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Outcomes of Related and Unrelated Donor Searches Among Patients with Primary Immunodeficiency Diseases Referred for Allogeneic Hematopoietic Cell Transplantation

Mary Joseph Acevedo[1], Jennifer S. Wilder[2], Sharon Adams[1], Joie Davis[1], Corin Kelly[1], Dianne Hilligoss[1], Ellen Carroll[1], Bazetta Blacklock-Schuver[1], Kristen Cole[1], Elizabeth M. Kang[1], Amy P. Hsu[1], Christopher G. Kanakry[1], Dimana Dimitrova[1], Jennifer A. Kanakry[1,*]

[1] *National Institutes of Health, Bethesda, Maryland*
[2] *Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research sponsored by the National Cancer Institute, Frederick, Maryland*

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Patients with primary immunodeficiencies (PIDs) are potentially cured by allogeneic hematopoietic cell transplantation (HCT). The spectrum of PIDs has expanded greatly beyond those that present in infancy or are diagnosed on newborn screening and require urgent, preemptive HCT. Many PID diagnoses are now made later in life, and the role of HCT is only considered for severe disease manifestations; in these cases, the kinetics and goals of a donor search may be different than for severe combined immunodeficiency. Across all PIDs, related donor searches have the additional selection factor of the inherited disease, and such searches may yield more limited options than searches for patients with hematologic malignancies; thus, unrelated donor options often become more critical in these patients. We retrospectively evaluated the outcomes of donor searches among patents with PIDs referred for HCT at the National Institutes of Health, where the minimum patient age for evaluation is 3 years and where donor options include matched sibling donors or matched related donors, HLA-haploidentical (haplo), or 7-8/8 HLA matched unrelated donors (mMUDs/MUDs). Patient (n = 161) and donor demographics, MUD search results, HLA typing, pedigrees, mutation testing, and donor selection data were collected. The National Marrow Donor Program HapLogic 8/8 HLA match algorithm was used to predict the likelihood of a successful MUD search and categorized as very good, good, fair, poor, very poor, or futile per the Memorial Sloan Kettering Cancer Center (MSKCC) Search Prognosis method. There were significant differences by PID mode of inheritance in patient age, disposition (receipt of HCT or not), donor source, and donor relatedness. A related or unrelated donor option could be identified for 94% of patients. Of living first-degree relatives (median, 3; range, 0 to 12 per patient), a median of 1 donor remained for autosomal dominant and X-linked (XL) diseases after HLA typing, mutation testing, and other exclusions, and a median of 2 donors remained for autosomal recessive (AR) diseases. Among patients with a PID of known mode of inheritance (n = 142), the best related donor was haplo for 99 (70%) patients, with 56 (39%) haplos age 40 years or older and 5 (4%) second-degree haplos; 13 (9%) had no family donor options. The best related donor was a heterozygote/asymptomatic carrier of the PID mutation in 36 (49%) patients with AR or XL disease (n = 73). Among patients with MUD search performed (n = 139), 53 (38%) had very poor/futile 8/8 MUD searches, including 6 (32%) of those with unknown PID mutation and therefore no family donor options. The MSKCC Search Prognosis was less favorable for those of non-European ancestry compared with European ancestry (P = .002). Most patients of Hispanic or African ancestry had very poor/futile MUD searches, 71% and 63%, respectively. No HCT recipients with very poor/futile MUD searches (n = 38) received 8/8 MUD grafts. Alternative donor options, including haplo and unrelated donors, are critical to enable HCT for patients with PIDs. MUD search success remains low for those of non-European ancestry, and this is of particular concern for patients with PIDs caused by an unknown genetic defect. Among patients with PIDs, related donor options are reduced and haplos age 40 years and older and/or mutation carriers are often the best family option.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for patients with inherited diseases of the immune and hematopoietic system, globally

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* Correspondence and reprint requests: Jennifer A. Kanakry, National Institutes of Health, 10 Center Drive, Building 10/CRC, Rm 4-3132, Bethesda, MD 20892.

E-mail address: jennifer.kanakry@nih.gov (J.A. Kanakry).

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referred to as primary immunodeficiencies (PIDs). Many of the more common and long-recognized PIDs have an autosomal recessive (AR) or X-linked (XL) mode of inheritance, such as Wiskott-Aldrich syndrome, chronic granulomatous disease (CGD), and severe combined immunodeficiency, wherein patients are typically diagnosed and treated with HCT or gene therapy at a very early age. For very severe PIDs that are diagnosed in infancy and referred quickly to HCT based solely on the genetic diagnosis, the goal is to find the most readily available (parent or sibling) donor as quickly as possible and move forward. However, more than 300 PIDs have now been identified, many with variable disease severity and phenotypes, asymptomatic affected family members, and late diagnoses. Many PIDs are inherited in an autosomal dominant (AD) fashion, with disease manifestations caused by gain-of-function mutations, such as activated *PI3K* mutations, or haploinsufficiency, such as *GATA2* mutations. These patients with PIDs may present much later for HCT, and thus the urgency/necessity to use the first available donor, often a carrier, may be a lesser driver of the donor search process, whereas other factors, including the time-consuming need to perform genetic testing on patients and potential related donors, may rise to the forefront.

