

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med* 2014;371:339-48. DOI: 10.1056/NEJMsa1311707

Appendix for HLA Match Likelihoods for Patients Seeking Unrelated Donor Grafts in the US Registry:

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Appendix A - Impact of International Registry Searches:

Improvement in interchange of stem cell products between international registries provides another opportunity for increasing US patient match likelihoods. Some patients who do not identify a suitably matched donor in the NMDP registry will identify a donor after conducting a global search. While just over half of the donors accessible through Bone Marrow Donors Worldwide¹ are listed in National Marrow Donor Program (NMDP) searches, for US recipients only 6.0% of transplants from adult donors and 9.2% of CBU transplants have come from non-NMDP international sources since 2008. Included in the models for this study are the 32.7% of the donors listed in the NMDP registry that live outside of the United States and are managed by other international registries. International collaborative efforts are underway to assemble suitable global population HLA haplotype frequencies that will be essential for modeling patient match likelihoods across all international registries².

Appendix B – Cross-Validation of Matching Models:

Results from two additional NMDP analyses confirm the accuracy of population genetic based models. First, NMDP conducted a prospective study in which 200 pseudo-patients were randomly selected for four broad race/ethnic populations from a January 2009 snapshot of the NMDP registry and HLA expert assisted donor searches conducted to identify 8/8 matched adult donors. All potentially matched donors were typed at allele-level to confirm matching until an 8/8 matched donor was identified or all potential matches were exhausted. The results showed that 8/8 match likelihoods considering availability were 68% for Caucasian pseudo-patients, 27% for African Americans, 45% for Asian / Pacific Islanders and 42% for Hispanics (Manuscript in preparation). The match likelihoods from this cohort-based study were within 10% of the end-of-year 2008 results from the detailed population genetic based models for all populations (Figure 2).

In another retrospective cross-validation analysis, we re-ran 1,000 patient searches per broad race/ethnic population on an end-of-year 2012 snapshot of the NMDP registry using the HapLogic matching algorithm to calculate 8/8 and 7/8 allele-level match predictions for each potentially matched donor and cord blood units (CBU). Overall 8/8 match likelihoods considering all potentially matched donors were 69% for Caucasian patients, 32% for African Americans, 41% for Asian/Pacific Islanders, and 47% for Hispanics. 7/8 match likelihoods were 97% for Caucasians, 85% for African Americans, 84% for Asian/Pacific Islanders, and 88% for Hispanics. This analysis did not consider adult donor availability. All match likelihoods were within 10% of the detailed population genetic model that did not consider donor availability (Table S1). 6/6 CBU match likelihoods considering cell dose for pediatric patients were 39% for Caucasians, 7% for African Americans, and 28% for Asian/Pacific Islanders, and 28% for Hispanics. 5/6 CBU match likelihoods for pediatric patients were 93% for Caucasians, 61% for African Americans, and 84% for Asian/Pacific Islanders, and 81% for Hispanics. 4/6 CBU match likelihoods for pediatric patients were 99% for Caucasians, 94% for African Americans, and 96% for Asian/Pacific Islanders, and 99% for Hispanics. All cord match likelihoods were within 5% of the detailed population genetic models (Table 1). This study design has the disadvantage that no additional HLA typing was done to confirm allele-level matches, unlike the above-described prospective analysis.

Two other notable prospective studies of patient match rates have been conducted. A study by Tiercy *et al.* of 412 Caucasian patient searches of Bone Marrow Donors Worldwide between 2002 and 2005 found that 46% had a 10/10 match (including matching at the DQB1 locus) while the NMDP population genetic models estimated that 67% of Caucasians would have an 8/8 match in that timeframe³. In another study by Pidala *et al.* of searches for 531 consecutive NMDP patients between March 2006 and December 2009, 7/8 match likelihoods considering availability were 90% for Caucasians, 76% for Hispanics, and 62% for African Americans⁴. All match likelihoods were within 5% of NMDP detailed population genetic models from this timeframe (Figure 2). These two study designs can thus account for additional practical factors wherein available fully-matched donors may exist in the registry but may be difficult to identify in sufficient time and/or cost when the number of potentially matched donors is large. Recent improvements in HLA typing resolution and the HapLogic matching algorithm software have since served to ease the task of identifying allele-matched donors.

