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Analysis

Urgent Time to Allogeneic Hematopoietic Cell Transplantation: A National Survey of Transplant Physicians and Unrelated Donor Search Coordinators Facilitated by the Histocompatibility Advisory Group to the National Marrow Donor Program

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A B S T R A C T

To characterize donor search and selection practices, the National Marrow Donor Program (NMDP) Histocompatibility Advisory Group developed a survey of allogeneic hematopoietic cell transplant (HCT) physicians and search coordinators. The objectives were to describe search practices, understand practices surrounding urgent time to HCT, and characterize strategies used when identifying a matched unrelated donor is unlikely. Participants included US physician members of the American Society for Transplantation and Cellular Therapy and donor search coordinators within the NMDP network. The web-based survey was conducted from February to May 2018. Three hundred seventeen of 858 physicians (37%) and 225 of 327 coordinators (69%) responded, of which 263 and 194, respectively, were eligible and included in the analysis. Most centers, 142 (95%), were represented; 108 (72%) had at least 1 physician and 128 (85%) had at least 1 coordinator respondent. Most (68% physicians, 61% coordinators) indicated donor selection decisions were made by individual physicians. Urgent time to HCT was most commonly (90% and 87% of physicians and coordinators, respectively) defined as HCT within 4 to 6 weeks of search initiation. Higher HCT urgency was associated with a higher disease risk index. For urgent cases with low probability of an 8/8 matched unrelated donor , 75% and 80% of physicians and coordinators endorsed a short (1 to 2 weeks) unrelated donor search before proceeding to an alternative donor source. NMDP-provided solutions to expedite donor identification were strongly endorsed. This survey clarified current donor selection practices in the United States and defined urgent time to HCT. These data provide insight to NMDP on potential solutions to support the path to transplant, such as highlighting futile searches and providing alternative donor options at the time of search initiation.

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INTRODUCTION

Identification of a suitable donor is a required initial component of facilitating allogeneic hematopoietic cell transplant (HCT) for patients with hematologic disorders. No uniform standards exist across HCT centers in this regard, and it is expected that the practices of individual HCT physicians differ according to multiple factors, including institutional standards, patient characteristics, and individual preferences. In addition, the interaction between HCT physicians and donor search coordinators to achieve a preferred donor source for HCT has not been examined.

Variations in these practices may be especially important for patients with increased disease risk, because relapse or disease progression represents the most common reasons why otherwise eligible patients do not reach HCT [1,2]. However, the concept of urgent time to HCT has not been investigated previously, and insight is needed into provider-level definitions of urgency and practices used in this context, with attention to barriers encountered and selection of alternative donors when well-matched unrelated donors (MUDs) are not

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available. Multiple existing and potential future strategies to improve the efficiency of donor identification are possible [3-6], yet physician and donor search coordinator acceptance of these solutions has not been explored.

The Histocompatibility Advisory Group to the National Marrow Donor Program (NMDP)/Be The Match is a key opinion leader group composed of experts in HLA science, unrelated donor registries, and HCT clinicians. The Histocompatibility Advisory Group conducted a national survey of practicing HCT physicians and unrelated donor search coordinators to characterize current donor search practices and examine urgent time to HCT and its association with disease risk, practices in the setting of low probability of MUDs, and acceptance of NMDP-provided solutions to optimize the efficient identification of a suitable donor.

METHODS

Participant Eligibility Criteria

Selection criteria included US HCT physician members of the American Society for Transplantation and Cellular Therapy (formerly the American Society for Blood and Marrow Transplantation) and unrelated donor search coordinators within the national NMDP network directly involved in donor/cord blood unit (CBU) selection. Member names, credentials, HCT center, titles, and e-mail addresses were obtained from American Society for Transplantation and Cellular Therapy and NMDP, and these membership lists were reserved for single use only for the purpose of this survey.

Survey Development and Content Areas

The survey was developed in 7 major content areas and refined by the Histocompatibility Advisory Group study group for face validity, clarity, and total expected time for completion. The survey was piloted with input from HCT physicians and search coordinators. Two parallel versions of the survey were developed to separately target practicing HCT physicians and unrelated donor search coordinators, and each was projected to require up to 25 minutes for completion. Content was largely identical in both surveys to permit study of concordance in responses across physicians and coordinators, except that only physicians were asked to characterize urgency according to disease and disease risk categories. The 2 surveys are provided as Supplementary Appendices S1 and S2.