Although the historical "gold-standard" donor was a HLA-matched sibling donor (MSD), only 25% to 30% of patients requiring HCT will have this option [1]. When the additional selection factor of an inherited disease needs to be considered, the availability of a suitable MSD may further decrease. In other inherited diseases, such as sickle cell disease (SCD), an AR disease, only 21% of patients referred for HCT have an unaffected MSD, and in one study, it was calculated that only 9% of HCT candidates with SCD went on to receive MSD HCT [2]. When considering patients with AD diseases for HCT, the chances of finding a suitable MSD may be even lower.

Considering parents, offspring, and siblings, it is generally observed that more than 95% of patients referred for HCT will have a readily available first-degree HLA-haploidentical (haplo) donor option, regardless of ethnicity. However, patients with PIDs may be less likely to have children (for reasons of young age, chronic illness, infertility as part of the disease phenotype, treatment with teratogenic drugs, fear of passing on the disease, etc), and relatives may be affected with PIDs as well. Thus, in the PID setting, consideration of haplo options may expand the donor pool for patients with PIDs but may not afford a donor option for nearly all patients with PIDs in need of HCT as is true for patients with noninherited hematologic malignancies.

When an MSD is not an option, matched unrelated donors (MUDs) are often considered a first alternative. The necessity of MUD options may be particularly relevant for patients for whom there is the additional donor selection factor of an inherited disease, potentially further limiting related donor options. However, it is well established that patients of non-European, particularly non-northern European, ancestry have variable and often poor chances of finding a MUD [3,4]. In 1 study, African Americans were found to have a MUD option in only 6% of searches using the National Marrow Donor Program [5]. In general, 50% of unrelated donor searches will not yield a suitable MUD despite international registry-based searches [6]. Furthermore, at present, gene therapy is not an available potential alternative to HCT for most PIDs.

Although the consideration of both haplos and MUDs as good alternatives to MSDs should improve the ability to offer HCT to anyone who requires it, the impact of an additional selection factor of an inherited PID on the breadth of donor options and the resulting ability (or inability) to move forward to HCT has not been studied. We hypothesized that the extent to which the additional donor selection factor of a germline PID affects the related donor pool and the receipt of HCT would depend on whether a specific disease-causing mutation could be identified, thus enabling the screening of family members to find a suitable donor, and the mode of inheritance of the PID. Herein, we evaluated the outcomes of related and unrelated donor searches for patients with PIDs referred for HCT at the National Institutes of Health (NIH), where only patients ≥3 years old can be evaluated, within a timeframe when donor types used were matched related donor (MRDs), 7-8/8 unrelated donors, and haplos.

PATIENTS AND METHODS

After institutional review board approval from National Cancer Institute, a retrospective review was conducted of HCT candidates referred to the NIH to screen for HCT (NCT03188419, clinicaltrials.gov). Patients referred for HCT at the NIH were all age 3 years or older, as intensive care resources that could be required by an HCT recipient are not available at the NIH Clinical Center for very young children. The timeframe of this retrospective study was limited to times when there was an actively recruiting clinical trial for a given PID that used MSDs or HLA MRDs, MUDs, and haplo donors. Thus, the time periods started on March 30, 2012, for HCT candidates with GATA2 haploinsufficiency; May 21, 2014, for HCT candidates for DOCK8 deficiency; January 1, 2015, for HCT candidates with CGD; and October 6, 2015, for all other PID HCT candidates. This study was performed by the same providers who conducted the original/actual donor searches, so it was possible to gather first-hand data regarding how each search actually proceeded in a retrospective manner. HCT candidates were included if, at the time of the actual donor search, HLA typing was performed, at minimum, on the recipient and if a pedigree of at least first-degree relatives was constructed. First-degree relatives included a candidate's biologic parents, full siblings, and children. Inclusion of patients for this retrospective study ended on July 27, 2018, for data analysis. Data related to the donor searches, mutation testing, donor and recipient demographics, recipient ancestry, and family history were collected using records in the Clinical Research Information Systems, Crimson, the HLA laboratory, and the transplant coordinator offices of the National Cancer Institute and the National Institute of Allergy and Infectious Diseases of the NIH. For recipients who underwent HCT at the NIH, more detailed data regarding the selected donor were collected; patients evaluated at the NIH but who underwent transplantation elsewhere were included if donor and HCT demographic data were known because of ongoing patient follow-up at the NIH.