Figure S1. Effective CBU inventory adjustments based on patient age and weight decile.

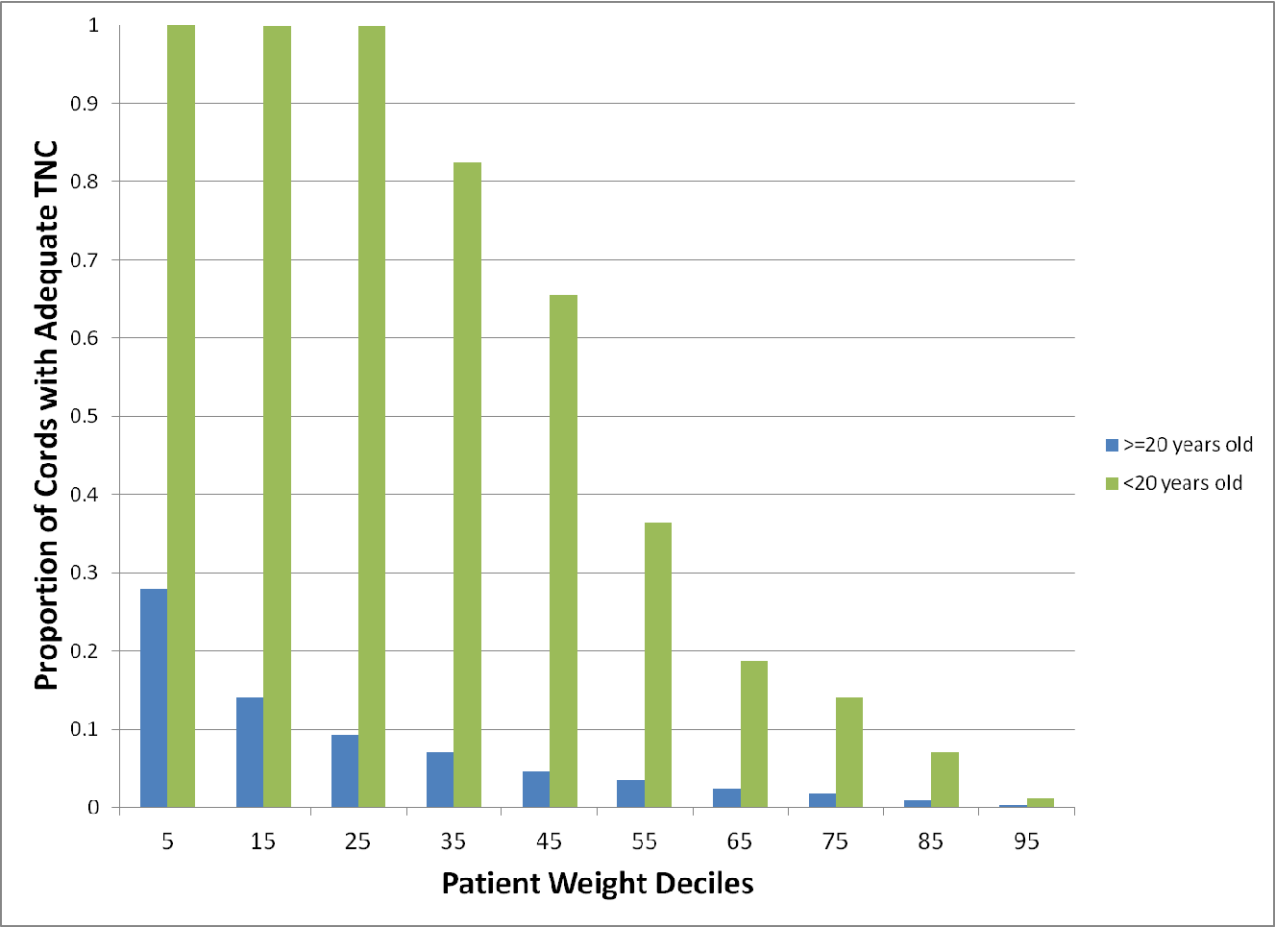


Figure S2. Match likelihoods for patients aged < 20 years: using the search strategy 8/8 HLA-matched adult donor first and then adequate-cell-dose CBU.