The 7 major content areas are as follows:

1. Respondent demographics, including identification of HCT center, patients treated (adult versus pediatric versus both), years of experience in HCT, and board certification. Search coordinators provided years of experience and certification.
2. Existing donor search practices at HCT centers, including usual unrelated donor or CBU search practices at the center, rank ordering of preferred donor types at search initiation, and physician/search coordinator communication in the search process. Finally, respondents were asked to affirm which NMDP-supported resources their center uses when evaluating unrelated donor and CBU search results.
3. Definitions of HCT urgency and associated practices in this setting, including urgency of timeline as defined from search initiation to HCT infusion, agreement in a shared definition of urgency at the HCT center, proportion of HCT patients in past year that required urgent time to HCT, presence of a uniform system to determine urgency at the HCT center, resources used to expedite urgent HCT, alternative graft sources considered when 8/8 MUD is not available, and association of urgency in time to HCT with varied types of disease risk groups (an abbreviated list of common disease/remission groups based on the published disease risk index) [7].
4. Barriers to reaching HCT on desired timeline [8,9], including those experienced when concurrently pursuing stem cell sources for HCT, barriers experienced in urgent cases, percentage of urgent cases where inability to promptly identify stem cell source affect desired timeline to HCT, and percentage of urgent cases not able to reach HCT on the desired timeline due to barriers.
5. Practices in the setting of low probability of 8/8 MUDs (defined in the survey only as low probability, not using specific search prognosis data or actual search results), including acceptable ongoing unrelated donor search time for urgent cases in setting of initial search results demonstrating low likelihood of an 8/8 MUD before pursuing other stem cell sources, acceptable ongoing search time for nonurgent cases in setting of initial search results demonstrating low likelihood of 8/8 MUD before pursuing other stem cell sources, and alternative cell sources pursued in setting of low likelihood of 8/8 MUD.
6. HCT physician and search coordinator communication, including confidence in estimating time to HCT at start of search initiation, search coordinator confidence in providing early feedback when preferred donor source is unlikely to be achieved, and prompt action on search coordinator feedback regarding low probability of achieving the preferred product.
7. Acceptance of current and potential future NMDP-provided solutions to facilitate timely identification of a suitable donor for HCT (a "STAT" service to identify HLA confirmatory typed and available unrelated donors within 14 days of formal activation or notification of alternate strategies [6], a "search prognosis" indicator within the coordinator search application [5], and HapLogic matching predictions supplied for entire Bone Marrow Donors Worldwide donor list [4]).

Survey Conduct

Potential participants were sent a personalized e-mail invitation to complete the survey through Snap Surveys (www.snapsurveys.com). The survey was released in February 2018 with 5 reminder e-mail blasts issued before survey closure in May 2018. Initial screening questions determined whether the physician or search coordinator was directly involved in unrelated donor/CBU search and selection decision-making for allogeneic HCT patients in the United States. The incentive was the possibility to win a $100 gift card by random drawing, with 100 possible winners. All participants agreed to participate in the research survey with the understanding that participation was voluntary and that answers would not be linked to any personally identifying information. The NMDP Institutional Review Board approved the study.

Analytic Methods

The primary aims of this study were descriptive in nature. We used descriptive statistics, including frequencies and percentages, to examine physician and coordinator responses to survey items. Chi-square and Fisher's exact tests were used to identify differences between physician and coordinators' practice and perceptions in urgent allogenic HCT. All statistical analyses were performed using SAS (SAS Institute, Inc., Cary, NC) Enterprise Guide (V6.1).

