Bone Marrow Donor Registries: The Relation Between Registry Size and Probability of Finding Complete and Partial Matches

By Frank A. Sonnenberg, Mark H. Eckman, and Stephen G. Pauker

In a registry of volunteer bone marrow donors, the relation between registry size and probability of finding an exact or partial match for a random recipient cannot be theoretically derived because it depends on specifics of the human leukocyte antigen (HLA) haplotype frequencies in the donor and recipient populations. The relation must be explicitly calculated using empirically determined HLA haplotype frequency data for all possible pairings between a donor and a recipient population. This report describes a general solution to this problem. The method shows that the relation of the probability of matching to registry size is sigmoidal, with small increases in probability at the extremes of registry size and a middle range of registry size within which the probability of matching increases most sharply. This range determines the approximate size of the most cost-effective registry. In addition, for any pairing of donor and recipient populations, there is a maximum probability of identifying a match of a given quality for a random recipient, which cannot be exceeded even if registry size were infinite. This upper limit is a function of the frequency of blank (or unknown) alleles in the donor and recipient populations; the higher that frequency, the lower the maximum probability of achieving any given quality of match. The determinants of the probability of achieving a given quality of match with a given registry size are (1) the genetic heterogeneity within the recipient and donor populations, which increases the registry size required to achieve a given probability of matching, and (2) the degree of genetic homology between the donor and recipient populations, which increases the maximum probability of matching and also lowers registry size requirements. The method described here can be used to estimate donor pool size requirements using any donor and recipient populations for which HLA frequency data are available.

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ORGAN TRANSPLANTATION is already standard therapy for a variety of diseases. Although renewable or duplicated organs can, in principle, be donated by living donors, the identification of donors adequately compatible with a given recipient severely limits the application of such techniques. Bone marrow transplantation (BMT) is perhaps the best example of such a treatment, because bone marrow can be donated with minimal risk and no long-term sequelae for the donor. BMT has become the standard therapy for aplastic anemia and has been used increasingly for treatment of the acute leukemias and other disorders. Many victims of radiation exposure from the nuclear accident at Chernobyl in the Soviet Union required BMT.

The most desirable donors, a human leukocyte antigen (HLA)-identical sibling is available for only approximately one third of candidates for BMT. Attempts have been made to use HLA-nonidentical relatives, but in general the results have not been good. For these reasons, attention has turned to nonrelated donors who are closely matched for the major HLA antigens. Transplants of marrow from nonrelated volunteer donors are now performed at many centers. To increase the availability of nonrelated donors, a national registry for volunteer bone marrow donors has recently been established in the United States. The Canadian Hematology Society has proposed a Canadian national registry, and the US Office of Naval Research has funded a large study of a nationwide network of local registries. More recently, McCullough et al. described the accumulated experience with a registry of 2.147 donors currently operating at the University of Minnesota.

The optimal size of donor registries remains to be determined. A cost-effectiveness analysis that addressed this question has been published elsewhere. A major consideration in determining the optimal size of a large donor registry is the relation between the size of the registry and the likelihood of identifying a matching donor. Beatty et al. addressed this question in a mathematical simulation that used a registry of cadaveric kidney donors to represent the donor pool. They calculated the probability of finding an HLA-identical match from registries of different sizes for a randomly selected recipient. They concluded that a registry of attainable size (250,000 individuals) could significantly increase the number of transplants performed but that even with large registries not all recipients will find a match. An analysis by Takahashi et al. examined the appropriate size of donor registries for HLA-matched platelet transfusion. However, the analysis of platelet donors is different than a comparable analysis for bone marrow donors because for the former, multiple donors are required and a graft-versus-host (GVH) reaction is not a consideration. Our methodology was similar to that of Beatty et al. but we extended the analysis to examine probabilities of finding partial HLA matches.

THE HLA SYSTEM AND BMT

Nomenclature

The human major histocompatibility complex is a cluster of genes found on the short arm of chromosome 6. Three

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major loci, HLA-A, HLA-B, HLA-C, and a region of loci HLA-D are defined. Loci A, B, and C code for Class I antigens which are detected serologically. The HLA-D region contains genes coding for serologically detectable Class II antigens. These are referred to as D-related antigens and are specified by loci in subregions of the D region, designated DR, DP, and DQ. D-related antigens may be the serologic expression of the HLA-D determinants which are responsible for stimulation in the mixed lymphocyte culture (MLC) reaction. Other D-locus determinants are defined, not serologically, but by reactivity in the MLC.

