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REVIEW

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Immunogenetics in stem cell donor registry work: The DKMS example (Part 1)

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Abstract

Currently, stem cell donor registries include more than 35 million potential donors worldwide to provide HLA-matched stem cell products for patients in need of an unrelated donor transplant. DKMS is a leading stem cell donor registry with more than 9 million donors from Germany, Poland, the United States, the United Kingdom, India and Chile. DKMS donors have donated hematopoietic stem cells more than 80,000 times. Many aspects of donor registry work are closely related to topics from immunogenetics or population genetics. In this two-part review article, we describe, analyse and discuss these areas of donor registry work by using the example of DKMS. Part 1 of the review gives a general overview on DKMS and includes typical donor registry activities with special focus on the HLA system: high-throughput HLA typing of potential stem cell donors, HLA haplotype frequencies and resulting matching probabilities, and donor file optimization with regard to HLA diversity.

KEYWORDS

DKMS, donor registry, HLA, unrelated hematopoietic stem cell transplantation

1 | INTRODUCTION

DKMS was founded in May 1991, growing out of the search for a stem cell donor for Mechtild Harf. Since then, the DKMS donor file has grown to 9,601,738 donors from six countries. DKMS donors have donated stem cells 80,847 times for patients from 57 various countries (cut-off date: 30 September 2019).

In this two-part review article, we describe, analyse and discuss aspects of DKMS's work that are related to immunogenetics or population genetics. Part 1 of the review includes, apart from a general overview on DKMS, typical donor registry activities that are closely related to the HLA system: high-throughput HLA typing of potential stem cell donors, HLA haplotype frequencies and resulting matching probabilities, and donor file optimization with

regard to HLA diversity. The second part of the review (Schmidt et al., in press), on the other hand, focuses on non-HLA parameters and DKMS activities beyond the scope of standard donor registry work. Topics addressed include donor typing beyond the classical HLA loci, impact of non-HLA parameters on donation probabilities, identification of novel HLA, KIR and MIC alleles, activities of the Collaborative Biobank and pharmacogenetics in the donor registry context.

We do not cover central donor registry issues as donor recruitment or donor safety comprehensively, but only related to immunogenetics or population genetics. Besides, we focus on adult donors and do therefore not include the activities of the DKMS Cord Blood Bank.

2 | DKMS OVERVIEW: DONORS AND DONATIONS

Figure 1 shows the quantitative development of the DKMS donor registry since 1991. At the end of 2018, it included 8.7 million donors, accounting for 24.2% of the global WMDA donor file of 35.9 million donors excluding cord blood units (WMDA, 2019).

The regional and ethnic compositions of the DKMS UK and DKMS Germany donor files are shown in Figures 2 and 3, respectively. Corresponding figures for the other DKMS country organizations are included as Supplementary Material (Figures S1–S4). The ethnic grouping applied in the various countries differs due to administrative and societal reasons. At DKMS Poland, no ethnic information is gathered. Donor numbers by ethnicities in the various national DKMS donor registries are also included in the Supplementary Material (Tables S1–S6). For these tables, ethnic categorization was converted into seven population groups: AFA (African/African American), API (Asian/Pacific Islander), EURO (European), HIS (Hispanic), MENA (Middle East/North Coast of Africa), NAM (Native American) and UNK (unknown, multiple ancestries or other). Due to the nature of the information available, all donors from DKMS Poland were regarded as EURO and all donors from DKMSBMST (Bangalore Medical Services Trust) Foundation India as API.

Considerable regional differences in the registered DKMS donors to total population ratio exist in all countries. In the United Kingdom, for example, the share of registered donors ranges from 0.3% to 3.2%. Similarly, the proportion of registered donors ranges from 3.8% to 15.0% in Germany. Though DKMS was founded after the German reunification, the territory of the former German Democratic Republic (East Germany) is considerably underrepresented in the DKMS donor registry. It is possible to focus donor recruitment efforts geographically in order to exploit regional HLA haplotype frequency differences (see paragraph *Donor file optimization*). However, the inter-region differences displayed in Figures 2 and 3 occur for other reasons including unequal activities of local supporter groups, spotty distribution of large patient-oriented donor drives, recruitment efforts of non-DKMS donor registries and socio-economic differences between regions.

Figures 2 and 3 also show significant differences in the share of donors of non-European and non-German descent, respectively, ranging from 0.3% to 85.3% for the United Kingdom and from 1.2% to 22.1% for Germany. (Donors of unknown descent were excluded from these analyses.) Rural areas generally show a lower share of donors of non-European (Figure 2) and non-German (Figure 3) descent. Registered donors of non-German descent are also underrepresented in East Germany. These differences correlate with the composition of the general population.

Figure 4 shows the development of donations (bone marrow and peripheral blood stem cells alone; donor lymphocytes and cord blood are not included) from DKMS donors over time. So far, DKMS donors

