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Research article

Availability of HLA-allele-matched unrelated donors and registry size: Estimation from haplotype frequency in the Italian population

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ABSTRACT

In Italy, an HLA-matched unrelated donor is currently the primary donor when a HLA matched sibling is not found for allogeneic haematopoietic stem cell transplantation (HSCT). Better outcomes for transplantation require optimal matching between donor and recipient at least at the HLA-A, -B, -C, and -DRB1 loci; therefore, the availability of HLA-matched unrelated donors is important. The enormous HLA polymorphism has always necessitated registries with a large number of individuals in order to be able to provide well-matched donors to a substantial percentage of patients. In order to increase the efficiency of the Italian Bone Marrow Donor Registry (IBMDR) in providing Italian patients with a suitable donor, the probability of finding an HLA-A, -B, -C, and -DRB1 allele-matched (8/8) or a single mismatch unrelated donor (7/8) was estimated in this study according to IBMDR size. Using a biostatistical approach based on HLA haplotype frequencies of more than 100,000 Italian donors enrolled in the IBMDR and HLA-typed at high-resolution level, the probability of finding an 8/8 HLA-matched donor was 23.8%; 33.4%; and 41.4% in simulated registry sizes of 200,000; 500,000; and 1,000,000 donors; respectively. More than 2 million recruited donors are needed to increase the likelihood of identifying an HLA 8/8 matched donor for 50% of Italian patients.

If one single mismatch at HLA I class loci was accepted, the probability of finding a 7/8 HLA-matched donor was 62.8%; 73.7%; and 80.3% in 200,000 donors; 500,000; and 1,000,000 donors; respectively.

Using the regional haplotype frequencies of IBMDR donors, the probability of recruiting a donor with a new HLA phenotype, in the different Italian regions, was also calculated. Our findings are highly relevant in estimating the optimal size of the national registry, in planning a cost-effective strategy for donor recruitment in Italy, and determining the regional priority setting of recruitment activity in order to increase the phenotypic variability of IBMDR as well as its efficiency.

1. Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) is largely used as a potential curative treatment for patients with malignant and non-malignant haematological diseases. An HLA-identical sibling is still considered the preferred donor, but 30% or less of patients in need of a HSCT have such a source of stem cells available. Consequently, for the remaining 70% of patients, alternative sources such as unrelated donors or haploidentical donors must be found.

Although cord blood or haploidentical donors are potential options [1–3], an unrelated donor that matches with the corresponding patient, at least for HLA-A, -B, -C, and -DRB1 at high-resolution (HR) (HLA 8/8 matched), is the best options [4].

Since 2008, Italy has had a higher number of transplants from unrelated donors than those from matched sibling donors, and

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Table 1
The 50 most common HLA haplotypes observed in the Italian population.

Rank	HLA Haplotype				Frequency
	A	B	C	DRB1	
1	01:01g	08:01g	07:01g	03:01g	*0.025357*
2	02:01g	18:01g	07:01g	11:04g	*0.011435*
3	30:01g	13:02g	06:02g	07:01g	*0.010879*
4	29:02g	44:03g	16:01g	07:01g	*0.010829*
5	03:01g	07:02g	07:02g	15:01g	*0.010167*
6	33:01g	14:02g	08:02g	01:02g	*0.009459*
7	24:02g	35:02g	04:01g	11:04g	*0.009276*
8	30:02g	18:01g	05:01g	03:01g	*0.008925*
9	03:01g	35:01g	04:01g	01:01g	*0.007673*
10	01:01g	57:01g	06:02g	07:01g	*0.006078*
11	11:01g	35:01g	04:01g	01:01g	*0.005041*
12	23:01g	44:03g	04:01g	07:01g	*0.004771*
13	02:01g	13:02g	06:02g	07:01g	*0.004577*
14	02:01g	35:01g	04:01g	14:01g	*0.004511*
15	02:01g	07:02g	07:02g	15:01g	*0.004326*
16	11:01g	35:01g	04:01g	14:01g	*0.004191*
17	24:02g	18:01g	12:03g	11:04g	*0.004070*
18	02:01g	18:01g	05:01g	03:01g	*0.003987*
19	02:05g	50:01g	06:02g	07:01g	*0.003841*
20	02:01g	08:01g	07:01g	03:01g	*0.003554*
21	24:02g	18:01g	07:01g	11:04g	*0.003441*
22	23:01g	49:01g	07:01g	11:01g	*0.003120*
23	26:01g	38:01g	12:03g	13:01g	*0.003038*
24	02:05g	58:01g	07:01g	16:01g	*0.002856*
25	24:02g	07:02g	07:02g	15:01g	*0.002715*
26	02:01g	51:01g	15:02g	11:01g	*0.002711*
27	02:01g	57:01g	06:02g	07:01g	*0.002604*
28	01:01g	52:01g	12:02g	15:02g	*0.002543*
29	01:01g	15:17g	07:01g	13:02g	*0.002512*
30	02:01g	44:02g	05:01g	04:01g	*0.002458*
31	02:01g	44:02g	05:01g	11:01g	*0.002458*
32	25:01g	18:01g	12:03g	15:01g	*0.002451*
33	01:01g	35:02g	04:01g	11:04g	*0.002418*
34	02:01g	51:01g	01:02g	11:01g	*0.002297*
35	11:01g	52:01g	12:02g	15:02g	*0.002279*
36	02:01g	18:01g	07:01g	11:01g	*0.002149*
37	02:01g	44:02g	05:01g	13:01g	*0.002074*
38	24:02g	13:02g	06:02g	07:01g	*0.002074*
39	01:01g	37:01g	06:02g	10:01g	*0.002046*
40	02:01g	39:01g	12:03g	16:01g	*0.001893*
41	24:02g	08:01g	07:01g	03:01g	*0.001840*
42	11:01g	35:01g	04:01g	11:01g	*0.001839*
43	02:01g	38:01g	12:03g	13:01g	*0.001800*
44	68:01g	44:02g	07:04g	11:01g	*0.001793*
45	03:01g	07:02g	07:02g	11:01g	*0.001788*
46	02:01g	51:01g	14:02g	11:01g	*0.001776*
47	02:01g	51:01g	02:02g	11:01g	*0.001755*
48	02:01g	18:01g	12:03g	11:04g	*0.001706*
49	01:01g	08:01g	07:01g	11:01g	*0.001701*
50	02:01g	35:01g	04:01g	01:01g	*0.001643*