The HapLogic matching predictions algorithm (National Marrow Donor Program, Traxis application, Minneapolis, MN) was used to determine the chance of a donor within the National Marrow Donor Program/Be the Match network being an 8/8 HLA allele match [7]. The Memorial Sloan Kettering Cancer Center Search Prognosis categorization was then used to categorize the predicted outcome of an 8/8 HLA allele match unrelated donor search, where the categorization was as follows: very good, ≥20 8/8 donors with an ≥85% chance; good, 5 to 19 8/8 donors with an ≥85% chance and/or ≥20 8/8 donors with a ≥70% chance; fair, 1 to 4 8/8 potential donors with an ≥85% chance and/or 1 to 19 8/8 potential donors with a ≥70% chance and/or ≥5 8/8 potential donors with a 40% to 69% chance; poor, 1 to 4 8/8 potential donors with a 40% to 69% chance and/or ≥1 8/8 potential donors with a 25% to 39% chance; very poor, ≥1 8/8 potential donor with a ≤24% chance; and futile, 0 8/8 potential donors [8]. For this study, the MUD search analysis was performed retrospectively, for a second time, with the initial search being the one performed for clinical purposes at the time of HCT referral. Thus, the repeat, retrospective search could potentially contain data on donor availability and predicted likelihood of matching that were more refined than the data available at the time of the initial MUD search.

For the purposes of this study, recipients with unknown PID mutations were considered to have no family donor options because related donors could not be screened for a specific mutation to determine suitability in these cases. Best family donor option for recipients with an identified genetic defect was retrospectively designated according to the following prioritization: (1) unaffected by the same mutation; (2) suitability, eligibility, and willingness to donate; (3) degree of HLA match; (4) age, prioritizing adults age <40 years over adults age 40 years or older; (5) avoidance of multiparous female donors, female donors for male recipients, and donors to whom the recipient had donor-specific anti-HLA antibodies (data not available for all haplos considered); (6) donor the same weight or larger than the recipient; and (7) between parents, preference of father over mother. As many related donor searches were truncated on finding a MUD, blood type, viral serologic status, and other donor selection factors that might have been considered in practice were not factored in retrospectively. Biologic parents and children of patients

referred to HCT were presumed to be guaranteed haplo options, even if HLA typing was not performed on those donors.

Descriptive statistics were used for patient, donor, and HCT characteristics. Groups were compared using the chi-square test for categorical variables and Kruskal-Wallis test for continuous variables (GraphPad Prism, version 8.0; GraphPad Software, La Jolla, CA).

RESULTS

Patient (n = 161), donor, and HCT (n = 109) characteristics are shown in Table 1, with significant differences in patient age, disposition (receipt of HCT or not), and, among those who underwent transplantation, donor relatedness and donor type, across PID modes of inheritance.

Related Donor Search Outcomes and Best Donor Options

For those with a disease of known mode of inheritance (n = 142), the results of each PID patient's related donor search were tabulated (Table 2), regardless of whether or not the patient went on to receive HCT. Of living first-degree relatives (median, 3; range, 0 to 12 per patient), a median of 1 donor remained for AD and XL diseases after HLA typing, mutation testing, and other exclusions, and a median of 2 donors remained for AR diseases. Only 20% of patients had an MRD as the best related donor option; 9% had no family donor options, even when searches were extended to second-degree relatives and beyond. The best related donor option was haplo for 100 (70%) patients, with 56 (39%) being haplos age 40 years or older and 5 being second-degree haplos. No patient had solely haplo options against whom donor-specific anti-HLA antibodies (DSAs) were present. The best related donor was a heterozygote/asymptomatic carrier of the PID mutation in 36 (49%) patients with AR or XL disease (n = 73).

Among those whose best family donor option was a haplo confirmed by HLA typing (excluding families with known close consanguinity, n = 9), 35 of 65 (54%) had a donor who was at least a 6/10 bidirectional HLA match or better, 17 (26%) had a donor who was at least a 7/10 bidirectional HLA match or better, and 8 (12%) had a donor who was at least a 8/10 bidirectional HLA match or better; none of the remaining mismatches were HLA-DQ mismatches for these patients having partial sharing on the unshared haplotype. For the 9 patients whose parents were first cousins, none had a suitable MSD, but 3 (33%) had an HLA-identical donor in the form of a parent or cousin.

Of the 19 patients with a PID of unknown genetic defect, all had living, healthy first-degree relatives who could have served as donors had a mutation been identified to inform donor screening. Ten of the 19 had full siblings who had HLA typing performed, often in the hopes that a mutation would be found during the course of the donor search, and 5 of the 10 (50%) had at least 1 HLA-matched sibling.

MUD Search Results

MUD searches were performed for 139 patients, with Memorial Sloan Kettering Cancer Center Search Prognosis categorization shown in Table 3. Most (88%) HCT recipients with very good/good MUD search predictions (n = 57) received a MUD HCT, while no patient with a very poor/futile MUD search (n = 53) went on to receive a 8/8 MUD graft (Table 4). Among the patients with very poor/futile MUD searches included 6 of 19 (32%) of those with PID of unknown genetic defect and therefore no mechanism to genetically screen family donors; 3 of these patients went on to receive HCT using a mMUD graft (n = 1) or, with trepidation, a family donor after extensive immunologic evaluations (n = 2), and 3 have not yet been offered HCT because of a lack of donor. Of the 65 patients whose best family donor was haplo and donor HLA typing was available, 30 (46%) had a very poor/futile MUD search.

