Based on Incidence of Disease

The third method used by NMDP is based on an estimate of the annual number of U.S. patients newly diagnosed from 1997 through 2000 with selected diseases that might benefit from unrelated stem cell transplants.⁴ The estimated number of potential recipients for each disease is obtained from disease incidence estimates, with adjustments for the likelihood that (1) the patient is young enough to benefit from transplantation, (2) disease severity is not so great as to make transplantation futile, and (3) an HLA-identical sibling donor is available, thereby making unrelated donor transplant unnecessary. The ratio of the annual number of NMDP-facilitated transplants for U.S. patients diagnosed with these selected diseases during this period to the estimated number of new U.S. patients with the diseases is used to assess utilization.⁵ (See table 6.) The ratio, for all patients with the selected diseases, corresponds to an estimated percentage of candidates obtaining transplants—10 percent—that is very close to the estimate obtained by the first method. The validity of this third method is constrained by the limited number of diseases for which data are available.

⁴R.P. Gale, "Potential Utilization of a National HLA-Typed Donor Pool for Bone Marrow Transplantation," *Transplantation*, vol. 42, no. 1 (1986), pp. 54-58.

⁵We have not related the number of potential recipients estimated in this third way with the numbers of preliminary searches for patients with the selected diseases, only with the numbers of transplants.

Appendix I: Methods of Assessing Registry Utilization

Table 6: Average Annual Unrelated Donor NMDP-Facilitated Transplants and Estimated Number of Potential Recipients for U.S. Patients with Selected Diseases Who Might Benefit from Unrelated Stem Cell Transplants, by Race/Ethnicity, 1997 through 2000

Race/ethnicity	Acute lymphocytic leukemia	Acute myelogenous leukemia	Chronic myelogenous leukemia	Non-Hodgkin's lymphoma	Total
African American	8	12	18	4	42
Caucasian	121	197	161	68	547
Hispanic	24	12	14	2	52
Native American	1	1	1	0	3
Asian/Pacific Islander	6	5	4	1	16
Other	2	1	2	0	5
Total number of NMDP-facilitated transplants	162	228	200	75	665
Estimated number of new U.S. patients with selected diseases who might benefit from unrelated stem cell transplants	1,359	662	761	4,081	6,863
Percentage of new patients who receive NMDP-facilitated transplants	12	34	26	2	10

Sources: GAO analysis of data from NMDP and the National Cancer Institute's Surveillance, Epidemiology, and End Results program.

Appendix II: How NMDP Achieves Network Compliance with Selected Standards and Procedures

NMDP requires that the organizations participating in its network comply with its standards and procedures. This appendix discusses how NMDP achieves the compliance by network organizations with standards and procedures for obtaining the informed consent of donors and patients, donor selection criteria, confidentiality of records, collection and transportation of marrow, laboratory standards, and maintenance of donor files in the Registry.

Informed Consent of Donors and Patients

At each stage of the search process, NMDP requires donors to sign informed consent statements for procedures performed at the donor and transplant centers.¹ A volunteer must sign an informed consent form before being listed as a donor on the Registry, and also before the collection of blood for initial and follow-up testing, infectious disease testing, and participation in research. In addition, consent must be obtained before notifying the transplant center that a donor is willing to proceed to marrow donation and before the administration of anesthesia. Consent must also be obtained before collecting blood specimens for research and before any proposed procedure for which the donor has not previously given consent.

According to NMDP officials, during each donor center site visit, NMDP staff members review about 35 randomly selected donor files. NMDP staff members check that each donor has signed all appropriate consent forms for the stages of the recruitment and search process the donor has completed. According to an NMDP official, since NMDP began performing site visits in 1998, missing or unsigned donor consent forms occurred in only a few cases, indicating that a high level of compliance has been achieved. The number of missing consent forms is not readily available because cumulative data are not permanently stored. Transplant centers are responsible for obtaining informed consent from each transplant patient, for collecting research blood samples that are sent to the NMDP repository, and for submitting baseline and follow-up data to the Registry. Some of the centers have separate consent forms specifically for the research samples and clinical data, whereas others incorporate consent for the research samples and clinical data into the informed consent document the patient signs for the transplant.

¹Informed consent refers to the process of helping an individual weigh the risks against the benefits of a procedure or treatment. By signing a form, an individual consents to undergo a procedure after being fully informed of the risks and benefits.

NMDP is currently collecting information on how transplant centers are handling the informed consent process for the research samples and clinical data submitted to NMDP. This information will be analyzed, and NMDP will evaluate whether changes in policies or procedures should be made to the consent process for obtaining NMDP data and research blood samples.

Criteria for Donor Selection

In order to be considered for stem cell donation, donors must be from age 18 through 60 and in good health. Individuals with serious illness or those who are significantly overweight are disqualified. The donor must provide a medical history and acknowledge in writing that the history is accurate. Pertinent donor medical information is evaluated for acceptance or deferral according to NMDP medical eligibility standards and criteria set by the medical director at the local donor center.