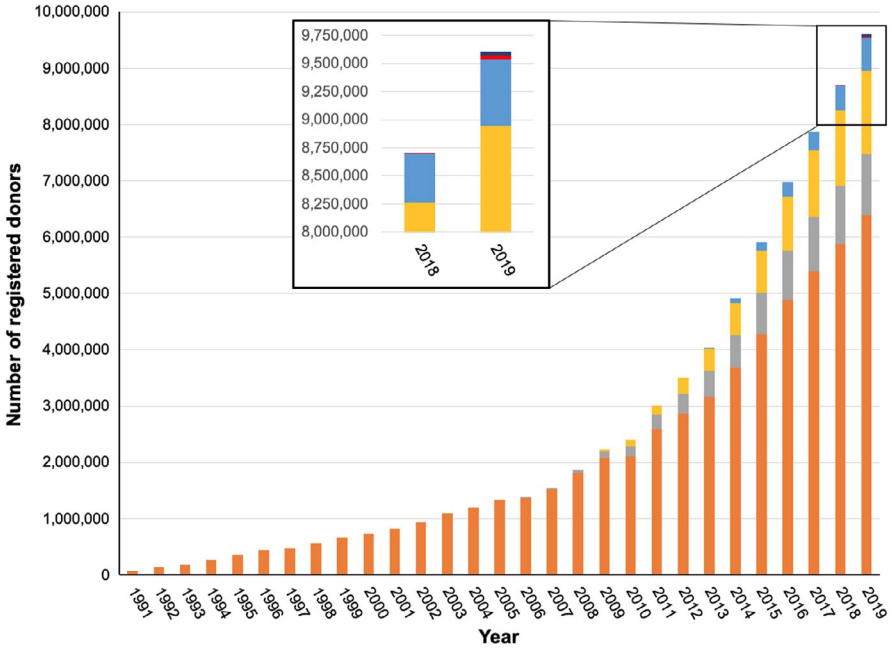

FIGURE 1 Number of registered DKMS donors by country and year. Germany: orange; United States: grey; Poland: yellow; United Kingdom: light blue; Chile: red; India: dark blue. Cut-off date: 30 September 2019 [Colour figure can be viewed at wileyonlinelibrary.com]

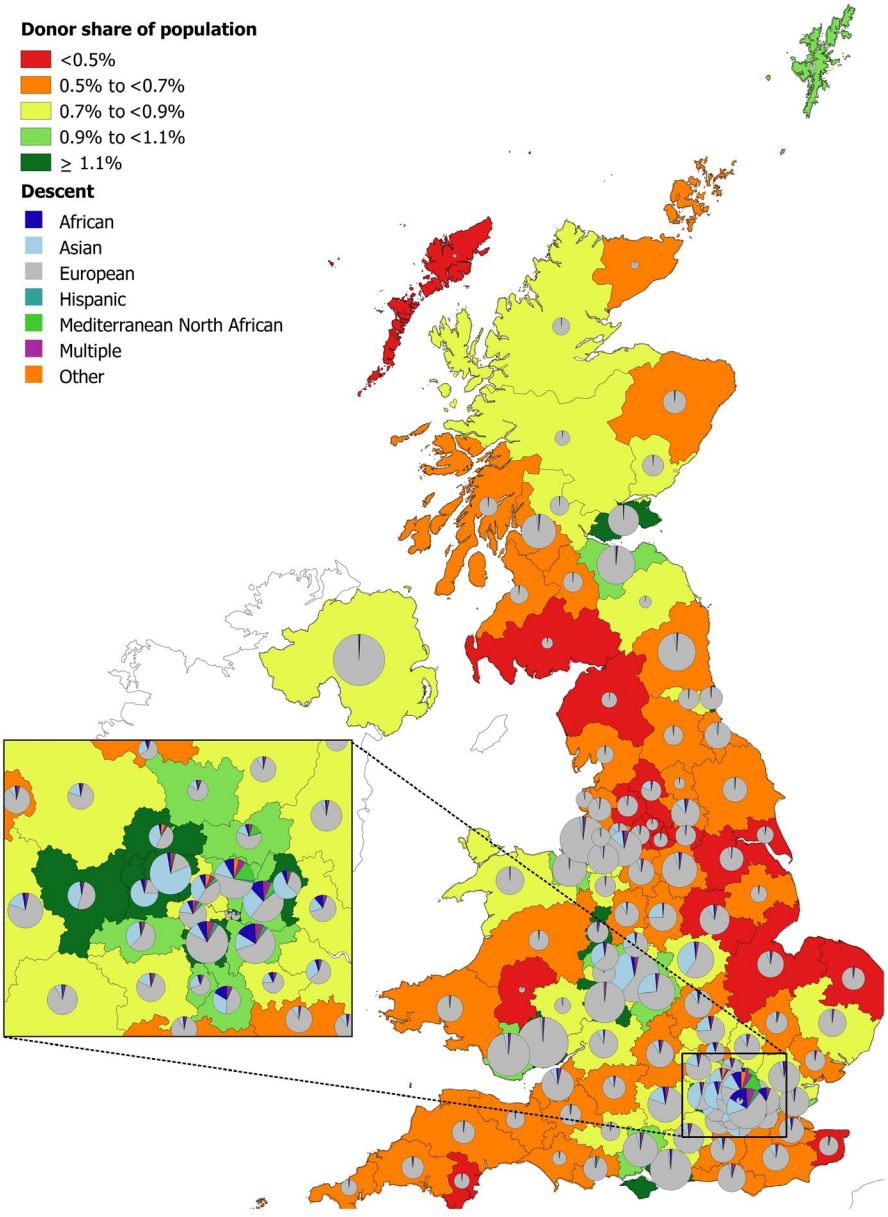

FIGURE 2 Postcode areas in the United Kingdom. For each area, the number of DKMS donors is represented by the size of the corresponding pie chart. Slices of the pie charts indicate the area-specific ethnic composition of the DKMS donor file. The share of donors of non-European descent ranges from 0.3% (postcode area KW = Kirkwall) to 85.3% (HA = Harrow). Colouring of the areas indicates the ratio between DKMS donors and the total population. The proportion of registered donors ranges from 0.3% (postcode area HS = Outer Hebrides) to 3.2% (WR = Worcester). The map was created with QGIS 2.12 software (QGIS Development Team, 2015). Shapefile © 2015 by Open Door Logistics (http://www.opendoorlogistics.comwileyonlinelibrary.com]) [Colour figure can be viewed at wileyonlinelibrary.com]