Although it was previously believed that a negative MLC is required for a successful BMT, several groups reporting data on BMT using unrelated or non-HLA-identical related donors have found that MLC cross-reactivity or HLA-D incompatibility did not correlate well with engraftment or with the incidence of GVH disease. The situation with respect to matching for the Class I (HLA-A and HLA-B) determinants is more controversial. Hows et al found that patients with HLA phenotypically identical matched donors did better than those mismatched for one or more antigens, but Gingrich et al found that a successful outcome did not clearly depend on a match for all Class I antigens. Because previous reports of BMT from HLA-nonidentical donors and the report of the operation of a functioning registry of McCullough et al have reported only HLA-A, HLA-B, and HLA-DR alleles, we consider only those alleles in this analysis. Specifically, HLA-C was not considered.

The Eighth International Workshop on Histocompatibility defined 17 alleles for HLA-A, 31 alleles for HLA-B, and 10 alleles for HLA-DR. In addition, a null type, designated as AX, BX or DRX is designated for each locus. In the tables reported by the Histocompatibility Workshop, null alleles in a haplotype designation represent either unrecognized or uncharacterized antigens or homozygosity for the corresponding locus.

Genetics of the HLA System

Each person has two copies of chromosome 6, providing a total of six alleles for HLA-A, HLA-B, and HLA-DR. The HLA genes, like ABO blood types, are codominant; that is, if two different alleles are present at a given locus, both are expressed.

Because the three loci on each chromosome are closely linked, they are inherited together as a single Mendelian trait—an HLA haplotype. Because one haplotype is inherited from each parent, barring crossovers, every person is said to be haploidentical to each parent. There is a 25% chance that any person will have inherited the same two haplotypes as a sibling. Such siblings are HLA identical.

Certain combinations of HLA genes (referred to as extended haplotypes) are found in the population at frequencies much higher than would be predicted by their individual gene frequencies. Such haplotypes are in genetic linkage disequilibrium and, as a consequence, the vast majority of observed HLA haplotypes consist of a small percentage of possible haplotypes. In the tables compiled by the Eighth International Histocompatibility Workshop the vast majority of entries (>99%) for A-B-DR three-locus haplotypes in the North American Caucasian (NAC) population consist of only 12% of the possible A-B-DR allele combinations.

Thus, a population is best characterized, not by frequencies of individual HLA alleles, but by frequencies of HLA haplotypes. Because we are concerned with combinations of HLA-A, HLA-B, and HLA-DR, we consider the A-B-DR three-locus haplotypes.

Genotype vs Phenotype

The set of HLA antigens detected on the cells of an individual is referred to as an HLA phenotype. For the purposes of this discussion, a complete phenotypic description consists of specifications of all HLA-A, HLA-B, and HLA-DR antigens detected (up to a maximum of six). If one or more of the loci code for a null antigen or if the two alleles at a given locus are, by chance, identical, then fewer than six distinct antigens will be detected. The HLA phenotype, on the other hand, specifies which genes are linked together on each chromosome and cannot be determined by tissue typing a single individual. Although not central to transplantation success, the genotypic specification is central to the calculation of the probability of finding a match from a registry.

Phenotypes (determined by the detection of cell surface antigens) are expressed without regard to the configuration of the corresponding genes on the chromosomes. For example, consider a prospective recipient whose genotype is

\[
\begin{array}{c|c|c|c|c|c|c|c|c}
M & P & M & P & M & P & M & P & M & P \\
A29 & A3 & A29 & A3 & B7 & B27 & B7 & B27 & DR5 & DR1 \\
\end{array}
\]

where \(M\) represents the maternal haplotype and \(P\) stands for the paternal haplotype. The corresponding phenotype would be \([A3,A29,B7,B27,DR1,DR5]\). A matching phenotype can result from any of the following combinations of haplotypes:

\[
\begin{array}{c|c|c|c|c|c|c|c|c}
1 & 5 & M & P & M & P & M & P & M & P \\
A29 & A3 & A29 & A3 & B7 & B27 & B7 & B27 & DR5 & DR1 \\
\end{array}
\]

\[
\begin{array}{c|c|c|c|c|c|c|c|c}
2 & 6 & M & P & M & P & M & P & M & P \\
A3 & A29 & A3 & A29 & B7 & B27 & B7 & B27 & DR1 & DR5 \\
\end{array}
\]

\[
\begin{array}{c|c|c|c|c|c|c|c|c}
3 & 7 & M & P & M & P & M & P & M & P \\
A29 & A3 & A3 & A29 & B7 & B27 & B7 & B27 & DR1 & DR5 \\
\end{array}
\]

\[
\begin{array}{c|c|c|c|c|c|c|c|c}
4 & 8 & M & P & M & P & M & P & M & P \\
A3 & A29 & A29 & A3 & B7 & B27 & B7 & B27 & DR5 & DR1 \\
\end{array}
\]
As a consequence of genetic linkage disequilibrium, even if they did not come from siblings, genotypes 1 and 2 would have more minor determinants in common with the recipient than would the other genotypes. Consequently, one would expect these two genotypes to provide the closest match to the prospective recipient. Each of these donor genotypes would have a different likelihood of a negative MLC when paired with the recipient.

For the remainder of this report the term HLA-identical will mean phenotypically identical (ie, the antigens detected are the same for both donor and recipient). This will also be referred to as a six-allele match. The term genotypically identical will mean that two individuals are haploidentical for both chromosomes, eg, the above recipient and donor 1 or donor 2.

**HLA COMBINATORICS**

**Number of Different Haplotypes**

The 17 A alleles, 31 B alleles, 10 DR alleles, plus a null type for each result in \((17 + 1) \times (31 + 1) \times (10 + 1)\), or 6,336 possible combinations.

**Number of Different Genotypes**

The number of possible combinations of N different objects taken two at a time is \(N(N - 1)/2\). When both objects can be the same, additional N combinations or the total of \(N(N - 1)/2 + N\) are possible. Algebraic simplification reduces this expression to \(N(N + 1)/2\). The set of 6,336 possible haplotypes results in 6,336 \(\times 6,337/2\) or 20,075,616 different possible genotypes.

**METHODS**

**Source of HLA Frequency Data**

Tables from the Eighth International Workshop on Histocompatibility Testing published in 1980 provided frequencies of HLA A-B-DR three-allele haplotypes for NAC. The 1984 update did not include new specifications for these haplotypes because they were assumed to have remained relatively constant. To assess the impact of ethnicity, the analysis was repeated with haplotype frequencies measured in a population of Japanese ancestry. Frequencies of two-allele haplotypes (A-B, A-DR, and B-DR) and single-gene frequencies for A, B, and DR were calculated by adding the corresponding entries for three-allele haplotypes. Genotype frequencies were calculated by multiplying the frequencies of the two three-allele haplotypes comprising each genotype.

The table of A-B-DR three-allele haplotypes for NAC contains 6,336 entries of which only 756 (12%) have non-zero frequency. Presumably, the remaining 5,580 haplotypes may exist with small frequencies but were not detected in the limited population sample used to construct the table. To allow for the possibility that additional haplotypes exist two limiting assumptions were used. **Alternate assumption 1:** "Whole world." This represents a worst case scenario and assumes that the entire population consists of only the 756 haplotypes found in the table. The 5,580 undetected haplotypes each have a frequency of zero. Under this assumption, only 286,146 genotypes needed to be considered.

**Alternate assumption 2:** "Assumed frequency." This represents a "best case" scenario and assumes that all possible haplotypes actually exist and those missing from the table are evenly distributed among the 5,580 undetected haplotypes. The frequencies of these "assumed haplotypes" sum to a small percentage of the total frequency. Percentage was arbitrarily chosen to be either 5% or 10%, in order to ascertain the qualitative effect on the analysis of errors in detection of rare haplotypes. It was felt that undetected haplotypes were unlikely to represent more than 10% of the total frequency in the actual population. However, because each haplotype frequency in the published tables has a different degree of statistical significance, it is not straightforward to estimate the probability that the undetected haplotypes exceed 10%. The frequencies of all other haplotypes were normalized so that the total frequency was unity. Under this assumption all 20,075,616 possible genotypes needed to be considered.