RESULTS

Participant Characteristics

Survey respondent characteristics are shown in Table 1. Three hundred seventeen of 858 physicians (37%) and 225 of 327 coordinators (69%) responded, of which 263 physicians and 194 coordinators met the eligibility criteria and were included in the analysis. The differential from number of respondents to eligible subjects was due to removal of ineligible subjects, most commonly because of partial completion of the survey, response indicating that the respondent had no direct role in donor search and selection practices, or failure to provide consent for the survey. Most centers (142/150 [95%]) were represented, and 72% and 85% of centers had at least 1 physician and 1 coordinator complete the survey, respectively. A greater proportion of physicians represented adult-only centers compared with coordinators. Oncology and hematology were the most common physician board certification, whereas search coordinators were most commonly registered nurses and/or certified hematopoietic transplant coordinators. A greater proportion of physicians reported greater than 10 years of experience than coordinators (64% and 41%, respectively; $P < .0001$).

Usual Donor Search Practices

When asked to select all that apply, the majority of both physicians (73.8%) and coordinators (80.4%) reported that donor search practices were guided by a center selection algorithm but final decisions were made by individual treating physicians. A group roundtable discussion (35.4% and 35.6%) or decision driven by research protocols (19.0% and 22.7%) were less commonly endorsed by physicians and coordinators, respectively. Other approaches, including strict adherence to a center selection protocol (10.6% and 10.3%), individual physician decision without a shared algorithm (8.0% and 8.8%), or a single center representative decision-maker (4.6% and 9.8%),

Table 1
Survey Respondent Characteristics.

Characteristics	Physicians (n = 263)	Coordinators (n = 194)	Total (N = 457)	*P* (determined by chi-square test)
Patient population				
Adults only	166 (63.1)	105 (54.1)	271 (59.3)	.0035
Pediatrics only	68 (25.9)	45 (23.1)	113 (24.7)	
Adults and pediatrics	29 (11.0)	44 (22.7)	73 (16.0)	
Years of experience in unrelated HCT				
<1	3 (1.1)	17 (8.8)	20 (4.4)	<.0001
1-5	46 (17.5)	60 (30.9)	106 (23.2)	
6-10	46 (17.5)	37 (19.1)	83 (18.2)	
>10	168 (63.9)	80 (41.2)	240 (52.5)	
Physician board certification*				
Hematology	132 (50.2)			
Oncology	130 (49.4)			
Internal medicine	112 (42.6)			
Pediatric hematology/oncology	90 (34.2)			
Pediatrics	47 (17.9)			
Other	11 (4.2)			
Search coordinator years at center				
<1		14 (7.2)		
1-5		44 (22.7)		
6-10		29 (14.0)		
>10		107 (55.2)		
Search coordinator credentials*				
Registered nurse		144 (74.2)		
Certified hematopoietic transplant coordinator		58 (29.9)		
Other†		84 (43.3)		

* Respondents could select all that applied.
† Other included oncology certified nurse (n = 25); bone marrow transplant certified nurse (n = 18); bachelor of science in nursing (n = 15); Master's degree (n = 9); Bachelor's degree (n = 8); medical technology (n = 6); none (n = 3).

were not commonly reported by both physician and coordinators, respectively.

Most physicians and coordinators (98% and 97%, $P = .37$) indicated that matched sibling donors were prioritized when available (ranked as first among the available donor options), and most (76% and 66%, $P = .02$) physicians and coordinators, respectively, ranked an 8/8 MUD as the second preferred donor option. Among alternative donor types, 41% and 37% ($P = .018$) of physicians and coordinators ranked haploidentical donors as third in priority, 24% and 18% ($P = .0007$) of physicians and coordinators ranked UCB third, and 15% and 10% (not significant) of physicians and coordinators ranked 7/8 unrelated donors third. Less than 8% of physicians and coordinators ranked the above alternative donor types as the first priority option among potential donor types.

Most physicians and coordinators either agreed or strongly agreed that there was good communication between the clinical team and unrelated donor search coordinator. However, physicians were more likely than coordinators to strongly agree (80% and 67%, respectively; $P = .17$) that there was good communication on urgency and timeline for a given patient's HCT and likelihood of availability of the preferred stem cell source (66% and 53%, respectively; $P = .017$).