Of the 139 patients with MUD searches performed, 105 (76%) went on to receive HCT, with no significant difference in rates by European compared with non-European ancestry (Table 4). However, use of MUDs as a graft type varied by patient ancestry, with 34 (53%) of HCT recipients of European descent (n = 64) receiving a MUD graft and 13 (32%) of HCT recipients of non-European descent (n = 41) receiving a MUD graft ($P = .03$). The predicted likelihood of a successful 8/8 MUD search was lower for those of non-European ancestry ($P = .01$). Most patients of Hispanic or African ancestry had very poor/futile MUD searches, representing 71% and 63% of prediction designations for these groups, respectively (Figure 1).

Receipt of HCT and Role of Alternative Donors

For most of these patients, the underlying PID diagnosis was not an absolute indication for HCT but rather was influenced by the genetic diagnosis and severe clinical manifestations. Thus, HLA typing was often performed early in the discussion of treatment options for PID, even before HCT was an immediate necessity; thus, the median time from HLA typing to HCT was 7 months (range, 1 to 50 months). Of patients referred to HCT, 70% have gone on to receive HCT, with an additional 25% pending HCT with a donor identified. Of those with PID of known mode of inheritance (n = 142) with an MRD option, 86% (24 of 28) have gone on to receive HCT, and 3 of the remaining 4 have HCT scheduled in the coming months. Although fewer MSDs were used for recipients with AR diseases, 44% of patients with AR diseases and parents who were first cousins had a donor who was 8 to 10/10.

Alternative donors were used in 77% of all PID HCTs; unrelated donors were used in 45% of the HCTs for this cohort, with the second most common donor type being haplo parents, comprising 22% of HCTs. As expected, patients receiving HCT for a PID of unknown genetic defect were more likely to receive an unrelated donor graft, but notably the disposition of these patients was also that they were more likely to have no donor found despite related and unrelated donor searches (Table 1). Of the 19 with PID of unknown genetic defect, 6 (32%) had no MUD option. Use of mMUD was observed only in patients with PID of unknown genetic mutation, and use of second-degree haplo donors was observed only in those with AD diseases. The most commonly used donor for AR diseases was a haplo parent, comprising 37% of the AR HCT grafts. Of those with PID of known mode of inheritance but no family donor options, 71% (10 of 14) have received HCT; of the remaining 4, 2 have MUD HCTs scheduled, 1 is well enough to defer HCT, and 1 died before a donor could be found.

DISCUSSION

In the modern era of successful approaches to haplo HCT such as post-transplantation cyclophosphamide (PTCy)-based platforms [9-11], the prevailing notion is that there is a readily available donor option for any patient in need of HCT. However, our study emphasizes the increased complexity of related donor searches for patients with inherited diseases. This complexity is further heightened by focusing on patients with PID who come to HCT later than those who present in and receive transplantation in infancy, in which there may often be, at minimum, an immediately available, unaffected, relatively young, and guaranteed HLA-haploidentical parent. Although family donors are usually considered more readily available than unrelated donors, the reverse may often be true for