**Probability of Matching for a Random Recipient**

The specific mathematical details of the calculations are presented in detail in the Appendix. This section describes in a general way how each probability of matching was calculated.

Each genotype in the recipient population was examined in turn and the probability of identifying a match of a specified quality for that recipient was calculated. The probability of identifying a match represents a complex calculation because, as previously discussed, more than one donor genotype may provide a match of a specified quality for a given recipient genotype; that probability is calculated by examining all donor genotypes and summing the frequencies of those which match the recipient. The total frequency of matching genotypes is then used, to calculate the probability that such a match will be found in a registry of a given size. This probability will depend on the registry size as shown in Equation 1 of the Appendix.

A weighted average of these probabilities is calculated based on the frequency of each recipient genotype and can be interpreted as the probability of finding a given quality of a match for a randomly selected member of the recipient population. Viewed another way, it represents the average probability of finding a match for a large number of recipients.

**DEFINING HLA MATCHES**

The most preferable donor matches the recipient for all of the (A, B, and DR) alleles. Based on preliminary work, Hansen in Seattle and Gingerich in Iowa have suggested that some donors who do not match the recipient for all six alleles can be used successfully.

McCullough et al recently reported a system for categorizing complete and partial HLA matches which is based on matching at the A and B loci. Their scheme presumes that all matches considered are identical for both DR alleles. The scheme is summarized and extended somewhat in Table 1. The notation used by McCullough assumes that one A and one B allele are already identical in donor and recipient (because worse qualities of match were not considered) and indicates only the second allele at each locus. The character I indicates that the second allele is identical in donor and recipient, the character M indicates that the second allele is mismatched between the donor and recipient, and the character U means that the allele is unknown in the donor. Thus, a perfect match (both A alleles and both B alleles matched between donor and recipient) is designated AI. The next best category defined by McCullough et al is designated ABU and indicates that second A and second B alleles are unknown in the donor (Although not specifically stated by McCullough et al, the remainder of this analysis assumes that the unknown alleles both may be found in the donor, both in the recipient, or one from each.) In a third and still less ideal category, one of the second alleles (either A or B) is identical and the other second allele is mismatched. Such a
match is designated AIBM (mismatching of one B allele) or AMBI (mismatching of one A allele). A fourth category, designated AMBU, is defined as having the second A allele mismatched and the second B allele unknown. We have extended the scheme of McCullough et al to include the categories AIBU and AUBI (mismatching of one second allele with the other second allele unknown) and category AUBM which is analogous to AMBU but with mismatching for one B allele instead of one A allele.

When an allele is unknown in the donor, we assume that either the allele in question is blank, or the donor is homozygous for the locus in question. The two alternatives cannot be distinguished by HLA typing an individual; thus, an allele designated as "unknown" may actually match the recipient identically.

For each category, Table 1 lists the number of distinct A and B antigens detected (in both donor and recipient) and the number of pairs of AB alleles matched, unknown, or mismatched. The maximum number of A and B antigens detected is eight; the maximum number of pairs of alleles matched is four. The categories in Table 1 are listed in descending order of hypothetical quality according to the number of matches, unknown pairings, and mismatches. It is assumed that a mismatch at any locus is worse than an unknown.

<table>
<thead>
<tr>
<th>Category</th>
<th>Recipient</th>
<th>Donor</th>
<th>AB Antigens Detected</th>
<th>AB Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,y</td>
<td></td>
</tr>
<tr>
<td>AIBU</td>
<td>x,y</td>
<td>w,z</td>
<td>x,y,?</td>
<td></td>
</tr>
<tr>
<td>AUBI</td>
<td>x,y</td>
<td>w,z</td>
<td>x,?</td>
<td></td>
</tr>
<tr>
<td>AUBU</td>
<td>x,y</td>
<td>w,z</td>
<td>x,?</td>
<td></td>
</tr>
<tr>
<td>AIBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,y,w,m</td>
<td></td>
</tr>
<tr>
<td>AMBI</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m</td>
<td></td>
</tr>
<tr>
<td>AMBU</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
</tbody>
</table>

The following eight genotypes will be phenotypically identical to the recipient:

<table>
<thead>
<tr>
<th>M</th>
<th>P</th>
<th>M</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ai, Aj]</td>
<td>[Ai, Aj]</td>
<td>[Bi, Bj]</td>
<td>[Bi, Bj]</td>
</tr>
<tr>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
</tr>
<tr>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
</tr>
</tbody>
</table>

Genotypes 1 and 2 are also genotypically identical to the recipient. However, because there is no way of distinguishing among the eight genotypes clinically all eight types would be counted as AIBI matches. (An exception is when the recipient is homozygous for one or two AB alleles in which case actual AIBI matches would appear to be unknown for the homozygous alleles and would thus appear to be AIBU, AUBI, or AUBU.)

**Table 1. Definitions of Complete and Partial Bone Marrow Donor Matches**

<table>
<thead>
<tr>
<th>Category</th>
<th>Recipient</th>
<th>Donor</th>
<th>AB Antigens Detected</th>
<th>AB Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,y</td>
<td></td>
</tr>
<tr>
<td>AIBU</td>
<td>x,y</td>
<td>w,z</td>
<td>x,y,?</td>
<td></td>
</tr>
<tr>
<td>AUBI</td>
<td>x,y</td>
<td>w,z</td>
<td>x,?</td>
<td></td>
</tr>
<tr>
<td>AUBU</td>
<td>x,y</td>
<td>w,z</td>
<td>x,?</td>
<td></td>
</tr>
<tr>
<td>AIBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,y,w,m</td>
<td></td>
</tr>
<tr>
<td>AMBI</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m</td>
<td></td>
</tr>
<tr>
<td>AMBU</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
<tr>
<td>AUBM</td>
<td>x,y</td>
<td>w,z</td>
<td>x,m,w,z</td>
<td></td>
</tr>
</tbody>
</table>

*Each match is represented by two sets of letters corresponding to the A and B loci considered (for HLA-A, for B, for HLA-A, B). Four loci (eight alleles) are represented for each match (two each for A and B). A alleles are represented by x and y; B alleles are represented by w and z. An "m" indicates a mismatch for the corresponding allele; a "?" for an allele indicates a blank (unknown) for the corresponding allele. Thus x,y,w,z would indicate that two A alleles and one B allele are matched. The second B allele is unknown in the donor. A separate line for the schematic is shown in Table 1. For example, the AIBU match can result from a blank for one B allele in the combination that would result in the designation shown in the "Category" column. For example, the AIBU match can result from a blank for one B allele in either the recipient or the donor."

For each category, Table 1 lists the number of distinct A and B antigens detected (in both donor and recipient) and the number of pairs of AB alleles matched, unknown, or mismatched. The maximum number of A and B antigens detected is eight; the maximum number of pairs of alleles matched is four. The categories in Table 1 are listed in descending order of hypothetical quality according to the number of matches, unknown pairings, and mismatches. It is assumed that a mismatch at any locus is worse than an unknown.

SELECTING MATCHES FROM THE DATA BASE

**HLA-Identical (AIBI) Matches**

We consider a recipient whose genotype is

<table>
<thead>
<tr>
<th>M</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ai, Aj]</td>
<td>[Bi, Bj]</td>
</tr>
<tr>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
</tr>
</tbody>
</table>

The following eight genotypes will be phenotypically identical to the recipient:

<table>
<thead>
<tr>
<th>M</th>
<th>P</th>
<th>M</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
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<td>[DRi, DRj]</td>
</tr>
<tr>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
</tr>
<tr>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
<td>[DRi, DRj]</td>
</tr>
</tbody>
</table>

Genotypes 1 and 2 are also genotypically identical to the recipient. However, because there is no way of distinguishing among the eight genotypes clinically all eight types would be counted as AIBI matches. (An exception is when the recipient is homozygous for one or two AB alleles in which case actual AIBI matches would appear to be unknown for the homozygous alleles and would thus appear to be AIBU, AUBI, or AUBU.)
Computing the Probabilities of Partial HLA matches (AIBU, AUBI, AUBU, AIBM, AMBI, AMBU, AUBM)