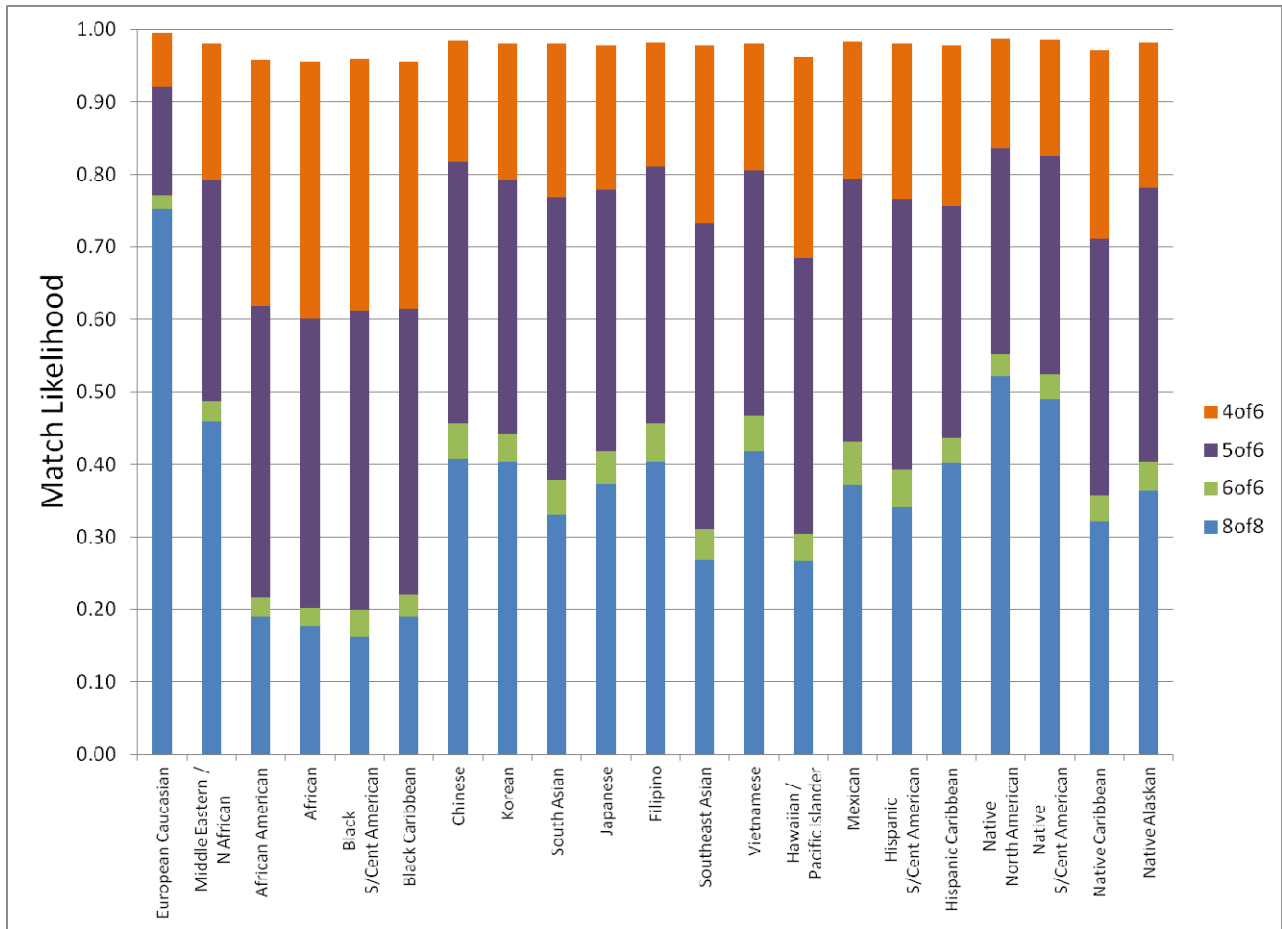


Figure S3. Match likelihoods for patients aged ≥ 20 years: using the search strategy 8/8 HLA-matched adult donor first and then adequate cell dose umbilical cord blood unit.