unrelated donation is currently the first source for allogeneic HSCT [5].

This is because of the large number of unrelated potential donors (currently more than 38 million adults) that have enrolled worldwide [6]. Despite the existence of these large registries, many patients cannot find a fully matched unrelated donor in time to have a successful transplant.

Unfortunately, owing to the high level of HLA polymorphism in the Italian population [7,8], less than 43% of Italian patients who need HSCT are currently able to find an HLA 8/8 unrelated matched donor in national and international registries [9], dramatically less than the rest of the white European descent population [10].

The Italian Bone Marrow Donor Registry (IBMDR), established in 1989, manages volunteer recruitment and the countrywide database search in order to facilitate the HSCT from unrelated donors. IBMDR currently comprises 460,000 potential donors, but only about 240,000 are typed with an HR method for the HLA-A, -B, -C, and -DRB1 alleles.

Therefore, the IBMDR is able to provide Italian matched donors only for 20–25% of Italian patients [11]. For the remaining patients, HSCT is performed by importing stem cell donations from international registries.

Nevertheless, considering 3210 Italian recipients transplanted in the last four years with an adult donor, we found that the percentage of fully matched pairs is higher for Italian patient/Italian donor pairs compared to the Italian patient/non Italian donor pairs (75.3% vs. 64.5%, $P < 0.001$) [11].

In a recent Italian analysis on behalf of GITMO (Italian Group for Bone Marrow Transplants), AIBT (Italian Association of Transplant Biology) and IBMDR [12], it was shown that the Italian pair's origin played a considerable protective role on the incidence of GvHD, suggesting that recipient–donor pairs, originating from the same geographic area, may be considered at lower risk of GvHD onset.

Further investigations with a larger number of pairs are needed to reveal the mechanisms as to how regional geographic similarity of pairs impacts transplant outcomes, but nevertheless this study

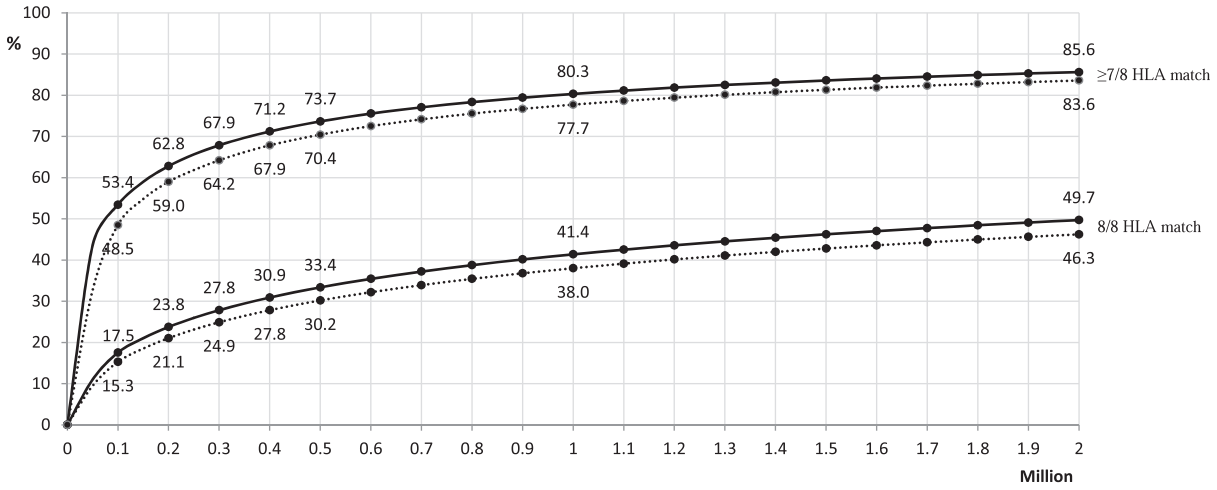


Fig. 1. Probabilities of finding a ≥7/8 or 8/8 matched donor in Italy. Likelihood of finding a 8/8 HLA match or ≥7/8 with a HLA-A, or -B, or -C mismatch, by different donor registry size in Italy (black) and estimated with the current rate of donor availability (dotted).

Table 2
Probabilities of finding a fully matched donor in Italian regions with a dataset >1000 donors.