When asked to report any/all NMDP-supported resources used when evaluating unrelated donor and CBU searches, 81% of coordinators reported using NMDP search strategy advice/HLA consultation, 68% reported using HapLogic donor and CBU match prediction output, and 84% reported using donor and CBU list view in Traxis. Less than 1% of coordinators indicated that they were unaware of the listed NMDP-supported resources. Similarly, less than 1% reported that they had not found them to not be helpful in the past.

HCT Urgency

Most physicians and coordinators (90% and 87%, $P = .19$) indicated that urgent cases had a timeline of 6 weeks or less from unrelated search initiation (assuming no matched sibling donor option) to HCT infusion (Figure 1). Interestingly, 62% and 84% ($P < .0001$) of physicians and coordinators indicated that the definition of urgency was shared among transplant physicians at their center, yet most physicians and coordinators (67% and 62%, $P = .23$) indicated that each physician has his or her own system to determine which patients are urgent rather than an agreed on system used by all physicians. More physicians than coordinators (81% and 58%, respectively; $P < .0001$) reported that ≤25% of HCT candidates at their center had to proceed to HCT within 6 weeks from time of unrelated donor search initiation.

Urgent time to HCT (defined here as HCT within 6 weeks from unrelated donor search initiation to HCT infusion) was associated with escalating disease/disease risk status (Figure 2). These disease/remission status/prognostic subgroup variants were selected to represent variation within each disease type across the spectrum of the disease risk index.

Many available strategies were commonly used to expedite time to HCT among urgent cases, with multiple donors requested concurrently for workup (70% and 53%), prioritized analysis of donor by transplant search coordinator (56% and 67%), requesting confirmatory typing and workup concurrently (51% and 63%), and selecting donors with recent contact status for improved donor availability (31% and 61%) as the

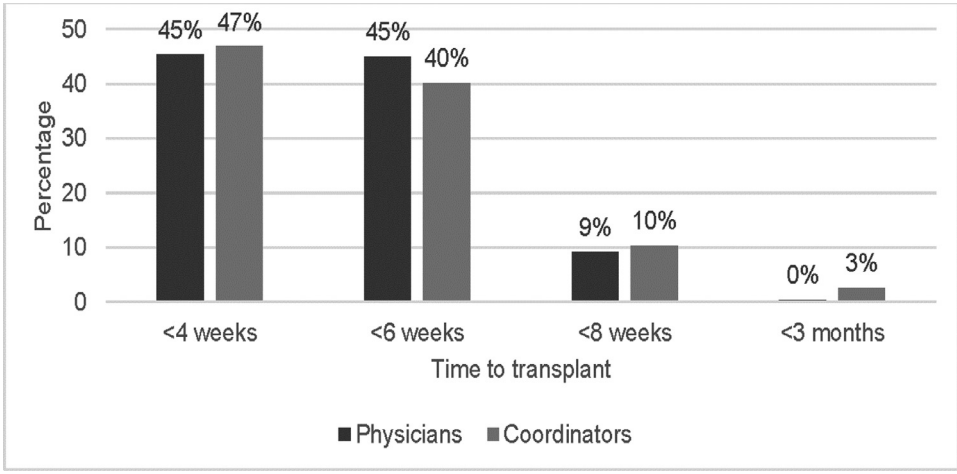


Figure 1. Physician and search coordinator definitions of urgent time to transplant defined as time from unrelated donor search initiation to cell infusion. *Percentages reported for each category. No significant differences between physicians and coordinators.