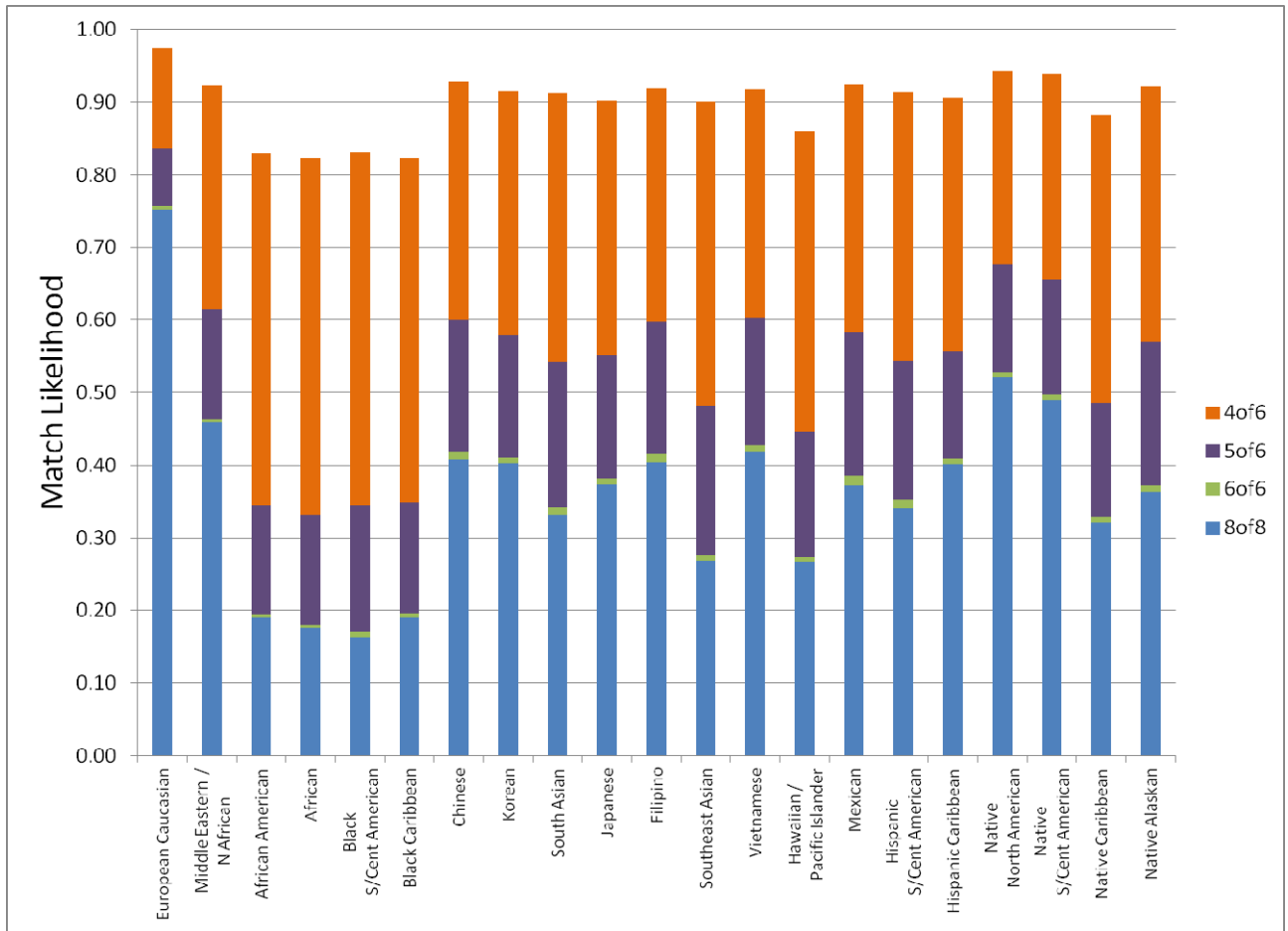


Figure S4. $\geq 5/6$ CBU match likelihoods for adult patients by year-end, extending recruitment trends to 2017. (TNC dose $\geq 2.5 \times 10^7/\text{kg}$).