Italian Region*	N Donors	Resident Population** 18–55 yy aged	Index***	MP by Size of Regional registries (× 1000)									
				50	100	150	200	250	300	350	400	450	500
Veneto	17,933	2,429,060	73.8	17.9	24.7	29.3	32.7	35.5	37.8	39.9	41.6	43.2	44.6
Lombardia	14,314	4,993,285	28.7	16.5	23.0	27.3	30.7	33.4	35.7	37.6	39.4	40.9	42.3
Piemonte	14,180	2,093,693	67.7	15.5	21.7	25.9	29.2	31.8	34.0	35.9	37.6	39.1	40.5
Emilia Romagna	12,023	2,169,343	55.4	16.6	23.2	27.7	31.1	33.8	36.1	38.1	39.9	41.4	42.9
Puglia	8015	2,051,204	39.1	17.3	24.2	28.9	32.5	35.4	37.9	40.0	41.9	43.5	45.0
Sicilia	5409	2,565,721	21.1	17.9	25.3	30.2	34.0	37.0	39.6	41.8	43.7	45.5	47.0
Sardegna	4611	832,729	55.4	46.5	54.4	59.0	62.2	64.7	66.7	68.3	69.8	71.0	72.1
Trentino	4384	532,149	82.4	24.1	32.2	37.6	41.5	44.7	47.3	49.6	51.5	53.3	54.8
Toscana	4133	1,795,467	23.0	18.9	26.4	31.4	35.3	38.4	41.0	43.2	45.2	46.9	48.5
Friuli VG	3498	577,164	60.6	23.0	32.0	38.0	42.4	46.0	48.9	51.4	53.5	55.4	57.1
Liguria	3201	714,161	44.8	20.8	28.7	34.0	38.0	41.1	43.8	46.1	48.1	49.8	51.4
Lazio	2927	3,010,711	9.7	18.2	26.0	31.4	35.5	38.8	41.6	44.0	46.1	47.9	49.6
Calabria	2286	998,358	22.9	21.9	30.9	36.9	41.5	45.2	48.2	50.8	53.0	55.0	56.8
Campania	2267	3,052,139	7.4	22.5	31.5	37.5	42.0	45.6	48.6	51.2	53.3	55.3	57.0

Likelihood of finding a 8/8 HLA matched regional donor for a random patient of the same Italian region.
*Italian region with less than 1000 donors (Umbria, Molise and Valle D'Aosta) were excluded from this analysis.
**ISTAT (Italian National Institute of Statistics) 1/1/2019.
***Ratio index calculated on the resident population having the same age as our donors (18–55 years) × 10,000.

suggests that ethnic origin of pairs may be considered an adjunctive prognostic factor, probably HLA-related, when selecting donors.

Consequently, there is the need to develop and maintain a useful and efficient national registry of unrelated donors; thereby increasing the possibility of identifying a fully matched donor and using available HLA allele and haplotype frequencies [13–15], to establish efficient recruitment and strategy planning.

Schmidt et al. reported that population-specific matching probabilities (MP) are a key parameter to assess the benefit of unrelated stem cell donor registries and need for further donor recruitment efforts [13]. In fact, the knowledge of population-specific HR HLA haplotype frequency distributions facilitates individual donor searches and provides the theoretical background for estimating the chance for a patient to find fully matched donors in the registry.

The availability of HLA 8/8 and 7/8 matched donors was estimated by applying the method used in previous studies [16,17]. Using the published haplotype frequencies from IBMDR HR HLA typed donors [18] at the national and regional levels, the MP according to the Italian donor registry size was calculated.

To the best of our knowledge, this is the first analysis to estimate the probability of finding an HLA-matched unrelated donor based on the largest Italian haplotype database.