As an example, consider AIBU partial matches which are defined as identical for both A alleles, both DR alleles, and one B allele. The remaining B allele is unknown. Consider a hypothetical recipient with genotype

\[
\begin{bmatrix}
A_i & A_j \\
B_i & B_j \\
D_{Ri} & D_{Rj}
\end{bmatrix}
\]

Two types of genotypes will provide the requisite matches. The first type consists of genotypes which match the recipient at both A alleles, both DR alleles, and have a blank or null for the remaining B allele. The following combinations meet these criteria (B? indicates the null allele for B):

\[
\begin{bmatrix}
1 & 5 \\
\{A_i & A_j\} & \{A_i & A_j\} \\
\{B? & B_j\} & \{B_i & B?\} \\
\{D_{Ri} & D_{Rj}\} & \{D_{Ri} & D_{Rj}\}
\end{bmatrix}
\]

\[
\begin{bmatrix}
2 & 6 \\
\{A_i & A_j\} & \{A_i & A_j\} \\
\{B? & B_j\} & \{B_i & B?\} \\
\{D_{Rj} & D_{Ri}\} & \{D_{Rj} & D_{Ri}\}
\end{bmatrix}
\]

\[
\begin{bmatrix}
3 & 7 \\
\{A_i & A_j\} & \{A_i & A_j\} \\
\{B? & B_i\} & \{B_j & B?\} \\
\{D_{Ri} & D_{Rj}\} & \{D_{Ri} & D_{Rj}\}
\end{bmatrix}
\]

\[
\begin{bmatrix}
4 & 8 \\
\{A_i & A_j\} & \{A_i & A_j\} \\
\{B? & B_i\} & \{B_j & B?\} \\
\{D_{Rj} & D_{Ri}\} & \{D_{Rj} & D_{Ri}\}
\end{bmatrix}
\]

In addition, another set of genotypes will provide an AIBU match: genotypes which match the recipient at both A alleles, both DR alleles, and are homozygous at the B locus with an allele that matches either of the B alleles of the recipient. This adds the following two genotypes homozygous for Bi:

\[
\begin{bmatrix}
1 & 2 \\
\{A_i & A_j\} & \{A_i & A_j\} \\
\{B_i & B_i\} & \{B_i & B_i\} \\
\{D_{Ri} & D_{Rj}\} & \{D_{Rj} & D_{Ri}\}
\end{bmatrix}
\]

and the following two genotypes homozygous for Bj:

\[
\begin{bmatrix}
1 & 2 \\
\{A_i & A_j\} & \{A_i & A_j\} \\
\{B_j & B_j\} & \{B_j & B_j\} \\
\{D_{Rj} & D_{Rj}\} & \{D_{Rj} & D_{Rj}\}
\end{bmatrix}
\]

Thus, the designation AIBU is an operational one based on phenotypic data and describes a group which is heterogeneous with respect to actual quality of matching. Note that the methodology described here allows one to calculate the probability that a match which is apparently AIBU is actually AIBI.

A process similar to that described for AIBU matches is involved in finding each of the other types of partial matches.

RESULTS

"Whole World" Assumption

The relation between registry size and probability of finding a match assuming that the frequency of haplotypes not listed in published tables is truly zero, is shown in Fig 1A. These data were obtained using a data base of NAC donors and recipients. The horizontal axis represents the log (base 10) of the registry size. The vertical axis represents the probability that a random recipient will have at least one match in a registry of a given size. The shape of the curve is sigmoidal. In the middle range, large changes in probability of matching are achieved with relatively modest increases in registry size. At a certain registry size each of the curves approaches a plateau probability above which further (even massive) increases in registry size provide little increase in the probability of matching. For AIBI matches (the highest quality), this plateau occurs above a log registry size of approximately 6.5 (corresponding to a registry size of approximately 3,000,000). Note that the probability of an AIBI match never exceeds 0.43. This is a consequence of the large number of genotypes in the recipient population which either have blanks for one or both of the DR alleles (41%) or are homozygous for one or more of the alleles (16%). For these genotypes (57% of the recipient population), an AIBI match as defined by McCullough et al cannot be defined.

Figure 1B shows the curve for AIBU matches from Fig 1A, along with curves showing the probability of finding matches of quality AUBU or better which have no mismatched alleles, and the probability of achieving any of the matches defined by McCullough et al. The probability of finding a match of unspecified type asymptotically approaches 0.58 when the log of registry size exceeds 5 (registry size of approximately 100,000). Further increases in registry size beyond 100,000 result in little further increase in the probability of finding a match.