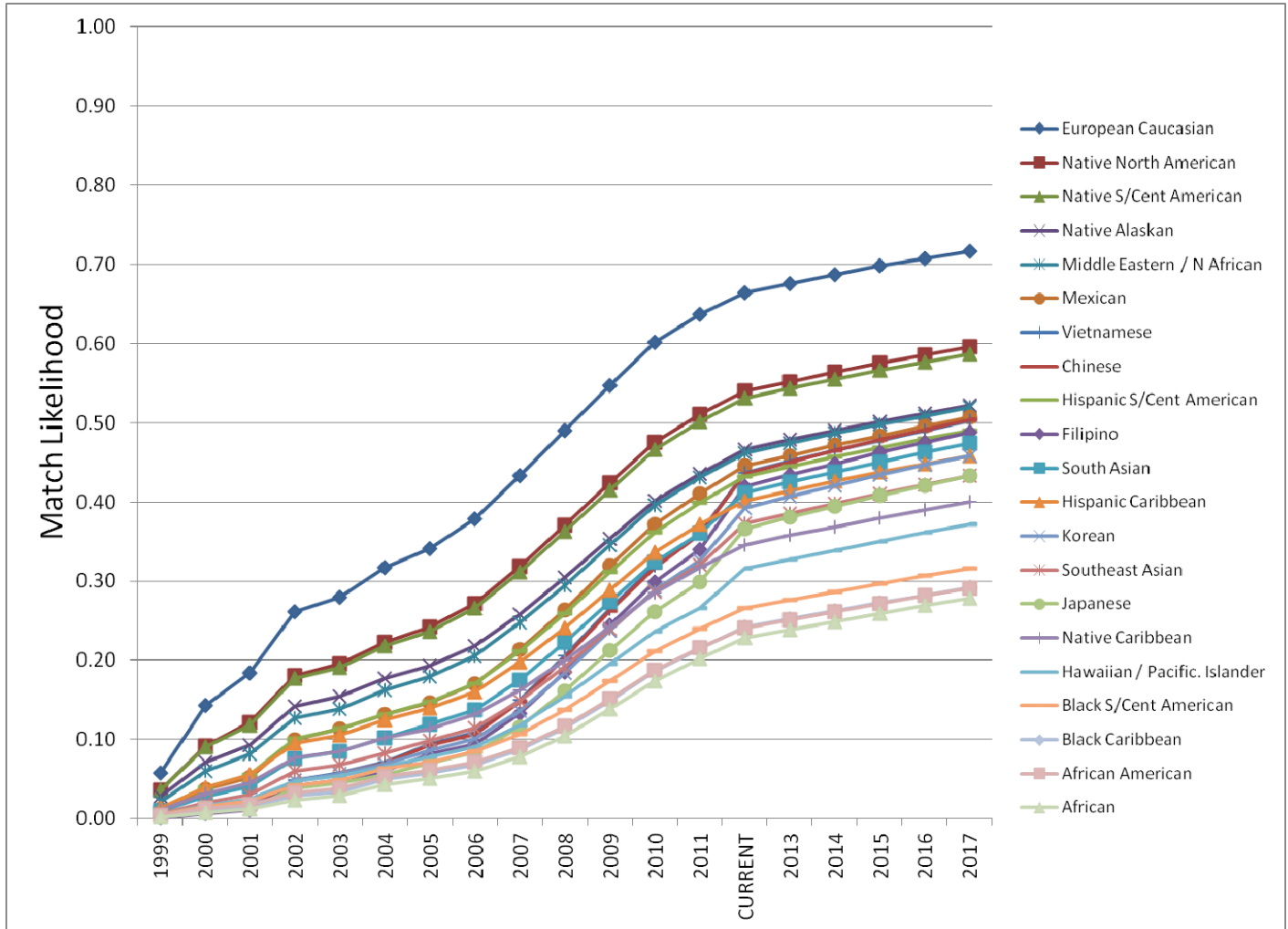