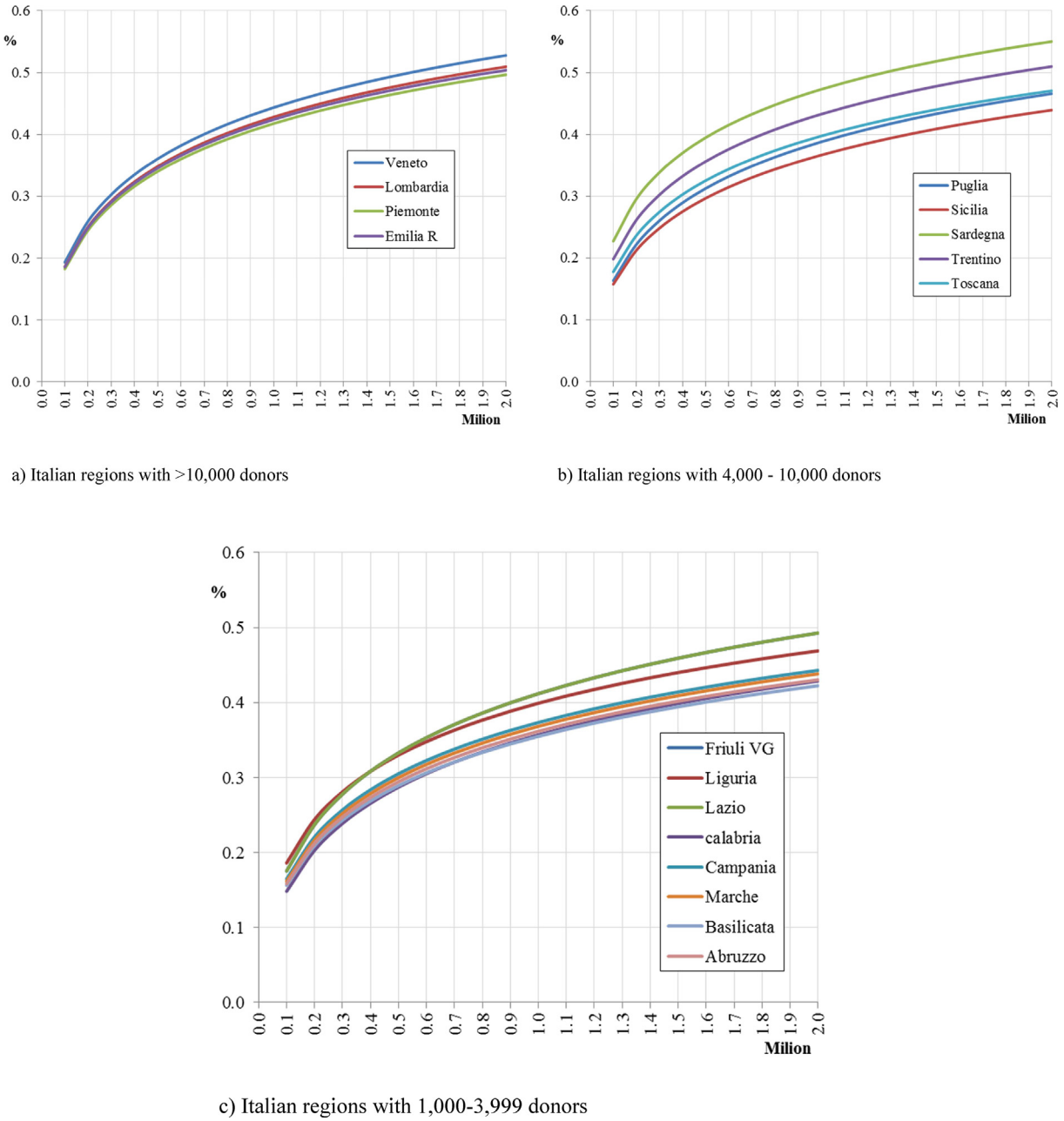
Therefore this study provides relevant insights and tools in estimating the optimal size of the Italian registry and in planning a cost-effective strategy for donor recruitment.

2. Materials and methods

2.1. Data source

The Italian national and regional HR four-loci haplotype frequencies, as reported previously [18], were used in this analysis. In brief they were obtained from the 120,926 HLA-A, -B, -C, and -DRB1 HR donors, typed at the recruitment step and registered in the IBMDR database at the end of December 2017.

The same approach of Schmidt et al. was applied: alleles with synonymous mutations inside or outside the relevant exons were merged to the corresponding two field alleles, and alleles that differed by nonsynonymous mutations outside the relevant exons were merged [13]. The resulting alleles were characterised through the letter "g" (for "group") that was appended to the first possible



a) Italian regions with >10,000 donors

b) Italian regions with 4,000 - 10,000 donors

c) Italian regions with 1,000-3,999 donors

Fig. 2. Likelihood of finding a 8/8 HLA match by different Italian regional registry size (× 1000) for a patient of the same regional origin estimated in the Italian regions with a dataset >1000 donors.

allele [19,20]. Finally, the national frequencies of the HLA-A, -B, -C, and -DRB1 alleles and haplotypes were estimated using the EM algorithm with the Arlequin software package (version 3.5.2.2; Excoffier & Lischer, 2010 [21]). This algorithm calculated the frequencies of the 25,057 most frequent HR four-loci haplotypes according to a cumulative frequency of 99.99%. The HLA haplotype regional frequencies were estimated in a study [18] using a dataset of 104,135 donors grouped into the 20 Italian regional populations according to the donors' birthplace.

To estimate if the regional sample sizes (RSS) obtained were representative of the specific regional population, we applied the same approach as in other studies [22] which define the RSS as acceptable when the ratio between sampled individuals/resident population is >5/10,000.

2.2. Statistical analysis

Genotype frequencies can be derived from known haplotype frequencies; using the same approach described by Schmidt et al., we estimated the probability of finding at least one HR HLA 8/8-matched donor in the Italian Registry for a random Italian patient [13].

For this purpose, we used the formula described below.

Given a population A characterised by n haplotypes with frequencies h_i ($i = 1,\ldots,n$) and a population B described by n' haplotype frequencies h'_i ($i = 1,\ldots, n'$), the probability $P(N)$ for a random individual from population A to find at least one HLA matching individual in a size N sample from population B was calculated as:

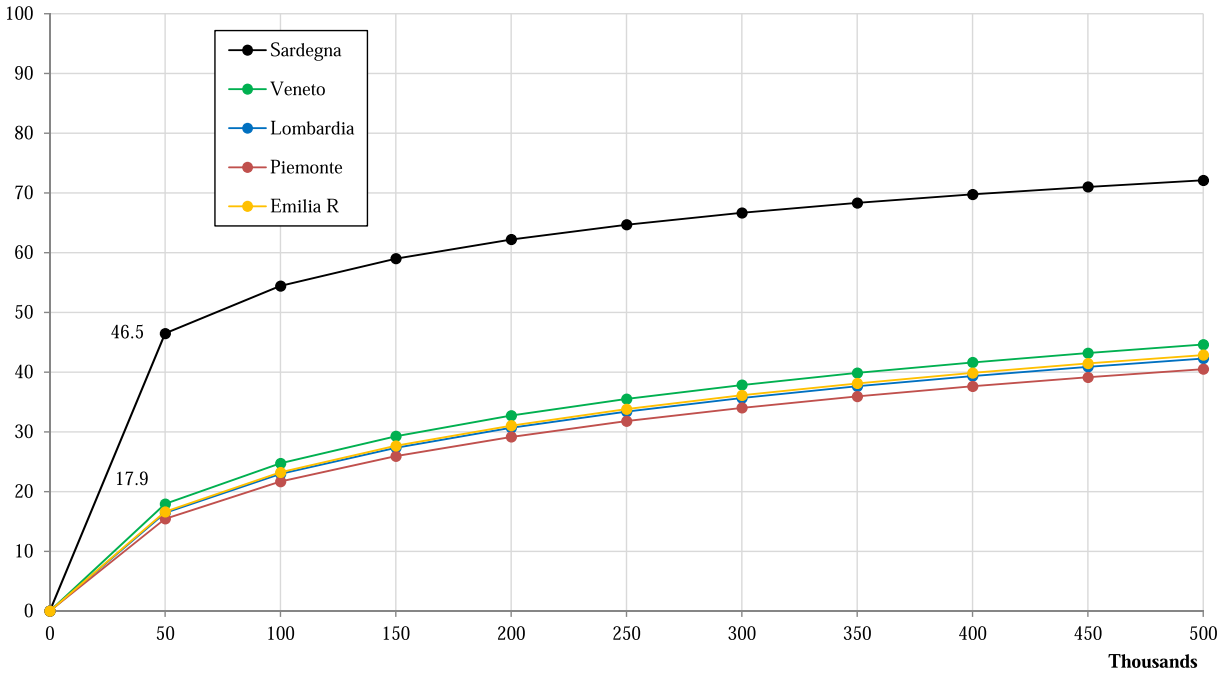


Fig. 3. Likelihood of finding a 8/8 HLA match donor for patients of the same regional origin estimated in Sardegna and in the Italian regions with more than 10,000 recruited/potential donors.

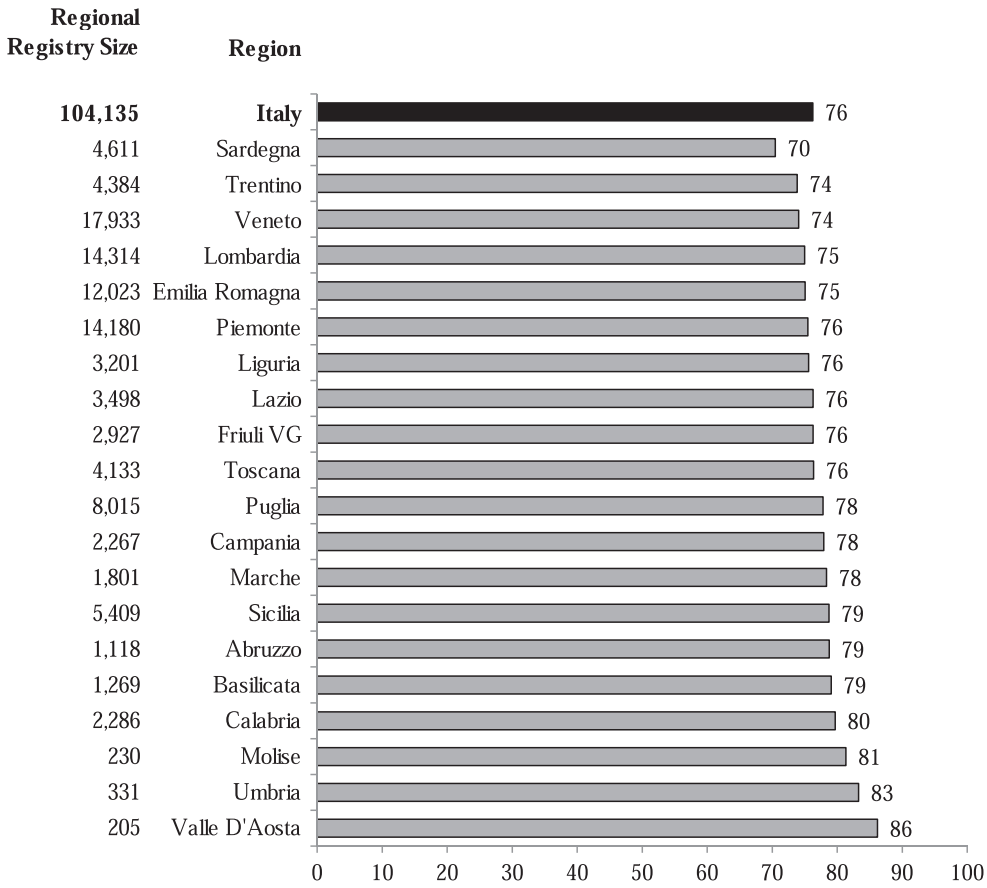


Fig. 4. Probability that a new donor recruited in a specific Italian region introduces a new HR HLA-A, -B, -C, and -DRB1 phenotype not yet existing in the current Italian national database.

$$P(N) = \sum_{i=1}^{n} \sum_{j=i}^{n} kh_i h_j \left(1 - (1 - p_{ij})^N\right)$$

where $k = 1$ if $i = j$, $k = 2$ if $i \neq j$, and p_{ij} indicates the probability of finding an individual 8/8 matching with genotype ij in population B using the following:

$$p_{ij} = \sum_{c=1}^{n'} \sum_{g=c}^{n'} wh'_c h'_g m,$$

where $w = 1$ if $c = g$, $w = 2$ if $c \neq g$ and, $m = 1$ only if the genotype cg is 8/8 matched with ij (otherwise $m = 0$).