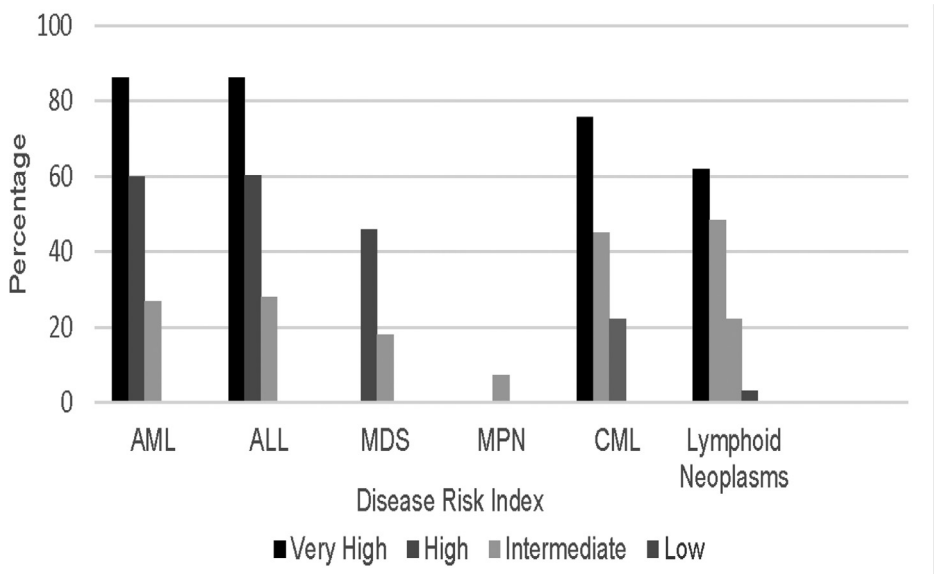


Figure 2. Variation in reported urgent time to transplant according to disease diagnosis and disease risk index categories. Percentage of physician respondents who classified the disease and risk characteristics scenario as urgent (defined here as no more than 6 weeks from unrelated donor search submission to infusion day). AML indicates acute myeloid leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; CML, chronic myeloid leukemia.

most prevalent among physicians and coordinators, respectively. Physicians and coordinators reported using 1 or more alternative donors for urgent cases when 8/8 MUDs were not available (90% and 94% haploidentical, 63% and 57% CBU, 46% and 43% mismatched unrelated, respectively).

Barriers to Reaching HCT on a Desired Timeline Among Urgent Cases

The most commonly reported barriers to reaching HCT on the desired timeline reported by physician and coordinators included receiving HLA typing results for patient and donor (48% and 57%), inability of the unrelated registry to provide timely donor collection date (61% and 62%), and insurance issues (58% for both). Less commonly reported barriers included scheduling additional tests for the patient (29% and 41%), hospital bed space (16% and 15%), scheduling HCT radiotherapy or other therapy (20% and 28%), or cell therapy lab schedule (22% and 21%), respectively.

Physicians and coordinators reported experiencing 1 or more of the following barriers when concurrently pursuing all HCT cell sources for urgent cases: insurance approval (64% and 60%), lack of time for search coordinator to analyze these options concurrently (29% and 34%), or other (15% and 16%). Less than 4% and 14% of physicians and coordinators, respectively, reported that they do not pursue different cell sources concurrently for urgent cases.

The ability to identify a stem cell source for urgent cases was not commonly selected as a significant barrier. Most physicians and coordinators (80%) reported that identifying a stem cell source limited the ability to proceed to transplant in the desired timeline in 25% or less of their usual urgent cases, with no significant differences between the 2 groups. Similarly, 83% of both physicians and coordinators reported that 25% or less of urgent cases could not reach HCT on the desired timeline because of barriers.

Search Practices after Low Probability of 8/8 MUD

In the setting of a perceived urgent case, respondents allowed little time for ongoing MUD search activity before proceeding to alternative donors when initial results indicated low probability of 8/8 MUD (additional search time of 1 week, 37%; 2 weeks, 40%; 1 month, 19%; or ≥2 months, 4%), with no significant differences between physicians and coordinators. Preferred strategies explored in this setting included haploidentical donors, CBU, and 7/8 unrelated donors, with non-HCT therapy, research protocol driven source selection, or other, less often pursued (Figure 3). In contrast, a greater proportion allowed additional unrelated donor search time in the setting of nonurgent cases (additional search time of 1 week, 4%; 2 weeks, 10%; 1 month, 38%; or ≥2 months, 48%), with no significant differences between physicians and coordinators.

HCT Physician and Coordinator Communication

More physicians than coordinators reported agreement (% agree or strongly agree) that "My unrelated donor search coordinator is (MD survey)/I am (coordinator survey) confident in estimating time to HCT from time of search initiation" (71% and 65%, respectively; $P < .0055$). Similarly, a greater proportion of physicians than coordinators (94% and 88%, $P = .018$) reported that "the clinical team acts promptly on feedback regarding low probability of achieving the preferred product." However, there were no significant differences between physician and coordinator responses when asked if "my unrelated donor search coordinator is (MD survey)/ I am (coordinator survey) confident in providing feedback early in a search when the preferred donor source is unlikely to be achieved" (89% for both).