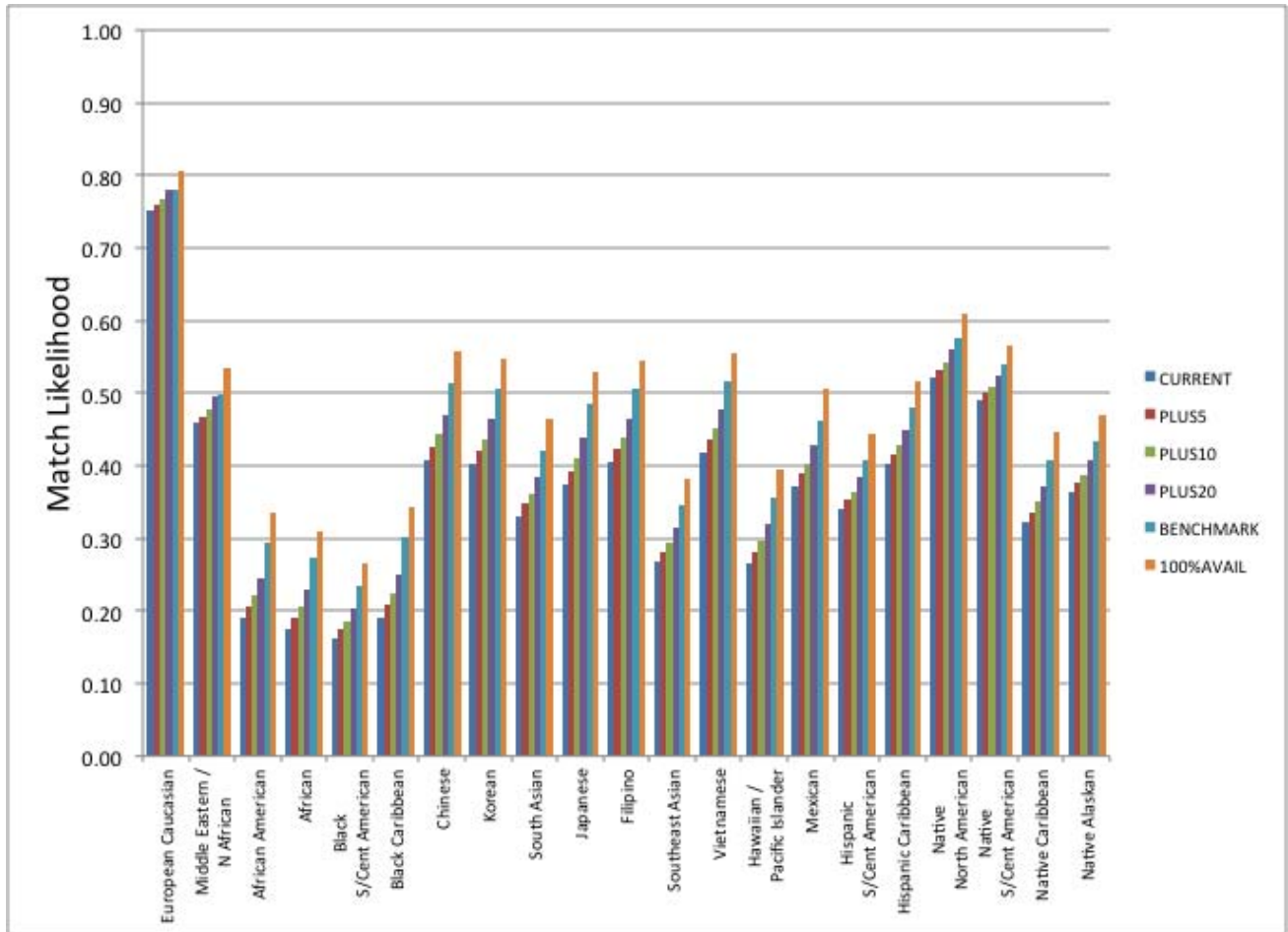