At verification typing and at work-up, IBMDR average rate of donor availability is 76% [11]. We also estimated the probability $P^{av}(N)$, for a random individual from population A, to find at least one HLA matching individual in a size N registry with a 76% availability rate, modelling the formula as:

$$P^{av}(N) = \sum_{i=1}^{n} \sum_{j=i}^{n} kh_i h_j \left(1 - (1 - p_{ij})^{0{,}76N}\right)$$

To conduct our study, we assume that the haplotype frequencies of patients are similar to those of the Italian donor population. If A represents the recipient population and B the donor population, and it is assumed that they are not different from each other, $P(N)$ indicates the probability that a randomly chosen Italian patient will find at least one HLA-compatible donor according to the size N of the Italian Registry. As the Italian regional HLA frequency is of potential relevance for the optimisation of stem cell donor recruitment, we also calculated these probabilities at the regional level.

In Italy, in cases of unsuccessful worldwide identification of an 8/8 HLA-matched unrelated donor, the majority of national transplant programmes preferably select unrelated donors with a single mismatch at HLA-A, HLA-B, or HLA-C loci, avoiding DRB1 mismatching.

In order to analyse the MP in a mismatched scenario, we applied the most frequent matching criteria currently used in our country. Therefore, we calculated the probability $P^*(N)$ that an Italian patient will find, as a minimum, an unrelated donor with one single HLA mismatched at class I and two matched HLA-DRB1 alleles, depending on the size N of the Italian Registry.

Similar to previous formulas, $P^*(N)$ depends on the p^*_{ij}, and the probability to find in population B an individual $\geq$ 7/8 matching with genotype ij is determined using:

$$p^*_{ij} = \sum_{c=1}^{n'} \sum_{g=c}^{n'} wh'_c h'_g m^*$$

where $m^* = 1$ if the genotype cg is $\geq$ 7/8 matched with ij and otherwise $m^* = 0$.

As above, we also estimated the probability to find in population B an available $\geq$ 7/8 matched individual by multiplying the sample size N by the coefficient 0.76.

The $P(N)$ value also represents the probability that a new donor randomly selected by the Italian population (A) has a phenotype already represented in a registry of size N (population B). Then, using the same formulas and estimation approach, it is possible to calculate the probability $P^{new}(N)$ that a new registered donor introduces a new HLA phenotype:

$$P^{new}(N) = 1 - P(N)$$

Applying the same methodology, the probability of finding a fully matched donor in a donor–patient combination of the same Italian region was also calculated in the regions with a dataset greater than 1000 donors to avoid bias due to the too small sample size of some regions.

3. Results

The list of the 50 most common four-loci haplotypes found in Italy is shown in Table 1. The cumulative frequency of these 50 haplotypes is 22%. The chance that an individual carries one or two of these 50 frequent haplotypes is 39%, computed as

$$1 - (1 - HF_{50})^2$$

Fig. 1 shows the curves of MP in case of an 8/8 HR matching donor and at least a 7/8 HR compatible donor with only one HLA I class mismatch.

The probabilities of finding a fully matched donor were 17.5% in 100,000; 23.8% in 200,000; 27.8% in 300,000; 30.9% in 400,000; 33.4% in 500,000; 41.4% in 1,000,000; and 49.7% in 2,000,000 donors.

As the registry size increased by 100,000; the probabilities increased by 6.3%, 4.0%, 3.1%, and 2.5%, respectively.

In addition, the probabilities of finding a $\geq$7/8 matched donor were 53.4% in 100,000; 62.8% in 200,000; 67.9% in 300,000; 71.2% in 400,000; 73.7% in 500,000; 80.3 % in 1,000,000; and 85.6%% in 2,000,000 donors.

The Fig. 1 shows also the 8/8 and 7/8 MP affected by the current IBMDR donor availability rate (AR). The impact of the donor AR causes a decrease of the theoretical matching probabilities from 2.2 to 3.4 in the 8/8 values and from 2 to 4.9 in 7/8 values.

The probability of finding a fully matched donor in a donor–patient combination of the same Italian region in the regions with a dataset greater than 1000 is reported in Table 2.

Fig. 2 shows the curves of 8/8 MP in these Italian regions, calculated for a patient of a given region searching in the same regional population.

Since it is well known by previous studies [18,22], that Sardegna has HLA haplotype frequencies significantly deviating from the national ones, we estimated the MP for Sardegna patient searching in Sardegna donor pool compared with patients from regions with more than 10,000 registered donors (Veneto, Lombardia, Piemonte and Emilia Romagna) searching in their respective regional pool of donors (Fig. 3).

Considering a hypothetical regional donor size of at least 50,000 donors, among the other regions, it is evident that Sardegna can guarantee a fully matched donor to 46.5% of patients from Sardegna.

In the other regions analysed with the same number of donors, the MP observed was considerably smaller (<20%).

The approach that utilises the previously obtained regional haplotype frequency data [18], was used to calculate the probability that a new donor recruited in a specific Italian region introduces a new HR HLA-A, -B, -C, and -DRB1 phenotype not yet existing in the entire Italian national database. This probability is between 74% and 86% in all Italian regions, except for Sardegna where it is lower (Fig. 4).