have donated stem cells 80,847 times (cut-off date: 30 September 2019). In 2018, there were 7,488 donations from DKMS donors; 5,592 (74.7%) cross-border. Patients receiving transplants from DKMS donors were from the United States (1,891, 25.3%), Germany (1,571, 21.0%), France (491, 6.6%), the United Kingdom (432, 5.8%), Italy (348, 4.6%) and 46 other countries (2,755, 36.8%). The DKMS share of all donations worldwide was 39.5% while the share of all cross-border donations was 59.7%. Given the DKMS share of the global donor pool of 24.2% at the end of 2018, potential donors registered with DKMS donated stem cells disproportionally often. A detailed analysis of the reasons for this fact is beyond the scope of this review. However, contributing factors may include donor age and gender distributions (Schmidt et al., in press, paragraph *Donation probabilities*), donor typing level (see paragraph *Donor typing: Classical HLA loci*; Schmidt et al., in press, paragraphs *Donor typing: Beyond the classical HLA loci* and *Donation probabilities*), donor availability, process speed and quality, and pricing of stem cell products.

3 | DONOR TYPING: CLASSICAL HLA LOCI

The rise of next-generation sequencing (NGS) technologies has dramatically changed donor registry HLA typing over the last few years. At DKMS Life Science Lab (LSL), NGS entered routine for high-throughput typing of new donors in early 2013. Since then, more than 6.1 million newly registered DKMS donors have been typed for the six "classical" HLA genes (A, B, C, DRB1, DQB1 and DPB1) at high resolution with an amplicon-based approach using Illumina devices (Lange et al., 2014; Schöfl et al., 2017).

High-throughput HLA typing using NGS technology showed substantial advantages over Sanger sequencing (Sanger, Nicklen, & Coulson, 1977): First, it enabled substantial typing cost reductions. Figure 5 shows full costs per sample for NGS-based compared with Sanger-based HLA typing at DKMS LSL. These "real-life" data are based on official financial reports, that is, they are not controlled for factors influencing full costs per sample as,