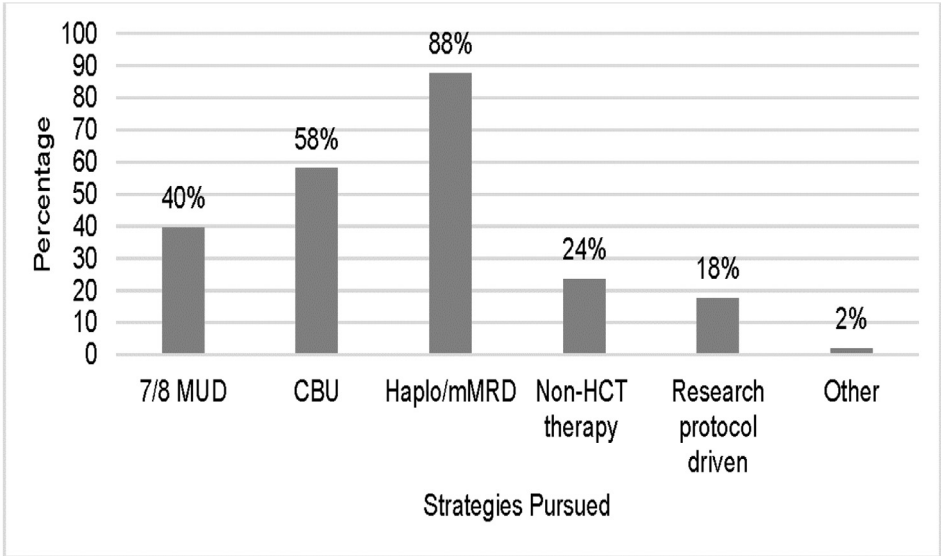
Acceptance of NMDP-Provided Solutions

Most physicians and coordinators highly supported (% agree or strongly agree) NMDP current or future potential solutions to facilitate rapid identification of suitable donors for HCT, including a "STAT" service to identify HLA confirmatory typed and available unrelated donors within 14 days of formal activation or notification of alternate strategies (86%), a "search prognosis" indicator within the coordinator search application (77%), and HapLogic matching predictions supplied for entire Bone Marrow Donors Worldwide donor list (78%), with no significant differences between physicians and coordinators.

DISCUSSION

This national survey of HCT physicians and donor search coordinators provides comprehensive insight into usual donor search and selection practices, urgent time to HCT, decision-making when MUD options are limited, and provider-level endorsement of strategies to enhance efficient identification of donors. The data indicate that, under usual practices, HCT physicians and search coordinators work together in a coordinated manner to achieve the desired donor in the desired time frame. Communication on urgency, preferred donor type, or donor alternatives does not appear to be a major barrier within the clinical team. With the assistance of existing NMDP search resources and guidance from center selection algorithms, HCT physicians largely individually drive donor selection decisions, using an expected donor priority ranking (preferential ranking of matched siblings, then MUDs, followed by heterogeneous use of alternative donors).

Because urgent time to HCT appears to be largely defined as within 4 to 6 weeks from unrelated donor search initiation to HCT infusion, strategies to efficiently identify suitable donors and reach HCT are needed. This rapid timeline appears to be indicated for some usual HCT candidates and is associated with increased disease risk. Under current practices, multiple means are already used to reach HCT quickly among urgent cases. Most indicated allowing no more than 2 weeks of additional unrelated donor search time after initial search, indicating a low probability of an 8/8 MUD, and use of alternative donor types were highly endorsed in this setting. Because most endorsed pursuing multiple donor sources concurrently, the inability to identify a suitable donor of any type is an uncommon barrier for the desired time to HCT for urgent cases. Additional innovative NMDP resources to enhance early notice of search prognosis and ultrarapid provision of available