4. Discussion

This study provides important information for defining donor recruitment targets in Italy and the consequent planning for resource allocation in order to support the registration and HLA typing of new donors.

According to our findings (Fig. 1) at a realistic registry size of 500,000 HR HLA-typed donors, 33.4% (30.2% with AR) of Italian patients have an 8/8 fully matched IBMDR donor and at a registry size of 1 million donors, the MP increases to 41.4% (38% with AR).

Table 3
Registry sizes and corresponding probabilities of finding a HLA A,B,C, DRB1 HR matched donor for IBMDR and ZKRD national registries.

	MP by Size of registries (× 1000)		
	25%	50%	75%
German Registry - ZKRD- European Caucasian population [23]	38	458	6292
Italian Bone Marrow Donor Registry - Italian population	248	2050	>15,000

Similar studies were conducted using other population haplotype frequencies as German [23], Japanese [14], USA Caucasian [10], and Polish [24] populations, and the MP estimated at the same size of these registries is significantly higher.

In Table 3 we compared our findings with those estimated in the German national registry [23], since they are calculated in a west European-Caucasian population.

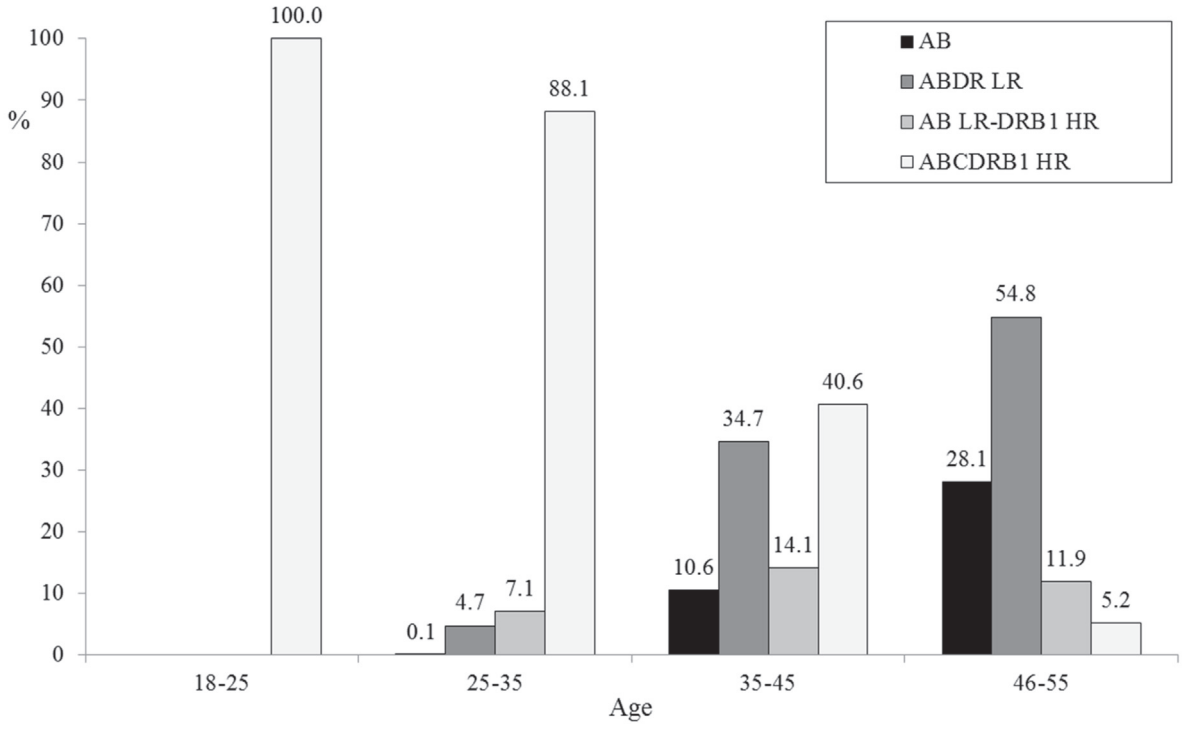
In the Italian registry the same percentage of patients capable of finding a 8/8 matched donor is obtained with a pool of donors dramatically higher than in the German registry, six-folds greater for MP 25%, four-folds for MP 50% and more than two-folds for MP 75%.

This is probably because of the high HLA polymorphism in the Italian population described in previous studies [7,8,22], suggestive of some evolutionary pressure toward allele diversification or resulting from several migratory waves, and it also partially justifies the consequent difficulties faced by Italian patients to find an 8/8 matched unrelated donor.

Starting from 2011 IBMDR decided to optimize its recruitment strategy by recruiting only donors younger than 36 years and by typing them in HR.

At the end of 2020, the IBMDR consisted almost 460,000 registered donors, and 184,837 (40.1%) were HR HLA-A, -B, -C, and -DRB1 loci typed and younger than 35 (Fig. 5).

These pool of donors are, obviously, more likely to be selected, since they are fully typed and it is well demonstrated the positive effect of younger donor age on survival [25].



	Age				
HLA typing	18-25	26-35	36-45	46-55	Total
AB	0	85	12,413	40,475	52,973
ABDR LR	0	5,640	40,794	79,111	64,563
AB LR-DRB1 HR	0	8,439	16,615	17,209	42,263
ABCDRB1 HR	79,888	104,949	47,817	7,467	240,121
Total	79,888	119,113	117,639	144,262	460,902

Fig. 5. HLA typing level and age of IBMDR donors (31/12/2020).