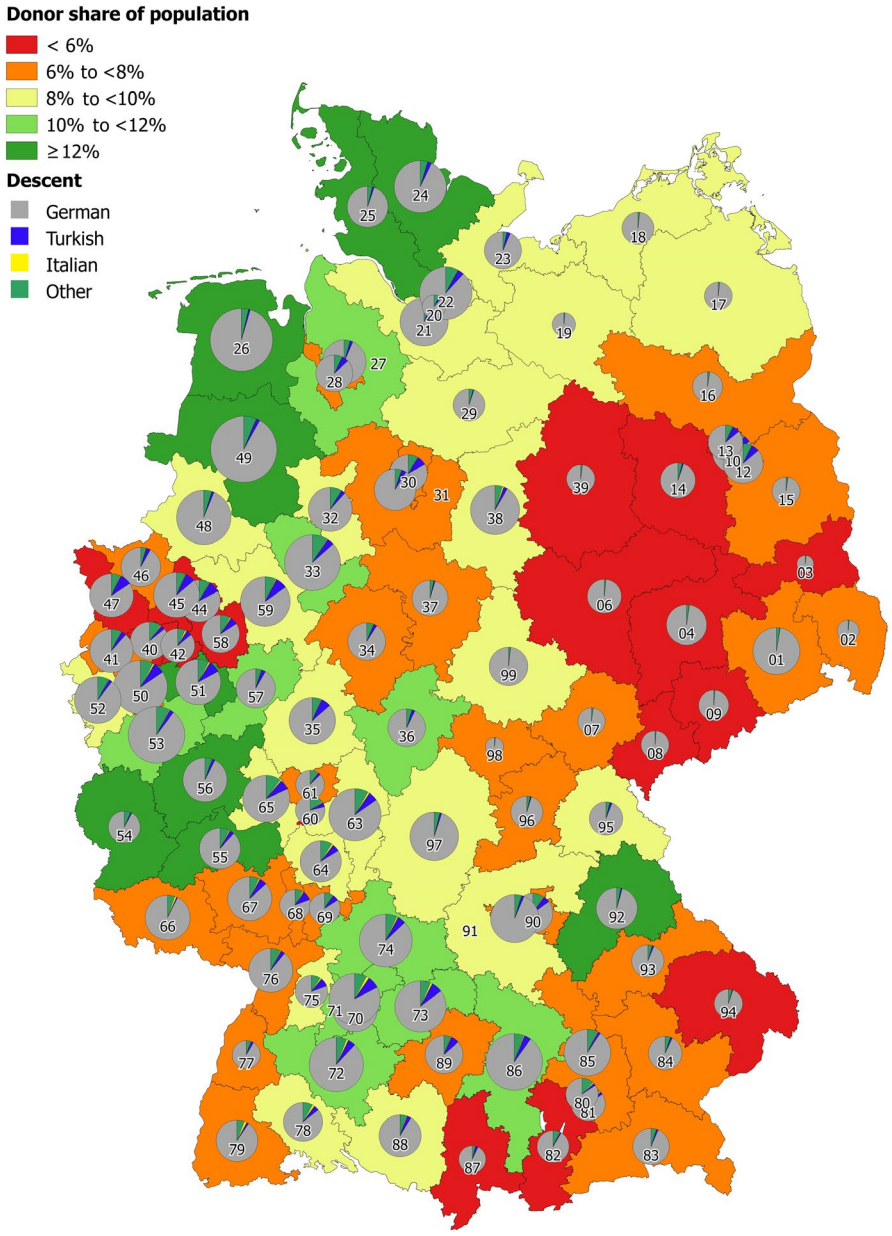

FIGURE 3 Two-digit postcode areas in Germany. For each region, the number of DKMS donors is represented by the size of the corresponding pie chart. Slices of the pie charts indicate the area-specific ethnic composition of the DKMS donor file. The share of donors of non-German descent ranges from 1.2% (postcode area 08 = Plauen) to 22.1% (70 = Stuttgart). Colouring of the areas indicates the ratio between DKMS donors and the total population. The proportion of registered donors ranges from 3.8% (postcode area 06 = Halle (Saale)) to 15.0% (56 = Koblenz and 49 = Osnabrück). The map was created with QGIS 2.12 software (QGIS Development Team, 2015). Shapefile © 2015 by Open Door Logistics (http://www.opendoorlogistics.comwileyonlinelibrary.com]) [Colour figure can be viewed at wileyonlinelibrary.com]

for example, typing volume, salary increases or inflation. However, the dramatic NGS-related cost reduction by 85.5% from 64.4 to 9.3 cost units per HLA typing is very clear in spite of these methodological limitations. Second, we were able to reduce ambiguities by applying NGS: we obtained high-resolution results for >99.9% of all HLA loci typed with NGS in the last 12 months compared to 95.0% with Sanger sequencing (Lange et al., 2014). Third, the typing error rate for NGS-based HLA typing was 3.5 times lower than the Sanger error rate. The low locus-wise error rate of 0.024% including sample switches (less than one error in 4,000 loci) even challenges the necessity of a standard confirmatory typing step before donor work-up (Baier et al., 2019). Fourth, the use of NGS facilitated the identification and whole-gene sequencing of novel HLA alleles (Albrecht et al., 2017; Schmidt et al., in press, paragraph *Identification of novel alleles*). Fifth, the quality and cost efficiency of NGS-based HLA typing allowed the realization of scientific projects at reasonable effort. For example, we could show that the HLA-DPB1 expression marker rs9277534 can be predicted from standard genotyping of DPB1 exons 2 and 3 with 100% accuracy (Schöne et al., 2018).

It is currently under debate whether donor selection should be based on donor-recipient matching of whole HLA genes (Mayor et al., 2019; Vazirabad et al., 2019) or whether HLA typing of gene regions coding for the antigen recognition domain (ARD) plus consideration of frequent null alleles is adequate for stem cell donor selection (Hurley & Ng, 2019; Hurley et al., 2019). While we have used NGS-related cost savings to extend the DKMS standard typing profile beyond HLA (Schmidt et al., in press), we have not included whole-gene HLA typing in the standard typing profile so far. This decision was the result of cost-benefit considerations: at DKMS LSL, the introduction of whole-gene HLA typing would have more than doubled typing costs for the extended standard

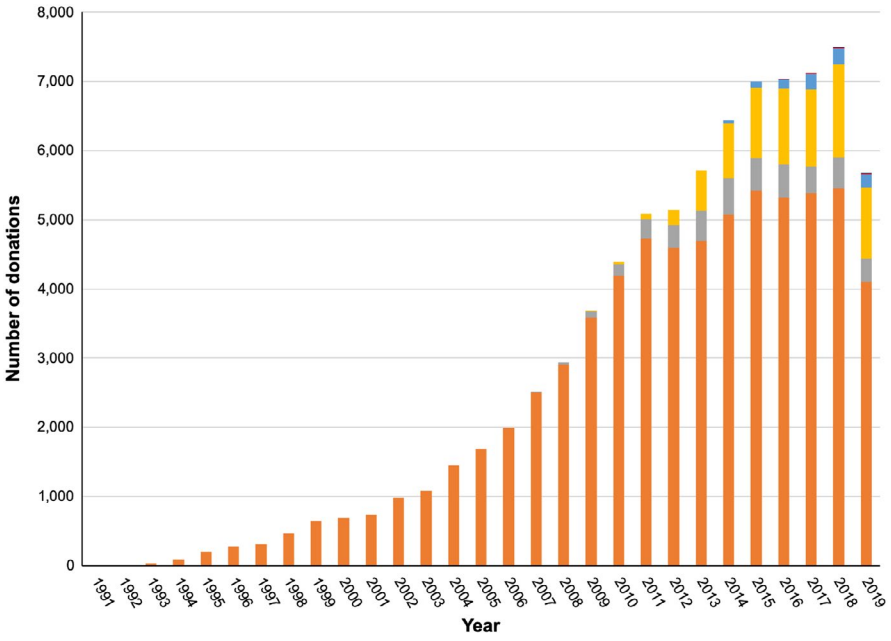

FIGURE 4 Number of stem cell donations by DKMS donors by country and year. Germany: orange; United States: grey; Poland: yellow; United Kingdom: light blue; Chile: red; India: dark blue. Cut-off date: 30 September 2019 [Colour figure can be viewed at wileyonlinelibrary.com]