Figure S5. Effective 8/8 allele match rates for adults by donor availability levels.¹



¹ PLUS5 increased availability by 5% in absolute terms, PLUS10 increased availability by 10%, PLUS20 increased availability by 20%, BENCHMARK increased availability to 71% (the highest availability rate observed in any of NMDP’s donor centers), and 100%AVAIL increased availability to 100%.

Table S1: Probability of identifying adult donor and umbilical cord blood units, without consideration of adult donor availability or cord blood cell dose.

Population	Match Likelihoods				
	Any Adult Donor ¹		Any Cord Blood ²		
	8/8	≥7/8	6/6	≥5/6	≥4/6
European Caucasian	0.81	0.98	0.51	0.97	1.00
Middle Eastern / North African	0.53	0.94	0.27	0.90	1.00
African American	0.33	0.89	0.10	0.79	1.00
African	0.31	0.85	0.09	0.77	1.00
Black South/Central American	0.27	0.78	0.12	0.78	1.00
Black Caribbean	0.34	0.86	0.10	0.79	1.00
Chinese	0.56	0.94	0.30	0.93	1.00
Korean	0.55	0.94	0.27	0.91	1.00
South Asian	0.46	0.91	0.23	0.89	1.00
Japanese	0.53	0.94	0.25	0.91	1.00
Filipino	0.55	0.91	0.31	0.92	1.00
Southeast Asian	0.38	0.85	0.19	0.88	1.00
Vietnamese	0.55	0.92	0.31	0.92	1.00
Hawaiian / Pacific Islander	0.40	0.83	0.17	0.82	1.00
Mexican	0.50	0.93	0.29	0.91	1.00
Hispanic South/Central American	0.44	0.88	0.27	0.89	1.00
Hispanic Caribbean	0.52	0.91	0.26	0.87	1.00
Native North American	0.61	0.95	0.35	0.92	1.00
Native South/Central American	0.57	0.91	0.36	0.92	1.00
Native Caribbean	0.45	0.87	0.21	0.84	1.00
Native Alaskan	0.47	0.89	0.26	0.90	1.00

¹Any adult donor is the probability of identifying an adult donor regardless of availability

²Any cord blood unit is the probability of identifying a unit regardless of cell dose

Table S2: Probability of identifying adult donors from within and outside of the patient’s racial/ethnic group incorporating consideration of donor availability.