Table 4
Rate of international and national donations on behalf of Italian recipients transplanted in 2019 and 2020, with inclusion and exclusion of Sardegna patients.

Set of patients	International donors	IBMDR donors	% IBMDR donors	TOTAL
Italian patients (Sardegna patients excluded)	1264	389	23.53	1653
SARDEGNA patients	19	15	44.12	34
Total	1283	404	23.95	1687
Test: Pearson Chi-Square		p = 0.005		

Consequently in 2020, 91% of donations (262/288) came from the pool of HR HLA-typed donors, and 81% (213/262) of these donors were younger than 35 years.

This means that the probability for an individual from this "younger HR HLA-typed donor" subset to be selected for stem cell donation is approximately 12/10,000, more than four-folds greater than the rest of IBMDR donors (approximately 2.7/10,000; $P < 0.0001$).

The number of Italian patients transplanted with an unrelated donors in 2019 and 2020 [11] was 1687, 1283 (76%) with international donors and 404 (24%) with IBMDR donors (Table 4).

As expected, the only region that is more self-sufficient than the rest of Italy is Sardegna: patients of Sardegna origin found a matched donor in IBMDR in 44.12% of cases, and mainly from Sardegna donor pool (9/15).

The rest of Italian recipients were transplanted with an IBMDR donor only in 24% of cases.

This is radically smaller than the MP for identifying $\geq$ 7/8 Italian matched donors. According to our findings, it would have been 63%, considering the HR HLA-typed donor dataset currently available (Fig. 1).

This is not due to the rate of unavailability of donors once selected for a specific patient, since its impact is limited and it evidently affects both 8/8 and 7/8 matched donors.

Therefore, this is not the main reason of a smaller selection of IBMDR mismatched donors for Italian patients.

In Italy the expenses of the unrelated donor search and donation are fully covered by the national health system (NHS), with no indication or preference in the selection of IBMDR donors rather than international ones. Therefore if a fully matched or 7/8 younger donor is found worldwide it is preferably selected for donation instead of a 7/8 IBMDR donor.

As consequences partially matched or low-resolution HLA-typed donors remain unselected [26] in the IBMDR pool even if it potentially matches with a specific patient according to the Search & match service [27] prediction search algorithms.

In fact in 2020 only 713 IBMDR donors were selected from IBMDR partially typed donor inventory for additional typing and only 26 of them donated [11].

In addition, we have to consider the great improvement of haploidentical transplant in Italy that competes with a mismatched unrelated donor. A relative donor is immediately available, and recent studies show that the overall survival rates in haploidentical and mismatched unrelated donor transplants are very similar [28].

Recent studies [29] show encouraging results with the use of post-transplantation cyclophosphamide GvHD prophylaxis after HSC transplantation from unrelated mismatched donors. This could have practical implications, allowing an increased selection of 7/8 mismatched IBMDR donors for high-risk patients.

Nevertheless, according to the above-mentioned considerations, our first goal must be to improve patients' chances of finding an optimal match. Therefore, the Italian recruitment strategy must be focused on increasing the MP of IBMDR-matched young donors.

Currently IBMDR database includes 240,000 (52%) of HR fully typed individuals.

If we consider a reasonable target of 500,000 young HR HLA-typed donors, more than 30% of Italian patients have a potential 8/8 fully matched IBMDR donor and 70% of patients could find at least an HLA I class mismatched available donor.

To reach this goal in a suitable time frame, considering the attrition rate of the deleted donors that is currently 12,000–15,000 individuals per year, and the donor unavailability rate effect we need to recruit donors massively in the next five years, registering at least 50,000/60,000 new donors per year.

In addition, we have to consider that the rate of increasing the MP of finding an HLA-matched donor will become smaller as the registry size increases because the probability of introducing a new phenotype decreases. Therefore, an efficient system of recruitment must increase the number of available HLA phenotypes, introducing new phenotypes while registering new donors. For this reason, it is also important to know which Italian regions have a greater impact on match probabilities for donor recruitment due to their higher polymorphism.

According to our findings, the recruitment in almost all Italian regions—except Sardegna,—can still introduce a new phenotype in 80% of cases.

The introduction of such large numbers of new donors has inevitable economic and resource-related implications that need to be carefully addressed. In Italy, the cost to register a new donor into the IBMDR is covered by the regional NHS. Furthermore, the regional NHS pays several million euros per year to international registries, in order to import 80% of donations from abroad.

The increase in the national usage of IBMDR donors consequently increases the self-sustainability of the national unrelated transplant programme, saving a large sum of the money that is currently utilised for HSC import.

This saved money can in turn be used as an investment in national recruitment of HR HLA-typed unrelated donors.

It needs to be emphasized that the model used in this work is focused strictly on patient benefits that were operationalized by the probability to find at least one HLA-matched donor.

Many factors can affect the economic implications of this plan, including the time needed to reach a major recruitment efficiency, cost of donor recruitment, donor attrition rate, and selection requirements such as donors' gender and ethnic backgrounds; therefore, an evaluation of its cost and efficiency would require a more in-depth analysis.

Nevertheless, our findings are helpful in estimating the optimal size of our national registry and in planning a cost-effective strategy for donor recruitment in Italy with regional priority setting of recruitment activity in order to increase the phenotypic variability of IBMDR as well as its efficiency.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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