*HLA, human leukocyte antigen; MUD, matched unrelated donor; CBU, cord blood unit; Haplo, haploidentical related donor; mMRD, mismatched related donor; HCT, hematopoietic cell transplantation. *Percentages reported for each alternative cell source (Select all that apply).*

Figure 3. Strategies pursued in the setting of low probability of an 8/8 HLA MUD. Haplo indicates haploidentical related donor; mMRD, mismatched related donor.

donors were highly endorsed. Because the use of haploidentical transplant increases and may benefit from related donors who may be highly engaged and located within proximity to the treating transplant program for readily available donation, more research is needed to understand whether the current speed possible for MUDs versus haploidentical donors should cause differential clinical decisions.

The main barriers identified by this survey included the time delay in receiving HLA typing results for patient and donor, inability of the unrelated registry to provide timely donor collection date, and insurance issues. The NMDP continues to seek to understand and implement processes that can better enable the search and selection of donors to achieve rapid patient time to transplant. New initiatives are aimed at obtaining the desired time to transplant at the initiation of the patient search, to better inform requested donors of the need, and to provide information back to the transplant center if other options should be pursued. Despite over two-thirds of physician and coordinator survey respondents being confident in estimating time to HCT at time of search initiation, NMDP currently receives data on less than one-third of patient cases (internal NMDP data). This is recommended as an area of opportunity for center practice. In addition, FastTrack Search is a new service that is intended for patients with urgent time to transplant and includes accelerated donor screening using the transplant center's prioritized list of potential donors, preferred product for the transplant, and target collection timeframe. HLA confirmatory testing is performed at a centralized laboratory with results in 3 business days. Comprehensive updates from the NMDP case manager provide progress so timely decisions can be made by the HCT clinical team. To address insurance coverage–based barriers, the NMDP has focused on implementing strategies and working with payers. This includes working with stakeholders to create an essential health benefit set for transplant to be used by payers, creating a care coordination toolkit for payers to have "one-stop" for information on care along the patient continuum, and creating resources and publishing articles on a set of standard indications for policymakers to use to address coverage for HCT. Additionally, NMDP has a grant program that offers financial assistance for patients who are not insured or do not have search assistance benefits in their insurance plan to cover the donor search process. NMDP intends to continue identifying specific insurance challenges inhibiting timely transplantation.

In addition, MatchSource was released in July 2019 as the HCT center software to manage the search and selection process, which applies the HapLogic algorithm assessment to all worldwide donors and CBU sources. Future provision of a search prognosis indicator into the HCT center software is also planned to better assist HCT centers in the characterization of difficult searches to encourage early decisions and escalation of selection expertise.

We acknowledge the following limitations of this work. First, although most surveyed HCT centers were represented, potential threats to this work include relatively low physician response rate, predominantly limited number of respondents per center, and representation of US centers only. Based on limited respondents per center, we could not adequately address variation in responses within centers. Second, we acknowledge that the survey content and presentation could not fully recapitulate real-world circumstances that inform providers' decision-making regarding donor selection, especially as required in urgent cases: We did not address the impact of race and ethnicity on search prognosis and donor selection [10] but rather focused generally on practices in the setting of low likelihood of well-MUDs. As well, the survey did not invoke potential differences in HCT outcomes according to alternative donor types. Also, survey content examining urgency as a function of disease risk appealed to an abbreviated set of disease risk index–based categories and did not examine either the full range of disease and disease remission subgroups or include other factors (eg, molecular markers of disease risk, nuances of treatment history and response, patient-level specific considerations) that likely play a role in usual decision-making. Finally, the section on urgency and disease risk did not include nonmalignant disorders, thus in part limiting relevance to pediatric HCT physicians.

This national survey clarified current donor selection decision-making practices in the United States and defined urgent time to HCT. These data provide insight to the NMDP on potential solutions to support the path to transplant, such as highlighting futile searches and providing alternative donor options at the time of search initiation. The NMDP recommends that transplant centers maintain a uniform selection process across providers, with close communication with their search coordinators and utilization of NMDP resources, to enable donor selection and transplantation in the preferred timeframe for optimal recipient outcomes.

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SUPPLEMENTARY MATERIALS

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