Table 1
Patient, Donor, and Disease Characteristics and Disposition

Characteristic	Patients with PID (n = 161)	AD (n = 69)	AR (n = 40)	XL (n = 33)	Unknown (n = 19)	*P* Value
Male	92 (57)	29 (42)	22 (55)	30 (91)	11 (58)	
Age, median (range), y[*]	24 (3.8-68)	25 (4.5-68)	19 (3.8-44)	24 (3.9-54)	27 (9.2-52)	.003
De novo mutation[†]	28 (17)	28 (41)	0	0	0	
Disposition						.04
Received HCT or gene therapy[‡]	112 (70)	44 (64)	27 (68)	28 (85)	13 (68)	
Pending HCT with donor found	40 (25)	22 (32)	12 (30)	3 (9)	3 (16)	
No HCT donor identified[§]	6 (4)	1 (1)	1 (2)	1 (3)	3 (16)	
Died before donor found	3 (2)	2 (3)	0	1 (3)	0	
Time from HLA typing to HCT, median (range), mo	7 (1-50)	7 (1-50)	7 (1-48)	8 (2-45)	7 (2-15)	NS
MUD search performed	139 (86)	59 (86)	33 (83)	28 (85)	19 (100)	
Donor type (of those receiving HCT, n = 109)						.01
MUD	47 (43)	17 (39)	9 (33)	13 (52)	8 (62)	
Haplo full-sibling	9 (8)	5 (11)	3 (11)	1 (4)	0	
Haplo parent	22 (20)	7 (16)	9 (33)	5 (20)	1 (8)	
Haplo second-degree relative	3 (3)	3 (7)	0	0	0	
Haplo child	1 (1)	1 (2)	0	0	0	
MSD	22 (20)	11 (25)	3 (11)	6 (24)	2 (15)	
MRD	3 (3)	0	3 (11)	0	0	
mMUD	2 (2)	0	0	0	2 (15)	
Donor relatedness (of those receiving HCT)						.04
Related	60 (55)	27 (61)	18 (67)	12 (48)	3 (23)	
Unrelated	49 (45)	17 (39)	9 (33)	13 (52)	10 (77)	
Donor HLA match and relation (of those receiving HCT)						NS
Matched related	24 (22)	11 (25)	5 (19)	6 (24)	2 (15)	
Unrelated	49 (45)	17 (39)	9 (33)	13 (52)	10 (77)	
Haplo related	36 (33)	16 (36)	13 (48)	6 (24)	1 (8)	
Female donor/male recipient (of those receiving HCT)	17 (16)	7 (16)	4 (15)	5 (20)	1 (8)	NS
Diagnosis						NA
GATA2 haploinsufficiency	33 (20)	33 (48)	0	0	0	
CGD	24 (15)	0	2 (5)	22 (67)[‖]	0	
PID of unknown genetic defect[¶,◊]	19 (12)	0	0	0	19 (100)	
PI3K gain of function[#]	17 (11)	17 (25)	0	0	0	
DOCK8 deficiency/hyper-IgE syndrome	16 (10)	0	16 (40)	0	0	
ADA2 deficiency/DADA2	8 (5)	0	8 (20)	0	0	
CTLA4 haploinsufficiency	6 (4)	6 (9)	0	0	0	
IFNGR1 deficiency	5 (3)	2 (3)	3 (8)	0	0	
MAGT1 deficiency/XMEN disease	4 (2)	0	0	4 (12)	0	
STAT3 deficiency/hyper-IgE syndrome	4 (2)	4 (6)	0	0	0	
RAG1/RAG2 deficiency	4 (2)	0	4 (10)	0	0	
STAT1 gain of function	3 (2)	3 (5)	0	0	0	
Other diagnoses[**]	18 (11)	4 (6)	7 (18)	7 (21)	0	

Data are presented as n (%) unless otherwise indicated. AR: PGM3 deficiency (n = 2), LRBA deficiency (n = 2), cartilage hair hypoplasia (n = 1), IL10R deficiency (n = 1), JAK3 deficiency (n = 1). XL: IL2RG deficiency (n = 2), XIAP deficiency (n = 2), CD40L deficiency (n = 1), NEMO deficiency (n = 1), and Wiskott-Aldrich syndrome (n = 1). NS indicates not significant; NA, not applicable; IgE, immunoglobulin E; DADA2, deficiency of ADA2; XMEN, X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia.

[*] Age at HCT, if transplanted; age at present, if not transplanted; age at death, if died before reaching HCT.

[†] De novo status designations were based on family history and mutation testing in parents and siblings, as appropriate.

[‡] A total of 109 received HCT; 3 received gene therapy for X-linked CGD.

[§] No donor identified after both 8/8 MUD search and related donor search.

[¶] For some patients with unknown mutations who proceeded to HCT, only related donor options were available, despite them being considered, for the purposes of this study, to have no related donor options.

[‖] X-linked, male (n = 20); X-linked, symptomatic female carrier (n = 2).

[◊] Phenotypes: chronic active Epstein-Barr virus (n = 4), monoMAC: monocytopenia and mycobacterial infection, syndrome (n = 4), idiopathic CD4 lymphopenia (n = 2), common variable immunodeficiency (n = 1), and other immunodeficiency phenotype (n = 8).

[#] *PIK3CD* (n = 16), *PIK3R1* (n = 1).

[**] AD: PLCG2 gain of function (n = 1), PTEN deficiency (n = 1), SAMD9L gain of function (n = 1), and NFKB1 haploinsufficiency (n = 1).

patients with PID, as determining related donor suitability requires genetic testing for the mutation, as well as at times subsequent immune profiling and evaluations of carriers to ensure that the heterozygous state is asymptomatic. This represents an additional time and resource burden as well as expertise to evaluate related donors in the PID setting. Notably, family members in this cohort were at times reluctant to undergo genetic testing, wishing to not know their own