"Assumed Frequency" Assumption

We repeated the entire analysis assuming that all 6,336 possible haplotypes exist and those not detected by the Eighth International Workshop exist in equal numbers to total either 5% or 10% of the population. Again we used data for the NAC population for both the donors and recipients. The results of this analysis for AIBI, AIBU, AUBI, AUBU, and AUBU or better are shown in Fig 2A. Figure 2B displays the results when the frequency of undetected haplotypes (henceforth referred to as "the assumed frequency") totaled either 5% or 10% of the population. Using the whole world assumption for comparison, the corresponding analysis is presented with solid symbols. The plateau probabilities are approximately the same for all three analyses, but under the assumed-frequency assumptions, the plateau is reached more gradually and at a higher registry size than that for the whole world assumption. The higher the assumed frequency, the more gradually the plateau frequency is reached. Thus, the whole-world assumption results in a slightly smaller estimate.
of the size of the registry needed to produce a given probability of matching. As the assumed frequency increases, the plateau probability increases slightly. This occurs because haplotypes with blank alleles for the DR loci (and therefore comprising genotypes ineligible for matches) are over-represented in the detected group. Consequently, the additional genotypes considered when undetected haplotypes are allowed include relatively more genotypes that would be eligible for matches. Because there is no way of knowing which assumption is a better approximation to the truth, we used the computationally faster whole-world assumption for all subsequent analyses.

**Effect of Using a Different Population for Donors and Recipients**

In the published tables for the Japanese population, fewer than 500 A-B-DR three-allele haplotypes are listed. This suggests that the Japanese population is more genetically homogeneous than the NAC population with respect to HLA haplotypes. This was also noted by Takahashi et al who found that smaller registry sizes would be required if both the donors and recipients were derived from the Japanese population. Analysis of donor and recipient pools consisting of only the listed haplotypes (and using the whole-world assumption) produced the results shown in Fig 3, which also summarizes the results for the NAC population for comparison. Note that for AIBI matches, the plateaus are lower for the Japanese population (compared with that for the NAC population) because the Japanese population includes a higher relative frequency of genotypes containing blank alleles and a larger frequency of genotypes with homozygous alleles. This is of less consequence for the AUBU-or-better category of match, which can include genotypes with blank alleles. Because the universe of genotypes is smaller using
Fig 2. Effect of the assumed-frequency assumption. (A) The horizontal and vertical axes are the same as for Fig 1. Again, all curves represent analyses for which both donor and recipient populations are of NAC ancestry and the assumed frequency represents a total of 5% of the population. A separate curve is shown for each quality of match better than or equal to AUBU and a composite curve for the probability of attaining an AUBU-or-better match. (B) The whole-world assumption is contrasted with assumed frequency totaling 5% and assumed frequency totaling 10% for AIBI and AUBU-or-better matches. See text for explanation of the assumed frequency.

For a registry of unrelated bone marrow donors, we have defined the probability of finding a matching donor for a random recipient as a function of registry size and match quality. For any combination of donor and recipient populations, and for any quality of match, the relation between the probability of match and the log registry size is sigmoidal, reaching a plateau above which further increases in registry size do not result in further increases in the probability of finding a match. The significance of the plateau for a given quality of match is that with increasing registry size, the probability of finding the match in question approaches unity for the fraction of the recipient population for which such a match is possible. A similar plateau phenomenon was found...
by Beatty et al in their analysis and also attributed to the occurrence of blank alleles. Note, however, that the analysis we have presented is based on an operational definition of HLA matching, one based on phenotype. Some donor matches which apparently have blank alleles are actually homozygous and therefore may be HLA-identical to the recipient. However, given the fact that potential donors are identified in a registry according to their phenotypes, this distinction could not be made before the selection of a potential donor from the registry. As HLA typing technology improves, the frequency of blank alleles should decrease and thus the estimated performance of a registry should improve accordingly.