NMDP monitors whether registered donors have filled out the appropriate medical history questionnaires, but NMDP does not store cumulative data on the number of missing medical history questionnaires. During each donor center site visit, NMDP staff members check a random number of health history questionnaires. However, NMDP is limited in how it monitors the donor selection process. Although NMDP tracks the number of donors who are unavailable for medical reasons, it cannot determine whether an unavailable donor's medical condition was preexisting, and therefore should have been caught in the health screening at the time the donor volunteered, or whether the donor's health changed during the period between registration and a request for testing prior to donation.

Methods to Protect Confidentiality

NMDP requires that each participating donor center have a system for safeguarding donor confidentiality. The Registry identifies donors by code number only. Donor centers maintain donor identity and location and limit access to this information by using locked file cabinets and locked rooms.

NMDP also requires that each participating transplant center have a system of confidentiality in place to protect the privacy of patients. It provides that transplant patient identification should not appear on papers or publications, and the patient's name and location should not be disclosed to the donor(s).

Marrow Collection and Transport

Organizations responsible for marrow collection and transport must meet certain participation criteria in order to be affiliated with NMDP. Among other things, participating cord blood banks must be accredited and licensed or registered by the Food and Drug Administration for collection of autologous blood. Marrow collection centers must provide emergency and intensive care services and must be accredited by the Joint Commission on Accreditation of Healthcare Organizations. In addition, each collection center must have a licensed medical director, an experienced marrow collection team that regularly collects bone marrow, and a designated site for management of collection activities.

NMDP has established standards to ensure the proper collection and transportation of marrow. These require that bone marrow collection centers have experienced personnel to collect marrow and adequate resources to support collection and management activities. In addition, NMDP requires that collection centers maintain written standard operating procedures and policies for collecting, testing, labeling, and transporting marrow.

Laboratory Standards

Laboratories responsible for HLA tissue typing must meet certain criteria in order to be affiliated with NMDP. Participating HLA typing laboratories must be accredited by the American Society for Histocompatibility and Immunogenetics (ASHI)² or the European Foundation for Immunogenetics for techniques required by NMDP. Laboratories must also comply with all state and federal regulations, including the Clinical Laboratory Improvements Amendments of 1988 (or their non-U.S. equivalent) for infectious disease testing, blood typing, red cell antibody screening, and other tests required by NMDP.

As part of NMDP's quality control program, participating laboratories must type blind samples provided by NMDP. The laboratories must maintain monthly error rates less than or equal to 1.5 percent. If a laboratory fails to meet quality control and quality assurance standards established by ASHI or NMDP, NMDP may require that laboratory to submit a corrective action plan. After the period allowed for corrective action, the laboratory's contract with NMDP may be terminated if it still does not meet the standards.

²ASHI is an accrediting body that has established standards that all histocompatibility laboratories must meet if their services are to be considered acceptable.

From February 2000 through April 2002, NMDP suspended five laboratories responsible for HLA tissue typing. The length of suspension ranged from 1 to 9 weeks, and reasons for suspension were related to electronic communication problems, overdue samples, and poor turnaround time.

Donor File Maintenance and Updates

NMDP's central database is updated when new donors are recruited and when information on existing donors changes or donors are deleted from the Registry. Information about newly recruited donors includes donor identification numbers, demographic data, and the donors' HLA types. According to NMDP procedures, domestic donor centers submit data on donors daily through NMDP's central database.

Appendix III: Comments from the Health Resources and Services Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Resources and Services Administration

Rockville, Maryland 20857

SEP 12 2002

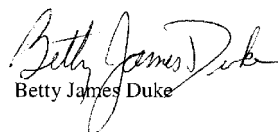
TO: Janet Heinrich
Director, Health Care – Public Health Issues

FROM: Administrator

SUBJECT: General Accounting Office Draft Report “Bone Marrow Transplants:
Despite Recruitment Success, National Program May Be Underutilized”
(GAO-02-994)

Thank you for the opportunity to provide comments on the subject draft report. Attached please find HRSA's comments.

Questions may be referred to John Gallicchio on (301) 443-3099.


Betty James Duke

Attachment

**HRSA Comments on the Draft GAO Report: “Bone Marrow
Transplants: Despite Recruitment Successes, National Program May Be
Underutilized” (GAO-02-994)**

General Comments

The Health Resources and Services Administration (HRSA) appreciates the opportunity to review the draft of the report: “Bone Marrow Transplants: Despite Recruitment Successes, National Program May Be Underutilized” (GAO-02-994). The report provides an accurate and helpful overview of the status of the National Bone Marrow Donor Registry, with respect to the study mandated in the National Bone Marrow Registry Reauthorization Act of 1998. The report notes the substantial progress that has been made in achieving the statutory goals for the Registry, and recognizes that the challenges facing the Registry today are not amenable to simple solutions. We are enclosing HRSA’s substantive comments on the draft report and a number of technical comments for your consideration as you develop the final report. We shared the draft report with HRSA’s National Marrow Donor Program (NMDP) and have incorporated their suggestions in our comments.