Table 2
Related Donor Search Results

Characteristic	Patients with PID (n = 142 with Known Mode of Inheritance)	AD (n = 69)	AR (n = 40)	XL (n = 33)	AD, De Novo* (n = 28)	AD, Familial* (n = 31)
Living first-degree family, median number of individuals (range)	3 (0-12)	3 (0-12)	3 (2-7)	3 (1-8)	3 (1-4)	3 (1-12)
Full-match potential (full sibling among living family members)	104 (73)	51 (74)	30 (75)	23 (70)	20 (71)	25 (81)
Living full siblings, median number (range)	1 (0-10)	1 (0-10)	1 (0-5)	1 (0-5)	1 (0-2)	1 (0-10)
Sibling excluded because of PID	33 (23)	13 (19)	12 (30)	8 (24)	0	12 (39)
Sibling excluded because of non-PID reason†	50 (35)	28 (41)	15 (38)	7 (21)	12 (43)	13 (42)
No siblings remaining after typing and medical evaluations	84 (59)	43 (62)	23 (58)	18 (55)	16 (57)	20 (65)
Haplo potential	141 (99)	68 (99)	40 (100)	33 (100)	28 (100)	31 (100)
Parent only	34 (24)	15 (22)	9 (23)	10 (30)	8 (29)	4 (13)
Offspring	14 (10)	9 (13)	3 (8)	2 (6)	1 (4)	7 (23)
Living guaranteed haplos, median number (range)	2 (0-7)	2 (0-6)	2 (1-4)	2 (0-7)	2 (1-2)	2 (0-6)
Offspring	0 (0-5)	0 (0-4)	0 (0-2)	0 (0-5)	0 (0-1)	0 (0-4)
Parents	2 (0-2)	2 (0-2)	2 (1-2)	2 (0-2)	2 (1-2)	2 (0-2)
Parent excluded because of PID	25 (18)	21 (30)	0	4 (12)	0	18 (58)
Parent excluded because of non-PID reason†	54 (38)	26 (38)	13 (33)	15 (45)	16 (57)	7 (23)
No parents remaining after typing and medical evaluations	29 (20)	20 (29)	2 (5)	7 (21)	7 (25)	7 (23)
Offspring excluded because of PID	6 (4)	6 (9)	0	0	0	6 (19)
Offspring excluded because of non-PID reason†	8 (6)	4 (6)	2 (5)	2 (6)	1 (4)	2 (6)
Percent of family excluded because of PID, median (range)	0 (0-100)	0 (0-100)	0 (0-40)	0 (0-100)	0 (0-50)	42 (0-100)
Percent of family excluded because of non-PID reason, median (range)	25 (0-100)	29 (0-100)	25 (0-83)	25 (0-100)	50 (0-100)	8 (0-75)
Percent of family remaining after typing and medical evaluations, median (range)	55 (0-100)	50 (0-100)	67 (17-100)	67 (0-100)	50 (0-100)	50 (0-100)
First-degree donor options after typing and medical evaluations, median (range)	2 (0-7)	1 (0-6)	2 (1-7)	1 (0-3)	1 (0-4)	1 (0-5)
Second-degree relative search performed	20 (14)	13 (19)	3 (8)	4 (12)	6 (21)	7 (23)
Number of first-degree family members remaining after evaluations, median (range)	1 (0-6)	1 (0-5)	2 (0-6)	1 (0-3)	1 (0-4)	1 (0-5)
Any family donor after typing and medical evaluations	128 (90)	59 (86)	40 (100)	29 (88)	23 (82)	29 (94)
Best family option after typing and medical evaluations‡						
None	13 (9)	9 (13)	0	4 (12)	3 (11)	3 (10)
MSD/MRD	30 (21)	14 (20)	9 (23)§	7 (21)	6 (21)	5 (16)
First-degree haplo, <40 years old	38 (27)	17 (25)	14 (35)	7 (21)	8 (29)	8 (26)
First-degree haplo, 40 years or older	56 (39)	24 (35)	17 (43)	15 (45)	8 (29)	13 (42)
Second-degree haplo	5 (4)	5 (7)	0	0	3 (11)	2 (6)
Best family option a heterozygote/carrier for mutation	36 (25)	NA	29 (73)	7 (21)	NA	NA

Data are presented as n (%) unless otherwise indicated.

* De novo versus familial AD disease designations were made based on family history and mutation testing in first-degree relatives, as appropriate. From the available information, not all patients with AD disease could be designated as de novo versus familial.

† Reasons for exclusion could include medical issues, estrangement, lack of willingness/availability to be typed/donate, or HLA disparity on HLA typing. Age, blood type, cytomegalovirus serostatus, parity, donor-specific anti-HLA antibodies, and asymptomatic mutation carriers were not counted here as reasons for exclusion.

‡ Best family option was determined by prioritizing the following among remaining family options: degree of HLA match (MSD, MRD, haplo with fewest mismatches on the nonshared haplotype), donor age (adults <40 years, minors, adults ≥40 years), parity/sex (avoidance of female donor for male recipient; otherwise equivalent male donor preferred to multiparous female), donor size/fitness/availability, family preference (parents of patients often requested that the donor be a parent if choosing among parent and sibling haplo options).

§ MSD = 6, MRD = 3.

mutation status or, in particular, parents wishing to not know the mutation status of their other children, the patient's siblings. This highlights the importance of proactively outlining the family tree and exploring related donor options as soon as a patient with PID is considered potentially in need of HCT. Inquiries into related donor options always have the potential to reveal intrafamily psychosocial tensions or unease, and these complicated dynamics seem to be more common in working with the PID population, in whom genetic testing also is required.