We began our analysis using the assumptions that donor and recipient populations have equivalent HLA haplotype frequencies and that the makeup of the populations are essentially as described by the Eighth International Workshop on Histocompatibility Testing. Given these assumptions, the maximum chance of an AIBI (HLA phenotypically identical) match is 43% and requires a registry containing approximately 3 million donors. A registry of that size will provide a 58% chance of finding at least one match which is equal to or better in quality than AUBU (DR-identical and no mismatched alleles).

Because of genetic linkage disequilibrium, a small number of common HLA haplotypes comprise most of the population. Consequently, any analysis must be based on empirically derived HLA haplotypes. These data, compiled periodically by the International Workshop, are imperfect because they are based on a limited sample size. With the enormous number of haplotypes in the population, it has not been practical to examine enough subjects to define frequencies for some of the rare types.

We made two alternative assumptions to deal with these limited data. We first assumed that the undetected haplotypes do not exist in the population, an assumption that should underestimate the required registry size. We then assumed that all of the minor types exist in equal frequencies, an assumption that should overestimate the required registry size. These boundary cases, which bracket the true relationship, are contrasted in Fig 2B. A different kind of extreme case—that in which the undetected portion of the population consists of only one single haplotype—is equivalent to adding one relatively common genotype to the population. The results would not differ significantly from the whole-world assumption. Only additional empirical HLA haplotype frequency data will be able to indicate which of these extremes is closer to the truth.

Patients with leukemia, who at this time make up the vast majority of bone marrow recipients, may have a different distribution of HLA haplotypes than members of the general population. Differences have been found in the frequency of certain HLA antigens in patients with leukemia, notably Cw3, but only one of these associations (AW19) is at an HLA locus known to be important in BMT. There is no way of knowing before hand how such an altered distribution would affect the performance of a registry; data sufficient to examine this hypothesis have not yet been published. Beatty
et al. used a registry of patients who had already received BMT to simulate the recipient pool.\textsuperscript{24} However, this group of patients is not necessarily representative of all BMT candidates because patients with more common HLA phenotypes were more likely to have found donors and therefore be included in the recipient registry. We simulated discordance between donor and recipient pools by performing an analysis of the relationship between registry size and probability of matching using a recipient pool of Japanese ancestry and a donor pool of NAC ancestry. In this simulation the probability of finding identical (AIBI) matches was drastically reduced, but the probability of finding less perfect matches was affected much less. If the recipient population were to contain common HLA haplotypes at a higher frequency or null alleles at a lower frequency than the donor population, the probability of matching actually could be better and the required registry size lower than our estimate.

We did not consider the likelihood that a given match will have a negative MLC because data about the relationship between match quality and MLC results are limited. If potential donors are to be rejected when the MLC results are positive, then our analysis will have somewhat underestimated the registry size requirements.

In 1985 a National Institutes of Health technology assessment conference\textsuperscript{29} concluded that a centralized national registry of volunteer bone marrow donors should not be established at that time. Nevertheless, a national registry has since been established and determining the optimal number of registered donors remains an important issue.

The method presented here provides a framework for determining probabilities of matching for any pairing of donor and recipient populations. It clarifies the major determinants of the probability of matching and consequent registry size requirements as follows: (1) homogeneity of the donor and recipient populations, which increases the rate at which the plateau probability is approached; (2) homology between donor and recipient populations, which affects both the magnitude of the plateau and the rate at which it is approached; and (3) the frequency of genotypes with blank and homozygous alleles in the donor and recipient populations, which affects the magnitude of the plateau.

A previous analysis\textsuperscript{24} yielded results that were qualitatively similar to ours. Our work has analyzed the extent to which discordance of the donor and recipient populations reduces the probability of finding donors and has extended the analysis to partial matches as defined by a currently functioning registry of unrelated donors.\textsuperscript{10}

The methodology can be extended to include other alleles such as HLA-C or the Class II alleles of DP and DQ as data regarding the importance and population frequency of these alleles become available. Application of the method should be a useful adjunct to future consideration of registries for bone marrow donors.

**REFERENCES**


29. Registries for Bone Marrow Transplantation: NIH Technology Assessment Meeting, May 13-15, 1985, sponsored by National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute and the National Cancer Institute, and the Office of Medical Applications of Research.
Bone marrow donor registries: the relation between registry size and probability of finding complete and partial matches [see comments]

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