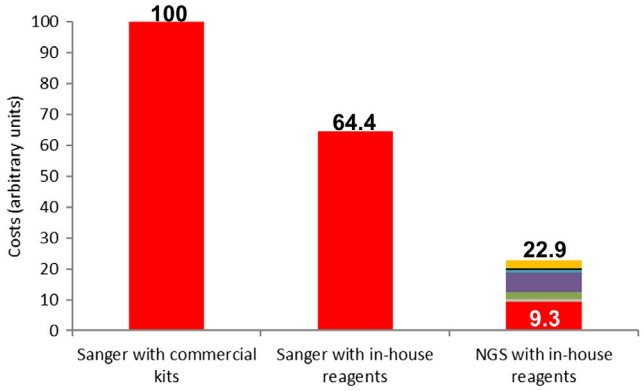

FIGURE 5 Typing costs at DKMS LSL by typing method. Red: HLA (6 loci at high resolution); grey: CCR5Δ32; green: ABO, Rh; purple: KIR (allele groups); blue: MICA/MICB; black: HLA-E; yellow: CMV (from swabs) [Colour figure can be viewed at wileyonlinelibrary.com]

typing profile shown in Figure 5. Besides, it is currently doubtful if these substantial additional costs will be outweighed by respective patient benefits due to optimized donor selection by whole-gene donor-patient HLA matching. With increasing evidence for potential benefits of whole-gene matching and/or decreasing costs for whole-gene HLA typing, possibly through the introduction of new sequencing devices (Lang et al., 2018), this decision may be re-assessed.

In contrast, "complete" HLA typing—at the very least the ARD of the 4 genes HLA-A, -B, -C and -DRB1 (Lee et al., 2007)—at donor recruitment is undoubtedly beneficial for patients as incompletely typed stem cell donors may not be identified in stem cell donor searches (Sauter, Solloch, Giani, Hofmann, & Schmidt, 2016; Schmidt, Solloch, Baier, et al., 2011a). Besides, incomplete donor HLA typing at recruitment does not adequately utilize donor commitment as incompletely typed donors advance to donation less often than donors who are better typed (Dubois et al., 2011; Müller, Feldmann, Bochtler, Morsch, & Schmidt, 2012; Nicoloso, Kürsteiner, Bussmann, Marbacher, & Tiercy, 2019; Schmidt, Stahr, Baier, Ehninger, & Rutt, 2006). The current donor selection guidelines by NMDP and CIBMTR recommend donor and patient HLA typing for at least 5 HLA genes (A, B, C, DRB1 and DPB1) at high resolution (Dehn et al., 2019).

However, many donor registries that have grown over decades still have donors with insufficient HLA typing profiles on their files. DKMS Germany, for example, currently (cut-off date: 30 September 2019) still includes 102,895 donors (1.6% of the total DKMS Germany donor file) who are typed only for two loci (HLA-A and -B). Five years ago (30 September 2014), the respective number was 283,436 (7.9% of the then donor file). Apart from usual donor attrition, for example by reaching the age limit, this decrease was the result of considerable re-typing efforts focused on young male donors. As a result, only 794 of the 102,895 poorly typed donors are males below 40 years.

The general question, if limited donor registry resources should rather be used for donor recruitment or for re-typing of insufficiently typed donors who are already on the donor file, is of considerable practical relevance. Unfortunately, it is hardly possible to determine the optimal trade-off between recruitment and re-typing quantitatively. However, it seems unwise to stop donor recruitment completely because newly recruited donors rejuvenate the donor file (Schmidt, Biesinger, Baier, Harf, & Rutt, 2008; Schmidt et al., in press, paragraph *Donation probabilities*). On the other hand, a complete waiver of re-typing efforts may not be appropriate, either, as poorly typed donors will become increasingly "invisible" for donor searches, and their donation probabilities will decrease over time.

4 | HAPLOTYPE FREQUENCIES AND MATCHING PROBABILITIES

In unrelated stem cell donation, the knowledge of population-specific HLA haplotype frequencies (HF) is desirable for two reasons: First, HF can be used to estimate the probability that the next patient of a defined population finds a matching donor in a donor registry of given size and ethnic composition (Beatty, Mori, & Milford, 1995; Bergstrom, Garratt, & Sheehan-Connor, 2009; Müller, Ehninger, & Goldmann, 2003). Obviously, such matching probabilities (MP) are highly relevant for strategic donor registry planning. Second, population-specific HF make it possible to estimate the chances of incompletely typed donors to be full HLA matches in specific donor searches. Today, such estimations are carried out automatically for large donor files by state-of-the-art donor search algorithms as OptiMatch (Bochtler, Beth, Eberhard, & Müller, 2008), HapLogic (Dehn et al., 2016) or Hap-E Search (Pingel et al., 2012).

Population-specific HF can be derived from unphased HLA genotype data of registered stem cell donors via an expectation-maximization (EM) algorithm (Excoffier & Slatkin, 1995). We developed the Hapl-o-Mat software for HF estimation from large data sets with heterogeneous resolution, typing ambiguities and missing loci, that is from typical donor registry data (Sauter, Schäfer, & Schmidt, 2018;

TABLE 1 Overview on published haplotype frequency (HF) and/or matching probability (MP) estimations based on DKMS donors