Although the most common haplo donor option for a patient with a hematologic malignancy may be a child or sibling given that the median ages of patients with hematologic malignancies are in fifth to seventh decades, the most common

Table 3
Memorial Sloan Kettering Cancer Center Search Prognosis Categorization by Ancestry

Characteristic	Total No. of Patients with MUD Searches (n = 139)	Very Good/Good (n = 57), n (%)	Fair/Poor (n = 29), n (%)	Very Poor/Futile (n = 53), n (%)	*P* Value
General ancestry					.002
European	83	44 (53)	14 (17)	25 (30)	
Non-European	56	13 (23)	15 (27)	28 (50)	
Detailed ancestry					.0003
NW European	73	42 (58)	9 (12)	22 (30)	
Hispanic	24	4 (17)	3 (13)	17 (71)	
Non-NW European or Slavic	12	3 (25)	5 (42)	4 (33)	
African	8	1 (13)	2 (25)	5 (63)	
Asian	8	3 (38)	3 (38)	2 (25)	
Middle Eastern	5	2 (40)	3 (60)	0	
European/Non-European mix	4	2 (50)	2 (25)	0	
Non-European mix	3	0	0	3 (100)	
Native North American	2	1 (50)	1 (50)	0	

NW indicates Northwest.

Table 4
MUD Search Outcomes by Memorial Sloan Kettering Cancer Center Search Prognosis Categorization and Ancestry

Characteristic	No. of MUD Searches Performed	No. of MUD Searches Formalized	MUD Identified, n (% of Formalized Searches)	Patients Receiving HCT, n (% of Patients with MUD Search)	8/8 MUD as Donor, n (% of HCT Recipients)
Total	139	65	54 (83)	105 (76)	47 (45)
Very good/good					
European	44	33	33 (100)	33 (75)	29 (88)
Non-European	13	10	9 (90)	10 (77)	9 (90)
Fair/poor					
European	14	9	5 (56)	12 (86)	5 (42)
Non-European	15	7	6 (86)	12 (80)	4 (33)
Very poor/futile					
European	25	3	0 (0)	19 (76)	0 (0)
Non-European	28	3	1 (33)	19 (68)	0 (0)

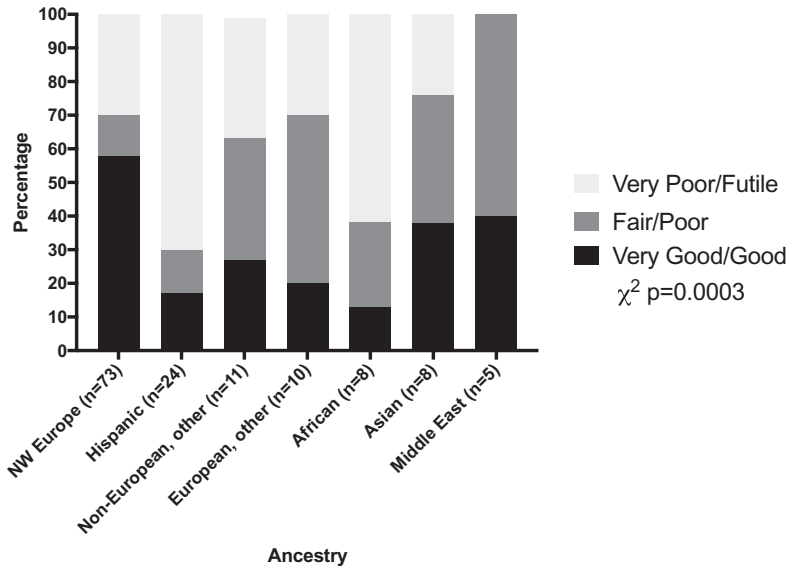

Figure 1. MUD search categorization, by recipient ancestry, using the Memorial Sloan Kettering Search Prognosis algorithm. There are significant differences in the likelihood of a successful MUD search by ancestry, chi-square *P* = .0003.

haplo donor for a patient with PID, who is typically younger, may be a parent, as shown in our cohort. The reliance on haplo parents in this cohort was as a result of small family sizes, lack of offspring among patients with PID, affected siblings, and also often parental preference to serve as donor if the patient's siblings were not fully matched and the best family option was a choice between haplo parent or haplo sibling. However, age is emerging as an important factor in donor selection, and

most haplo parents in our series were age 40 years or older. In Center for International Blood and Marrow Transplantation Research (CIBMTR) studies of unrelated donor factors that affect HCT survival outcomes, donor age was a major factor, with decreases in overall survival with increasing donor age on multivariable analysis [12,13]. On adjusted analysis, survival was superior if MUDs age <33 years were used [13]. Smaller studies also have shown that matched related or unrelated donors age >39 years are associated with inferior overall survival [14] and that MUDs age <30 years are associated with improved overall survival compared to MRDs and older MUDs [15]. Age has been shown to be a detrimental factor in hematopoietic stem cell function, as well as associated with an increased risk of clonal hematopoiesis [16,17]. How these data on donor age generalize to haplo donors with PTCy-based approaches requires further investigation, although at least 1 major HCT center that uses PTCy, Johns Hopkins, has moved to selecting donors based on younger age over degree of HLA match, including second- or third-degree family members within the pool of potential donors [18,19].