Population	Effective Registry Size	8/8 HLA-matching			≥7/8 HLA-matching		
		Within Ethnic Group	Outside Ethnic Group	Total	Within Ethnic Group	Outside Ethnic Group	Total
European Caucasian	3485714	0.74	0.01	0.75	0.97	0.003	0.97
Middle Eastern / N African	198813	0.24	0.22	0.46	0.755	0.146	0.90
African American	152220	0.14	0.05	0.19	0.65	0.11	0.76
African	10435	0.02	0.16	0.18	0.23	0.48	0.71
Black S/Cent American	1786	0.004	0.16	0.16	0.05	0.61	0.66
Black Caribbean	12178	0.03	0.16	0.19	0.28	0.46	0.74
Chinese	44677	0.34	0.07	0.41	0.795	0.086	0.88
Korean	34777	0.33	0.08	0.40	0.775	0.092	0.87
South Asian	83100	0.25	0.08	0.33	0.745	0.096	0.84
Japanese	11019	0.26	0.11	0.37	0.69	0.18	0.87
Filipino	22687	0.36	0.04	0.40	0.738	0.096	0.83
Southeast Asian	12541	0.07	0.20	0.27	0.38	0.38	0.76
Vietnamese	19516	0.33	0.09	0.42	0.73	0.11	0.84
Hawaiian / Pacific Islander	5154	0.15	0.12	0.27	0.451	0.265	0.72
Mexican	138605	0.215	0.157	0.37	0.702	0.164	0.87
Hispanic S/Cent American	77843	0.11	0.23	0.34	0.516	0.285	0.80
Hispanic Caribbean	61214	0.192	0.209	0.40	0.59	0.24	0.83
Native North American	18021	0.16	0.36	0.52	0.56	0.35	0.91
Native S/Cent American	2984	0.06	0.43	0.49	0.25	0.62	0.87
Native Caribbean	7220	0.06	0.26	0.32	0.228	0.546	0.77
Native Alaskan	693	0.04	0.32	0.36	0.24	0.59	0.83

Table S3: Probability of identifying $\geq 5/6$ HLA-matched umbilical cord blood units with adequate cell dose from within and outside of the patient's racial/ethnic group

Population	Patients aged <20 years			Patients aged ≥ 20 years		
	Within Ethnic Group	Outside Ethnic Group	Total	Within Ethnic Group	Outside Ethnic Group	Total
European Caucasian	0.847	0.017	0.87	0.62	0.04	0.66
Middle Eastern / N African	0.35	0.40	0.75	0.10	0.36	0.46
African American	0.41	0.17	0.58	0.12	0.12	0.24
African	0.07	0.49	0.56	0.01	0.22	0.23
Black S/Cent American	0.01	0.57	0.58	0.002	0.264	0.27
Black Caribbean	0.09	0.48	0.58	0.016	0.225	0.24
Chinese	0.59	0.18	0.77	0.27	0.16	0.43
Korean	0.50	0.23	0.73	0.18	0.21	0.39
South Asian	0.51	0.22	0.73	0.19	0.22	0.41
Japanese	0.405	0.316	0.72	0.13	0.23	0.37
Filipino	0.58	0.18	0.76	0.27	0.15	0.42
Southeast Asian	0.16	0.54	0.70	0.03	0.34	0.37
Vietnamese	0.52	0.24	0.76	0.217	0.217	0.43
Hawaiian / Pacific Islander	0.20	0.44	0.64	0.042	0.274	0.32
Mexican	0.55	0.20	0.75	0.24	0.20	0.44
Hispanic S/Cent American	0.41	0.32	0.73	0.14	0.29	0.43
Hispanic Caribbean	0.38	0.33	0.71	0.12	0.28	0.40
Native North American	0.034	0.763	0.80	0.01	0.53	0.54
Native S/Cent American	0.01	0.78	0.79	0.0008	0.53	0.53
Native Caribbean	0.005	0.66	0.66	0.0007	0.35	0.35
Native Alaskan	0.003	0.75	0.75	0.0003	0.47	0.47

Appendix References:

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