Country	Population	Sample size	Source	Remarks/Specific focus
Germany	German	8,862	Schmidt, Baier, et al. (2009a)	• 3- and 4-locus HLA haplotypes at low resolution (LR) and high resolution (HR) • Impact of matching requirements on matching probabilities (MP)
Germany	German	319,009	Schmidt et al. (2010)	• 3-locus HLA haplotypes at LR • Regional HLA differences
Germany	German	1,099,735	Eberhard et al. (2010)	• 3-locus HLA haplotypes (class I at LR, class II at HR) • Impact of selective HLA-DRB1 typing (based on class I typing results) on HF estimations
Germany	German	370,856	Sauter et al. (2016)	• 5-locus HLA haplotypes at HR • Impact of completeness of donor HLA typing on search success
Germany	German	100,000 (20,000)	Figures 7, 9, S5; Table S7	• 5-locus HLA haplotypes at HR
Germany	Turkish	9,086	Schmidt, Solloch, et al. (2009b)	• 3-locus HLA haplotypes at LR • Impact of ethnic diversity recruitment efforts
Germany	Turkish	100,000	Figure 7, S5; Table S8	• 5-locus HLA haplotypes at HR
Germany	17 minority populations	1,028–33,083	Pingel et al. (2013)	• 4- and 5-locus HLA haplotypes at HR • Impact of population-specific HF on individual donor searches
Germany, Poland, United States	21 populations	1,028–33,083	Schmidt et al. (2014)	• 4-locus HLA haplotypes at HR • Includes also non-DKMS donors (from NMDP) • Optimization of global donor recruitment efforts • Sample size effects
Poland	Polish	20,653	Schmidt, Solloch, Pingel, et al. (2011b)	• 4-locus HLA haplotypes at HR • Validation of implementation of EM algorithm • Impact of donor recruitment in Poland on MP for Polish patients
Poland	Polish	123,749	Schmidt et al. (2013)	• 4-locus HLA haplotypes at HR • Regional HLA differences • Sample size effects
Poland	Polish	100,000	Figure 7, S5; Table S9	5-locus HLA haplotypes at HR
United Kingdom	English/Scottish/Welsh	100,000 (20,000)	Figures 7, 9, S5; Table S10	5-locus HLA haplotypes at HR
United Kingdom	English	20,000	Figure 8, S5; Table S11	5-locus HLA haplotypes at HR
United Kingdom	Indian	20,000	Figure 8, S5; Table S12	5-locus HLA haplotypes at HR
United Kingdom	Scottish	20,000	Figure 8, S5; Table S13	5-locus HLA haplotypes at HR
United Kingdom	Welsh	20,000	Figure 8, S5; Table S14	5-locus HLA haplotypes at HR
United States	European	100,000	Figure 7, S5; Table S15	5-locus HLA haplotypes at HR

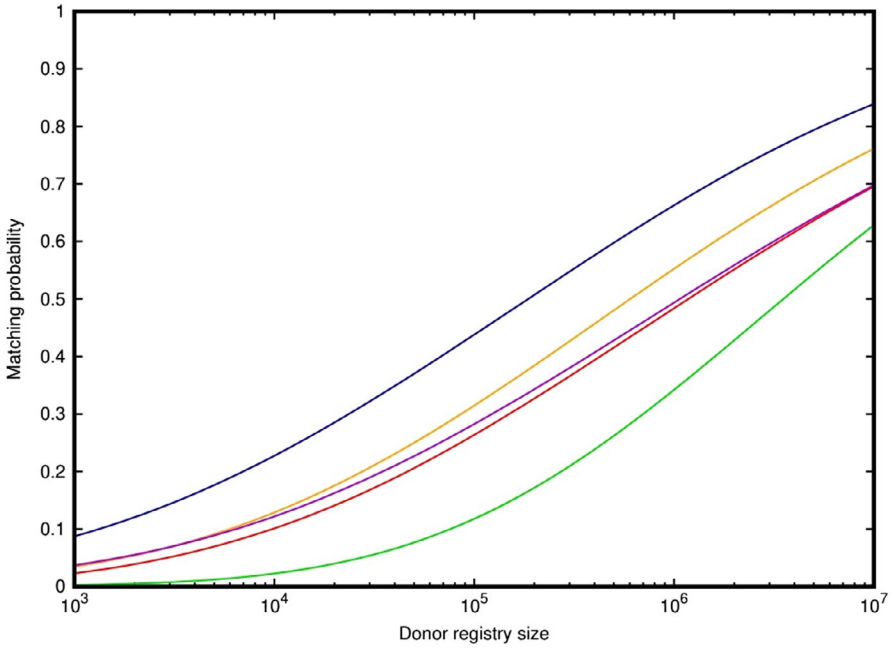

FIGURE 6 Matching probabilities by donor registry size for various populations (all sample sizes n = 100,000). Red: Germany (country of recruitment), German (population); green: Germany, Turkish; orange: Poland, Polish; blue: United Kingdom, English/Scottish/Welsh; purple: United States, European [Colour figure can be viewed at wileyonlinelibrary.com]

Schäfer, Schmidt, & Sauter, 2017). Hapl-o-Mat is freely available at https://github.com/DKMS/Hapl-o-Mat.

Table 1 gives an overview on published HF and MP estimations based on DKMS donor data. For this article, we added estimates for further populations (also included in Table 1). The respective HF are given in the Supplementary Material (Tables S7–S15). Cumulative frequencies of the 1,000 most frequent haplotypes range from 0.572 (Turkish minority in Germany, sample size n = 100,000) to 0.839 (Scottish, n = 20,000; see Figure S5). Corresponding MP for scenarios in which donor and patient populations are identical are shown in Figures 6 and 7. In good accordance with HF estimation results, MP are especially high for Scottish donors and patients (p = .537 at donor registry size n = 100,000) and especially low for Turkish donors and patients (p = .122; n = 100,000). The more realistic scenario with combined donor populations, thus simulating global donor searches, has been discussed in the literature (Bergstrom et al., 2009; Schmidt, Sauter, Pingel, & Ehninger, 2014).