We would like to comment on four aspects of the draft report. The first is progress in improving minority access to transplants through the Registry. The report notes that recruitment efforts focused on minority populations have increased the representation on the Registry of the major minority population groups to levels approximately equal to their shares of the U.S. population, and that for all racial and ethnic groups the likelihood of finding a match through the Registry has increased as the Registry has grown. Still, the likelihood of finding a match differs by race, with African Americans having the lowest probability of finding a match, in large part because of their greater variety in HLA types. The report concludes that some minority groups, especially African Americans, may never achieve the same probability of finding a match as Caucasians, and that attempting to close the gap through recruitment of donors with rare HLA types is expensive and may divert resources from another statutory goal for the program, increasing the overall number of patients who find a match and receive a transplant through the Registry.

We agree that recruitment of donors cannot be the sole strategy for improving access to unrelated donor transplants for minority patients, or for other patients with unusual HLA types. Also important are learning which less-than-perfect HLA matches may still lead to successful transplants, and how to more effectively manage complications that arise in unrelated donor transplants; improving the retention of donors who have joined the Registry; encouraging patients who may need an unrelated donor transplant (and their physicians) to begin a search of the registry soon after their diagnosis; providing expert assistance in difficult searches; and increasing the effectiveness of umbilical cord blood as a source of blood stem cells for patients who cannot find a matched adult donor. The Registry is actively involved in all these areas. We think these efforts, along with continued recruitment of donors to replace those who are lost to attrition and to add

unique HLA types to the Registry, can result in further improvements in access for all populations. The appropriate level of recruitment in the future will depend, among other things, on whether the cost of tissue typing continues to decline.

With respect to current minority representation on the Registry, we would note that the Registry donor file is comprised of two distinct components defined by the amount of HLA typing data available. The larger portion (3,081,642 as of June 30, 2002) has donors fully typed for HLA-A, -B and -DR. The remainder (35%) is typed only for HLA-A and -B. The vast majority of actual donors (>98%) are selected from the fully typed portion. In this most active portion of the donor file, each racial and ethnic group, with the exception of Caucasians, comprises a larger proportion of the file than their representation in the U.S. population.

The report also concludes that the Registry is underutilized. We agree that many patients who could benefit from an unrelated donor transplant never consult the Registry or do so too late in the course of their illness. Many of the ongoing efforts listed above aim to increase utilization of the Registry as well as increase the probability that a patient will find a matching donor on the Registry. We question, however, one specific GAO finding, that the percentage of patients in need of an unrelated donor transplant who search the Registry is much greater for African American, Hispanic and American Indian patients than for Caucasians. The method used to estimate the number of patients in need, as reported in Table 2, may involve an incorrect assumption. The calculation used data from the International Bone Marrow Transplant Registry reporting the race of related donor transplant recipients. GAO combined these data with fertility data to compute an estimated number of transplant candidates without matching sibling donors. This approach assumes that all appropriate candidates for sibling transplant are in fact transplanted. That is, there are no disparities in access to related donor transplant between racial and ethnic groups. Since many studies have found that minorities do not have the same access to health care as Caucasians, this assumption may be incorrect.

Finally, we wish to comment on the time required to complete a search of the Registry. The report notes that the median search time has been decreasing, but that searches still frequently take many months and sometimes over a year. The median search time for all patients is a convenient way to present data, but many factors affect search duration including the optimal timeframe for transplantation for each patient. For example, a transplant center may initiate a search for a patient at the same time they enroll the patient in a clinical trial of a new pharmaceutical agent. If the patient responds, he or she may not be a transplant candidate for several years but the transplant center may want to identify a potential donor, in case the patient's clinical condition changes suddenly. In situations like this, a search may be ongoing for a long period of time without disadvantaging the patient. Alternatively, a patient with acute leukemia may need a transplant as soon as a suitable donor can be identified and prepared for donation. Decreasing search times for those patients who need to proceed to transplant rapidly is a major priority of the program. The NMDP has shown in a pilot project that it is possible to complete medically urgent searches in 14-21 days. Drawing on the lessons of the pilot project, the NMDP has made numerous procedural changes and beginning in September,

2002 will offer transplant centers the option of requesting that an urgent search be completed in 21 days or 45 days. The percentage of these urgent searches completed in the requested timeframe will be a more useful measure of performance than an overall median search time.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-3407

Acknowledgments

The following staff members made important contributions to this work: Donna Bulvin, Charles Davenport, Donald Keller, Kelly Klemstine, Behn Miller, and Roseanne Price.

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