In addition to age considerations when using haplo parents as donors, mutation carrier status is also a factor in AR and XL diseases. In our series, mutation carriers were used for over one third of AR HCTs. Although carriers were evaluated with diligence to confirm that they were asymptomatic, there may be unknown consequences to using a heterozygote as donor in some newly identified PIDs. As an example, it was noted that a donor who was a carrier for ADA2 deficiency (DADA2) had a very low cell count yield on bone marrow harvest [20]. To secure a sufficient graft dose, the donor had to undergo urgent mobilization for peripheral blood stem cell collection to augment the marrow graft. Whether this was a donor-specific issue or a feature among heterozygotes of *ADA2* (*CECR1*) mutations is not presently known. Furthermore, there are reports of symptomatic patients heterozygous for *ADA2* mutations, with plasma ADA2 activity levels in the carrier range and reports of these patients at times presenting with milder or later-onset disease manifestations [21-23]. Another example is the association between discoid lupus erythematosus and CGD, which is reported primarily not in patients with CGD but in the female carriers of XL CGD mutations, as well as heterozygotes of AR CGD [24-26]; this association is not well understood but is clearly an example of the uncertainty in the true health of carriers of certain mutations. Interestingly, in evaluating the haplo parents of a patient in our cohort with *IL10RA* mutation (AR inheritance), the father was excluded for a history of tumid lupus, the susceptibility to which may be related, at least partially, to his *IL10RA* mutation carrier status [27]. These cautionary examples serve to illustrate our incomplete understanding of the potential risk associated with using carriers as donors. Finally, another consideration is that mixed chimerism may be insufficient to correct a disease phenotype, as has been demonstrated mathematically in SCD and hemoglobinopathies [28,29]. The use of a carrier donor in PID HCT might make it necessary to achieve higher donor chimerism in critical cell lineages for phenotype reversal.

The lack of an MSD does not always equate to no matched related donor options. A high percentage of patients with AR diseases and close consanguinity of their parents had MRDs in this study and more likely could have been found with more extensive family typing. In addition, haplo donors are frequently more closely matched than 5/10, sharing additional HLA alleles from the nonshared haplotype. In our series, even 8/10 bidirectionally matched haplos were found in families without consanguinity. In sum, all haplo donors are not equal with regard to the degree of HLA disparity, but discerning how this should inform donor selection, if at all, remains unclear at this time, and there may be no clinical differences in outcome based on degree of HLA disparity among haplo donors with PTCy-based approaches [30,31]. Nonetheless, we note the degree of matching in the graft-versus-host and host-versus-graft direction for all haplo donors during the donor search evaluation. Furthermore, DSAs were not an issue that limited haplo donor options in this study, perhaps reflecting several somewhat unique features of this patient population compared with patients with hematologic malignancy referred for HCT [32], including lower parity of females with PID, less exposure to transfusions, and perhaps less propensity to form DSAs by nature of their immunodeficiency and/or its treatment.

Demonstrated here is the great importance of unrelated donor options for these patients, as the number of eligible and suitable family donors was often small and weighed heavily on haplo parents, who were typically age 40 years or older. Thus, in our practice, we have initiated a MUD search immediately upon referral for HCT, so as to know as quickly as possible what donor options exist, anticipating delays or potential difficulties in the course of related donor searches. This is distinctly different from the current approach to donor searches for hematologic malignancies, in which not all patients require and benefit from a MUD search [4]. The mMUDs were used only for patients with PID of unknown genetic defect, speaking to the willingness to use haplo donors over mMUDs as an alternative donor source when non-HLA selection factors, such as the underlying mutation, were known and therefore could be evaluated in family members. The donor search process for patients with PID of unknown genetic defect can be quite agonizing when the MUD search is unpromising. The process of trying to deem suitable a related donor for a patient with an unknown genetic defect is time-consuming; often unsettling for the patient, family, and transplant physician; and ultimately guesswork at best in an effort to weigh the relative risks and benefits of proceeding with HCT versus continued evolution of the underlying PID. Although umbilical cord blood (UCB) grafts were not considered in this study, as PID HCT protocols at the NIH during the study timeframe did not use UCB grafts, UCB provides an additional alternative donor source for patients who lack HLA-matched donors. Adequate cell dose cord blood units mismatched at 1 or 2 HLA loci are likely available for nearly all pediatric patients and for most adults, regardless of ethnicity [3]. Thus, patients in this study may have had UCB options that could have been considered in the alternative donor search. Gene therapy is also a potential option for a small subset of patients with specific PIDs [33] but currently does not provide an alternative to HCT for most patients with PID.

Approaches to HCT that successfully use alternative donors are critical for extending this potentially curative therapy to all eligible patients with PID. At the NIH, PTCy-based approaches are used for most PID HCTs, even when using matched related or unrelated donors. Yet, although identifying successful platforms to enable alternative donor HCT is one hurdle that has been largely cleared for patients with PID, a remaining hurdle is the donor search itself in this unique patient population. Awareness of and attention to the complexities that surround donor searches for patients with PID, as highlighted here, are necessary to successfully bring those patients with PID in need of HCT to HCT in an optimal and timely fashion.

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