One major methodological difficulty of combining HF and MP estimations lies in dealing with small HF. Figure 8 shows plateaus in the HF distribution curves that are corresponding to small integer multiples of $f = 1/(2n)$—the frequency of a haplotype that occurs exactly once in the sample—as the HF are approaching that value (Pappas, Tomich, Garnier, Marry, & Gourraud, 2015). These HF plateaus that are more prominent for smaller sample sizes are artefacts and affect subsequent MP estimations. Furthermore, estimated HF smaller than $1/(2n)$ are generally of limited informative value as they correspond to less than one occurrence of the respective haplotype in the underlying sample. However, all haplotypes with estimated $f \geq 1/(2n)$ sum up to, for example, only 93.0% (90.6%) in the sample with n = 100,000 (n = 20,000) German donors. Therefore, it seems to be not appropriate to ignore all haplotypes below that threshold for MP estimations. For the estimations shown in Figures 6 and 7, we started with the most frequent haplotypes, considered all haplotypes up to a cumulated HF of 99.5% and then normalized all HF above this threshold (Schmidt et al., 2014).

5 | DONOR FILE OPTIMIZATION

It is well known that the marginal benefit of donor recruitment efforts decreases considerably with increasing donor file size as new donors often carry HLA genotypes that are already on the file. Therefore, the large number of registered DKMS donors raises questions regarding the efficiency of ongoing donor recruitment efforts. DKMS and other donor registries have developed and applied several strategies aimed at maximizing donor recruitment efficiency with regard to a stronger MP increase, especially for patients from population groups that have been underserved so far. These strategies include:

1. Ethnic diversity donor recruitment. It is a common understanding that, if the population living in the geographical area where a donor registry recruits donors is not homogeneous, it is important to target donor recruitment efforts not only at the majority population but also at the minority population(s) (Confer, 2001; Fingrut, 2015; Heinemann et al., 2019; Johansen, Schneider, McCaffree, Woods, & Council on Science and Public Health, American Medical Association, 2008; Schmidt, Solloch, et al., 2009b). This approach increases the efficiency of donor recruitment as the genetic diversity of a donor registry grows more quickly. It is an imperative for fairness to aspire to equal chances to find HLA-matched donors for patients from all populations, although this target may be difficult to achieve due to different levels of intra-population diversity or donor availability (Gragert et al., 2014; Maiers, Gragert, & Klitz, 2007).

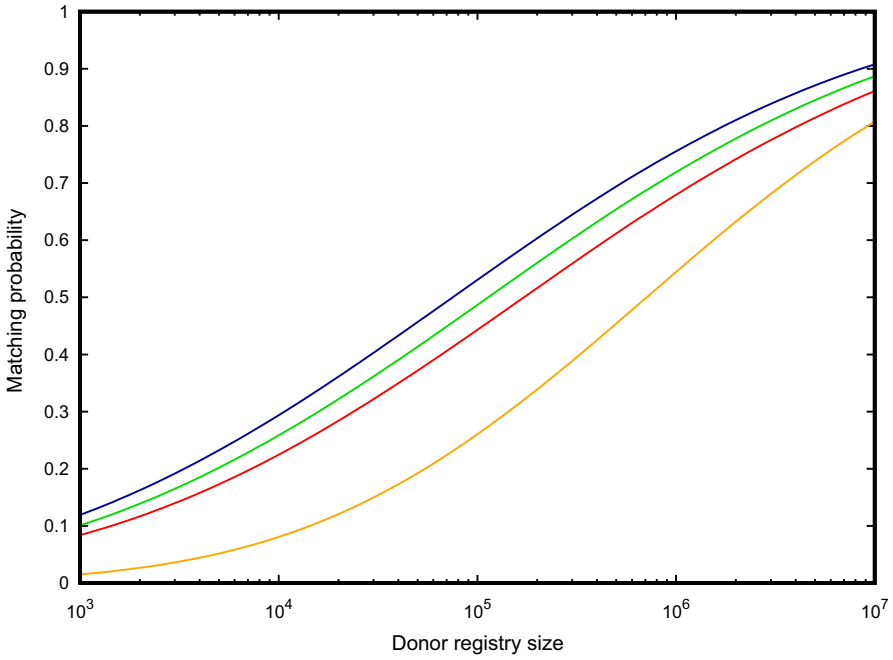

FIGURE 7 Matching probabilities by donor registry size for various populations (all samples from DKMS UK donors, all sample sizes n = 20,000). Red: English; orange: Indian; blue: Scottish; green: Welsh [Colour figure can be viewed at wileyonlinelibrary.com]

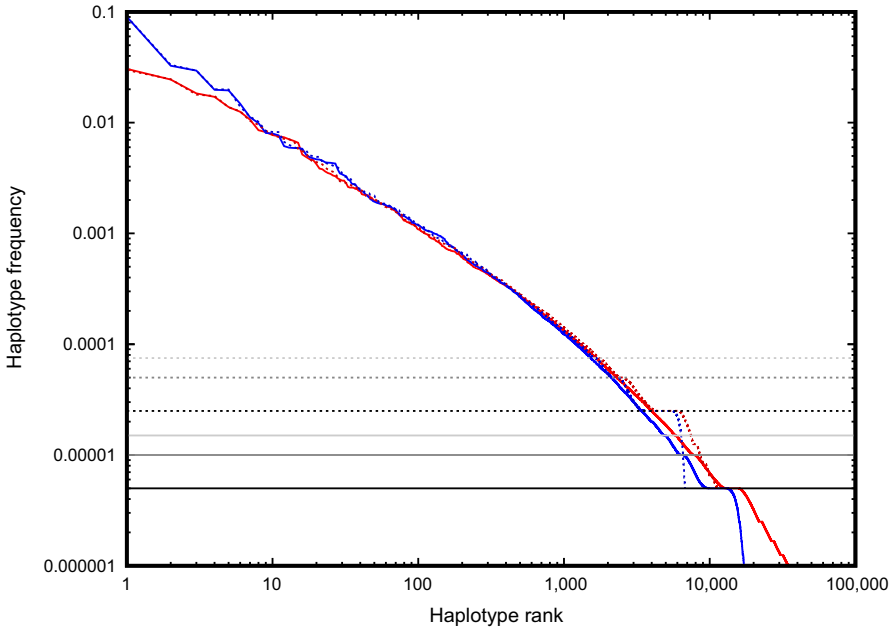

FIGURE 8 Haplotype frequencies (HF) for two populations and two sample sizes. Red: Germany (country of recruitment), German (population); blue: United Kingdom, English/Scottish/Welsh. Solid: sample size n = 100,000; dashed: n = 20,000. Horizontal lines indicate HF that correspond to one (black), two (dark grey) or three (light grey) haplotype occurrence(s) in the samples with size n = 100,000 (solid) or n = 20,000 (dashed) [Colour figure can be viewed at wileyonlinelibrary.com]

At DKMS Germany, ethnic diversity recruitment activities are focused specifically at individuals of Turkish descent as they are the largest ethnic minority in Germany (Schmidt, Solloch, et al., 2009b). Programme elements include specific minority donor drives, use of marketing materials in Turkish language, commitment by prominent representatives of the Turkish community in Germany, co-operation with media preferably used by the Turkish minority and native speaker support by DKMS employees at recruitment and through the various process steps prior to stem cell donation. Currently, 211,613 self-reported donors of Turkish descent are registered with DKMS in Germany. Donors of Turkish descent from DKMS Germany have donated stem cells 1,476 times so far; 318 times for patients in Germany, 222 times for patients in Turkey and 936 times for patients elsewhere (cut-off date: 30 September 2019).

2. Regional focus of donor recruitment activities. Several groups have analysed regional HLA frequency differences within defined countries and their relevance to strategic donor registry planning (Buhler, Nunes, Nicoloso, Tiercy, & Sanchez-Mazas, 2012; Lonjou, Clayton, Cambon-Thomsen, & Raffoux, 1995; Rendine et al., 1998). In many Central European countries as, for example, Germany (Schmidt et al., 2010) or Poland (Schmidt et al., 2013) genetic differences within the majority population are relatively small. As a result, the benefits of setting a geographical donor recruitment focus based on regional HLA differences of the majority population are limited, especially compared with benefits of

ethnic diversity donor recruitment. Therefore, it is promising to combine approaches (a) and (b) by setting the recruitment focus on regions where many individuals from minority populations live.

The situation is different in large, multi-ethnic countries as, for example, India (Maiers et al., 2014; Schmidt, 2014). So far, donor recruitment of DKMS BMST Foundation India has a strong focus on Bangalore and the state of Karnataka (see Figure S4). However, choosing this starting point for our Indian donor recruitment efforts resulted from organizational, socio-economic and feasibility reasons rather than from population genetics considerations. Due to the large genetic variation within this huge country, an ambitious donor recruitment strategy in India will have to include several foci in various regions of the country.

3. Selective recruitment of donors with rare HLA genotypes. Unfortunately, surrogate parameters for individuals with rare HLA genotypes do not exist. Otherwise, donor recruitment would be much more efficient as one could focus on donors with rare HLA genotypes that are not yet on the file multiple times. This idea triggered several Ancestry projects (formerly named Roots projects) at DKMS (Schmidt et al., 2007). These projects include the following elements: identification of registered donors with rare HLA genotypes (exact definitions of "rare" vary between projects), communication with these donors including the appeal to inform their relatives that they would probably be especially interesting stem cell donors, and recruitment of interested relatives. We showed that donors who had been recruited via Ancestry projects indeed had rarer HLA genotypes than other donors (Schmidt et al., 2007). DKMS has recruited 20,400 donors in various project runs in Germany since 1997, and 317 of these donors have donated stem cells until 30 September 2018. For such initiatives, it must be ensured that the use of HLA genotype information of registered donors for donor recruitment purposes is in accordance with donor informed consent and national regulations.
4. Extension of the geographical region of donor recruitment. For an organization that is responsible for patients from a defined geographical area, it seems appropriate to focus donor recruitment efforts on that specific area if all populations living there are addressed adequately. The statutes of DKMS, on the other hand, give no preference to supporting patients from specific countries or regions. Against this background, it became obvious that ongoing donor recruitment in Germany alone would not be optimal. For example, we showed substantial patient benefits from same-population donor recruitment in calculations based on a model with 21 populations under consideration of cross-border stem cell exchange (Schmidt et al., 2014). This result was in accordance with earlier analyses regarding donor recruitment in Germany and Poland (Schmidt, Solloch, Pingel, et al., 2011b). We demonstrated that intense donor recruitment efforts in Poland would increase matching probabilities for Polish patients substantially in spite of the large German donor file and the geographical and genetic proximity of both countries. The desire to increase HLA diversity among registered stem cell donors and thus to improve matching probabilities for patients in need of a stem cell transplant on a global level is the main driver for initiating donor recruitment efforts in a "new" country or region. However, some non-HLA-related criteria have to be considered in the corresponding decision process as well, including country-specific legal framework, openness of government authorities, availability of potential partners or supporters, current local stem cell transplantation activities, access to stem cell transplantation for patients from the respective country and general socio-economic parameters. The current international DKMS donor registry with donors from six countries results from the basic wish to increase donor file HLA diversity and efficiency and the application of these additional criteria. We plan to further expand our donor recruitment activities in the near future, especially to countries with mainly non-European populations.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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